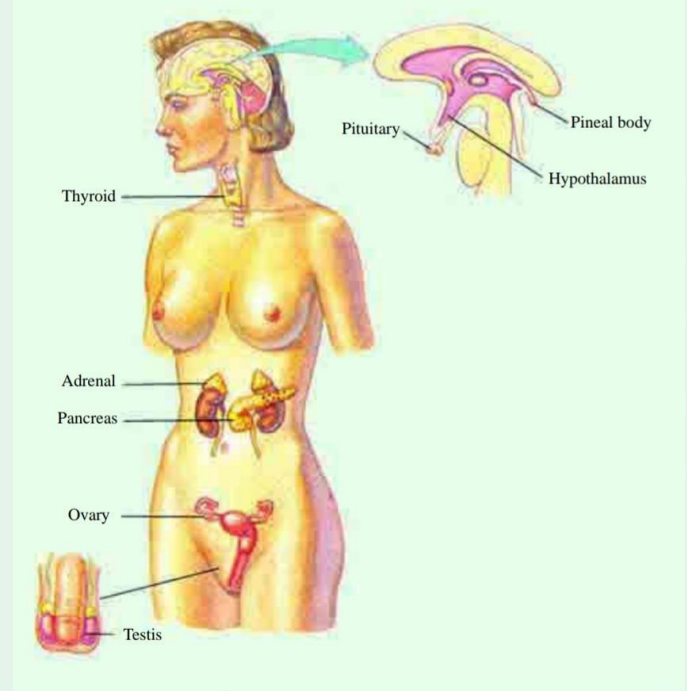
Steroidal Hormones

Carbon-21 carbon -19 carbon-18

Vertebrate hormones



Steroidal Hormones

STEROID HORMONES

C_{18} STEROIDS

1. **Ovarian Hormones**
   - β-estradiol
   - Estriol
   - Estrone

C_{19} STEROIDS

2. **Testicular Hormones**

   From testes
   - Testosterone
   - Androsterone
   - Dehydroepiandrosterone

   From adrenal gland
   - Androst-4-ene-3,17,dione
   - Androst-4-ene-3,11,17-trione

C_{21} STEROIDS

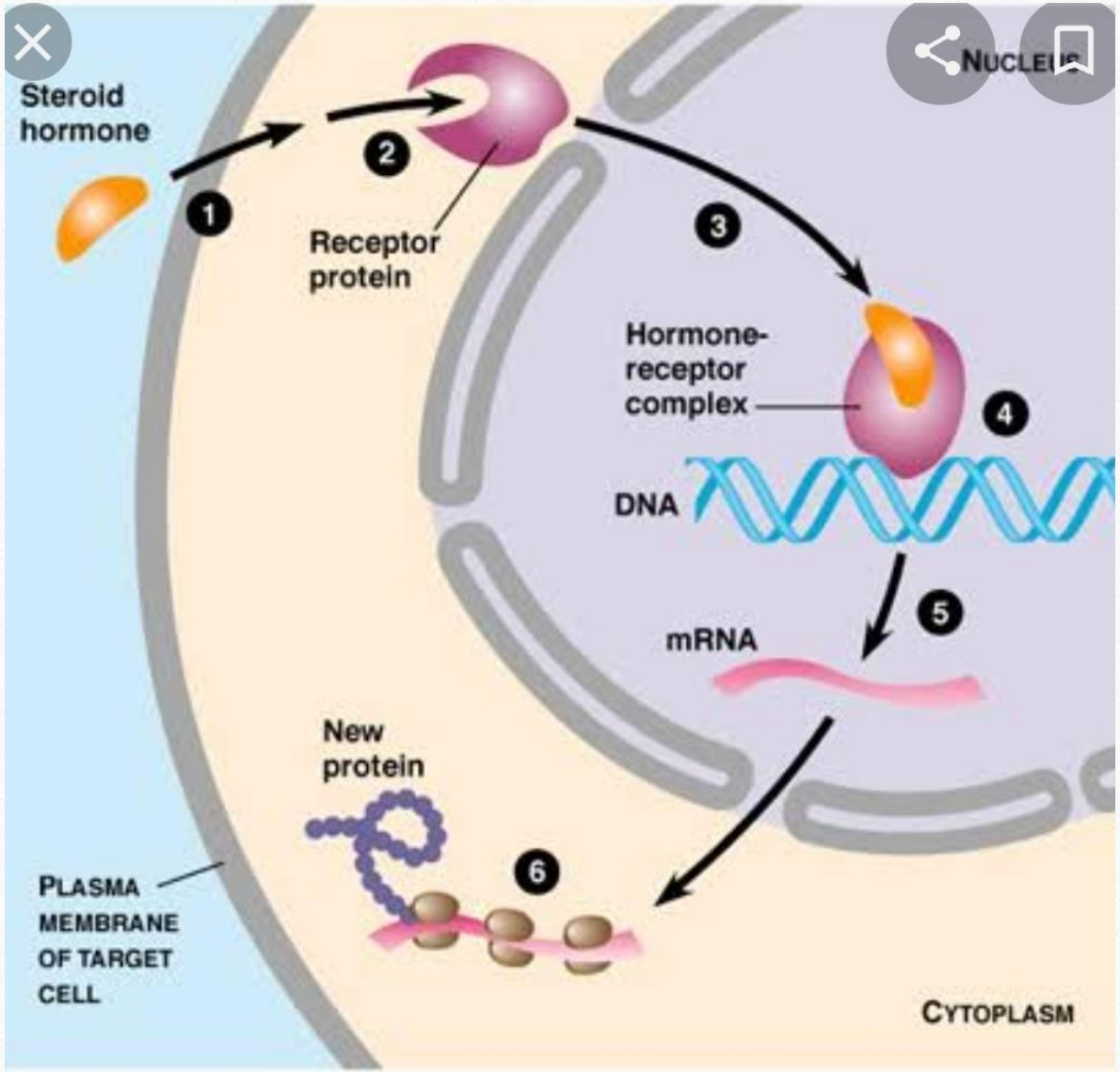
3. **Adrenal Cortical Hormones**

   Mineralocorticoids
   - Aldosterone
   - Deoxycorticosterone

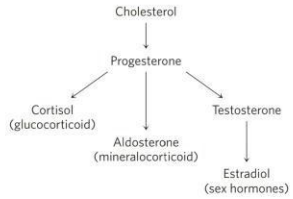
   Glucocorticoids
   - Cortisone
   - Cortisol
   - Corticosterone

4. **Corpus Luteal Hormone**
   - Progesterone

C18	C19	C21
Estradiol	Testosterone	Progesteron e Cortisol

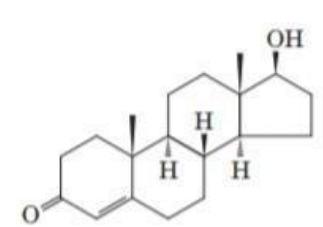

Steroid hormone
1
2
Receptor protein
3
Hormone-receptor complex
4
DNA
5
mRNA
New protein
6
PLASMA MEMBRANE OF TARGET CELL
CYTOPLASM

Mechanism

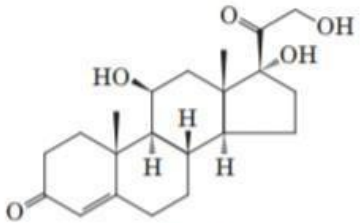


They travel to their target cells through the bloodstream, bound to carrier proteins. More than 50 corticosteroid hormones are produced in the adrenal cortex by reactions that remove the side chain from the D ring of cholesterol and introduce oxygen to form keto and hydroxyl groups. Many of these reactions involve cytochrome P-450 enzymes (see Box 21–1). The corticosteroids are of two general types, defined by their actions. Glucocorticoids (such as cortisol) primarily affect the metabolism of carbohydrates; mineralocorticoids (such as aldosterone) regulate the concentrations of electrolytes (K^+, Na^+, Ca^{2+}, Cl^-) in the blood. Androgens (such as testosterone) and estrogens (such as estradiol; see Fig. 10–19) are synthesized in the testes and ovaries. They affect sexual development, sexual behavior, and a variety of other reproductive and nonreproductive functions. Their synthesis also involves cytochrome P-450 enzymes that cleave the side chain of cholesterol and introduce oxygen atoms.

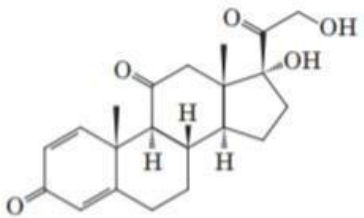
All steroid hormones act through nuclear receptors to change the level of expression of specific genes (see Fig. 12–30). They can also have more rapid effects, mediated by receptors in the plasma membrane.



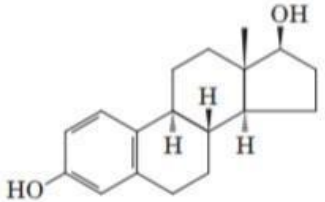
Testosterone



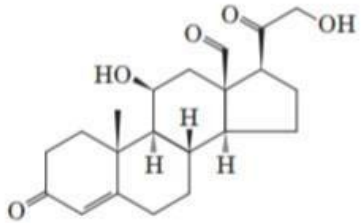
Cortisol



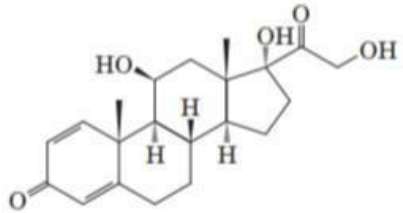
Prednisone



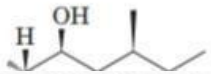
β-Estradiol



Aldosterone



Prednisolone



STEROID HORMONES

These include the sex hormones and the hormones from adrenal cortex. These are synthesized in mammals by the ovary (or testis), adrenal cortex, corpus luteum and the placenta. The activity of sex hormones appears to be controlled by the hormones secreted by the anterior lobe of the hypophysis (= adenohypophysis). Because of this, the sex hormones are, sometimes, referred to as *secondary sex hormones* and the hormones of the adenohypophysis, which are of proteinaceous nature, are called as *primary sex hormones*. Three types of sex hormones are recognized :

(*a*) the estrogens (female or ovarian or follicular hormones)

(*b*) the androgens (male or testicular hormones)

(*c*) the gestogens (corpus luteal hormones).

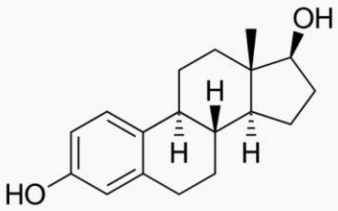
The sex hormones are concerned with the sexual processes and the development of secondary characteristics which differentiate males from females. The adrenal cortical hormones perform a variety of important functions related to cell metabolism.

Based on the number of carbon atoms present in the molecule, the steroid hormones may be named as C_{18}, C_{19} or C_{21} steroids.

Ovarian Hormones (Estrogen)

The female sex hormone, and one that teenage girls know all too well, is responsible for setting off puberty. Produced primarily in your ovaries, estrogen regulates your menstrual cycle, maintains pregnancy and keeps bones strong for women and men too! Watch out, world.

Estrogen or **oestrogen**, is a category of sex hormone responsible for the development and regulation of the female reproductive system and secondary sex characteristics. There are three major endogenous estrogens that have estrogenic hormonal activity: estrone (E1), estradiol (E2), and estriol (E3). Estradiol, an estrane, is the most potent and prevalent. Another estrogen called estetrol (E4) is produced only during pregnancy.

Estrogen
Drug class
 Estradiol, the major estrogen sex hormone in humans and a widely used medication.
Class identifiers
Use — Contraception, menopause, hypogonadism, transgender women, prostate cancer, breast cancer, others

There are different types of estrogen:

Estrone

This type of estrogen is present in the body after menopause. It is a weaker form of estrogen and one that the body can convert to other forms of estrogen, as necessary.

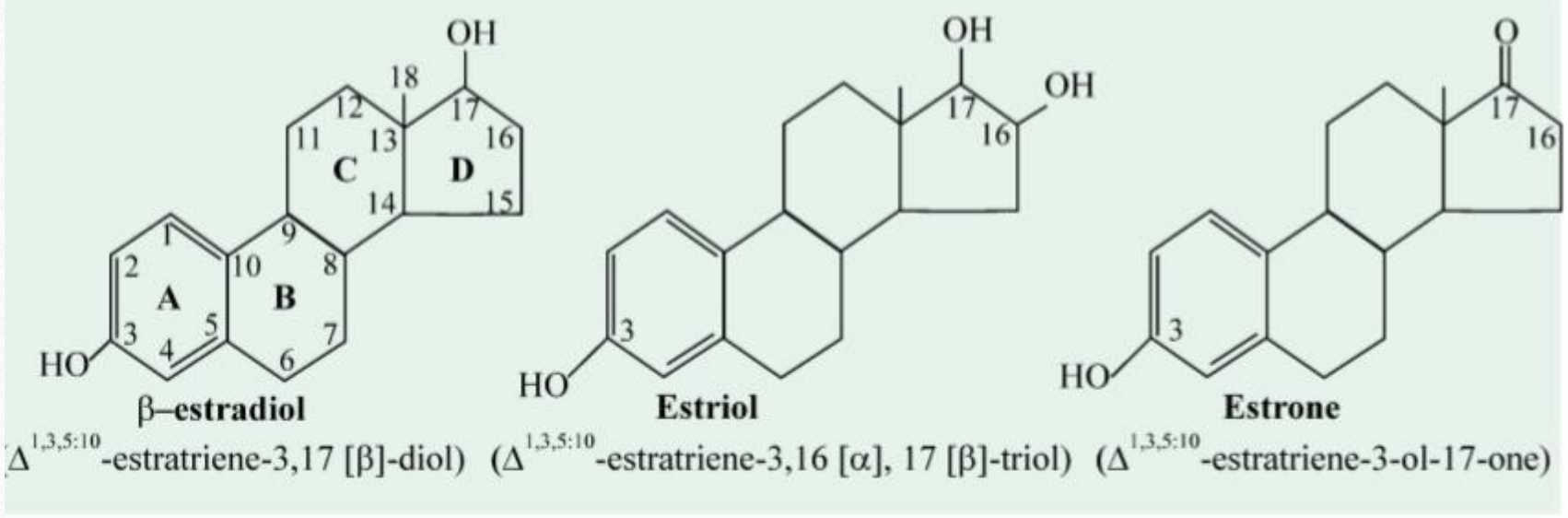
Estradiol

Both males and females produce estradiol, and it is the most common type of estrogen in females during their reproductive years.

Too much estradiol may result in acne, loss of sex drive, osteoporosis, and depression. Very high levels can increase the risk of uterine and breast cancer. However, low levels can result in weight gain and cardiovascular disease.

Estriol

Levels of estriol rise during pregnancy, as it helps the uterus grow and prepares the body for delivery. Estriol levels peak just before birth.


OH
18
12
17
11
13
16
C
D
14
15
9
1
2
10
8
A
B
3
5
7
4
6
HO
β–estradiol
(Δ1,3,5:10-estratriene-3,17 [β]-diol)
OH
OH
17
16
3
HO
Estriol
(Δ1,3,5:10-estratriene-3,16 [α], 17 [β]-triol)
O
17
16
3
HO
Estrone
(Δ1,3,5:10-estratriene-3-ol-17-one)

Function

Estrogen enables the following organs to function:

Ovaries: Estrogen helps stimulate the growth of the egg follicle.

Vagina: In the vagina, estrogen maintains the thickness of the vaginal wall and promotes lubrication.

Uterus: Estrogen enhances and maintains the mucous membrane that lines the uterus. It also regulates the flow and thickness of uterine mucus secretions.

Breasts: The body uses estrogen in the formation of breast tissue. This hormone also helps stop the flow of milk after weaning.

Levels of estrogen

Estrogen levels vary among individuals. They also fluctuate during the menstrual cycle and over a female's lifetime. This fluctuation can sometimes produce effects such as mood changes before menstruation or hot flashes in menopause.

Factors that can affect estrogen levels include:

- pregnancy, the end of pregnancy, and breastfeeding
- puberty
- menopause
- older age
- overweight and obesity
- extreme dieting or anorexia nervosa
- strenuous exercise or training
- the use of certain medications, including steroids, ampicillin, estrogen-containing drugs, phenothiazines, and tetracyclines
- some congenital conditions, such as Turner's syndrome
- high blood pressure

An imbalance of estrogen leads to:

- irregular or no menstruation
- light or heavy bleeding during menstruation
- more severe premenstrual or menopausal symptoms
- hot flashes, night sweats, or both
- noncancerous lumps in the breast and uterus
- mood changes and sleeping problems
- weight gain, mainly in the hips, thighs, and waist
- low sexual desire
- vaginal dryness and vaginal atrophy
- fatigue
- mood swings
- feelings of depression and anxiety
- dry skin

Signs and Symptoms of Low Estrogen

Physical Symptoms:

- Hot flashes
- Insomnia
- Vaginal dryness
- Irregular periods

Psychological Symptoms:

- Panic attacks
- Mood swings
- Memory lapses
- Low self-esteem

Signs of Low Estrogen:

- **Microscopy:** vaginal, bacterial fungal growth
- **ECG:** abnormal results
- **Blood tests:** low serotonin levels
- **Estrogen tests:** low levels

Table 31–1. **Body changes at puberty in girls (=Secondary sex characters in females)**

Characters	*Changes*
1. External genitalia	Enlargement of uterus and vagina; Widening of pelvis.
2. Internal genitalia	Periodic vaginal bleeding that occurs with the shedding of the uterine mucosa (i.e., menstruation).
3. Voice	Larynx retains its prepubertal proportions, i.e., small in size; Voice stays high-pitched.
4. Hair growth	Less body hair and more scalp hair; Hair line on scalp resembles that of a child and does not recede anterolaterally (Fig. 30–10); Hair appear in axillae (axillary hair) and around vagina; Pubic hair have a characteristic female pattern, i.e., flat-topped; Hair on face absent i.e., no beard.
5. Mental	Less aggressive; Passive attitude; Interest in opposite sex less pronounced.
6. Body conformation	Narrow shoulders and broad hips, which are popularly called as 'hip pads'; Thighs that converge and arms that diverge, i.e., a wide carrying angle; Distribution of fat in the breasts and buttocks takes place, leading to their enlargementÂthe breasts also have high pigmentation in the areola which becomes even more intense during the first pregnancy; Muscles not pronounced.
7. Skin	Sebaceous gland secretions become more fluid and thus counter the effect of testosterone and inhibit formation of comedones ('black-heads') and acne (a hard, red inflamed pimple)
8. Weight gain	Tend to gain weight from the waist down.

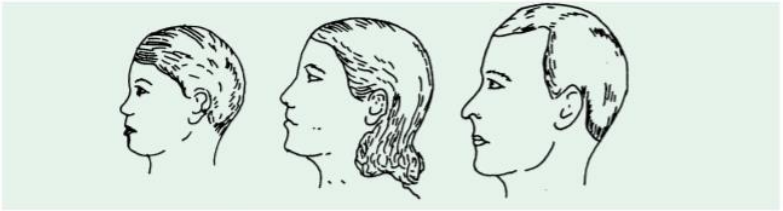


Fig. 31–10. **Hair line pattern of child, woman and man**

The hair line of the women is like that of the child, whereas that of the man is indented in the lateral frontal region. (*Adapted from Grenlich et al, 1942*)

Estrogens also influence to a great deal (*a*) the inorganic metabolism of Ca and P and (*b*) the organic metabolism of proteins and lipids.

Castration (*castratus*^{L} = to prune). Removal of the ovary in females is known as ovariectomy. In females, castrated prior to puberty (*pubertas*^{L} = of ripe age, adult), both the menstrual as well as the reproductive cycles never appear. The typical pelvic enlargement fails to occur and the pubic and axillary hair become scanty. Post-pubertal castration results in suspension of menstrual cycle and atrophy of uterus and vagina. Also, mammary glands become involuted and osteoporosis gradually appears.

Castration is the act of pruning in any of its senses.

Puberty is the state of physical development at which persons are first capable of begetting or bearing children. In law, the age of puberty is usually fixed at 14 in the male and 12 in the female.

Stilbesterol– Stilbesterol is a synthetic product with marked estrogenic properties. It is an amino acid derivative and obviously does not resemble estrogens in chemical structure. However, it produces practically all the physiologic effects that estradiol does. Its diethyl derivative, diethylstilbesterol (Fig. 31–11), is more potent physiologically. Stilbesterol is administered orally and in some cases certain unpleasant side effects spring up. However, if the dosage is controlled carefully, these effects can be alleviated.

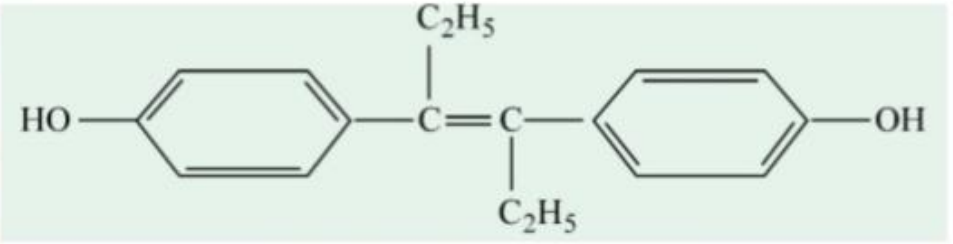


Fig. 31–11. Diethylstilbesterol

C-19 Steroids

Testosterone hormone

1. *Testosterone*
2. *Endosterone*

C_{19} STEROIDS

2. Testicular Hormones

Structure. These hormones are secreted mainly by the testes, the male reproductive organs and are called as androgens (*andros*[G] = male). Chemically, these are derivatives of a C_{19} hydrocarbon, *androstane* (Fig. 31–12).

There are many hormones secreted from testes with androgenic activity. The three important ones (Fig. 31–13) are :

1. Testosterone, $C_{19}H_{28}O_2$
2. Androsterone, $C_{19}H_{30}O_2$
3. Dehydroepiandrosterone, $C_{19}H_{25}O_2$

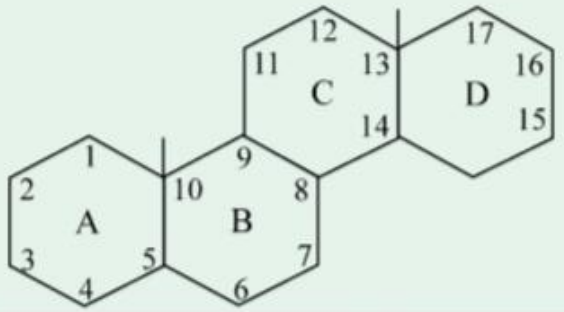
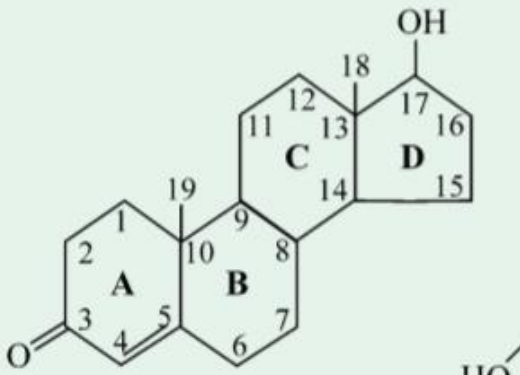
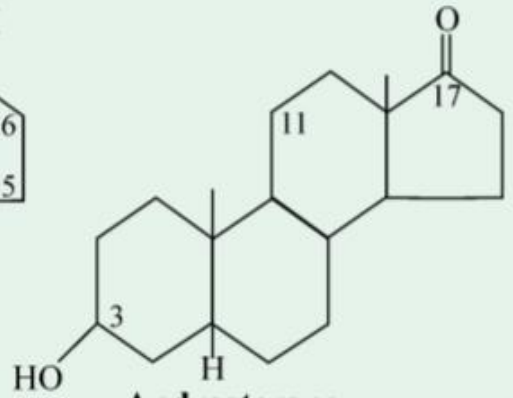


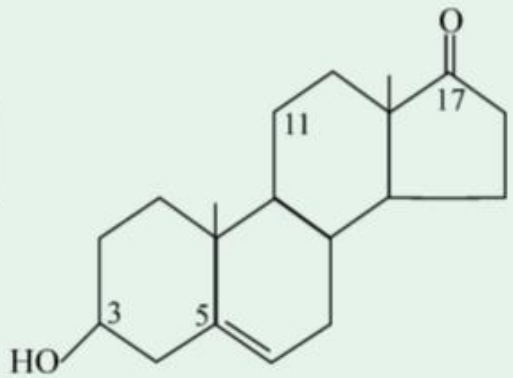
Fig. 31–12. Androstane
(parent hydrocarbon of androgens)



Testosterone
(3-keto-17-hydroxy-Δ^4-androstene)



Androsterone



Dehydroepiandrosterone, DHEA
(3-hydroxy-17-keto-Δ^5-androstene)

How do I know if my androgen levels are normal?

Everyone has their own unique "normal." Since "normal" changes over the course of a person's life, symptoms may be more important than results from a hormone test. (But in case you are curious, we have also included information about typical androgen levels given by hormone tests below this section.)

Symptoms of high androgen levels include:

- Hirsutism (excess hair growth)
- Acne
- Irregular periods
- Absent periods (amenorrhea)
- Anovulation
- Infertility (10,11)

Conditions that can cause or are associated with high androgen levels include:

- Polycystic ovarian syndrome (PCOS)
- Tumors on the adrenal gland
- Tumors on the ovaries
- Hyperprolactinemia
- Cushing's disease (9,10,12)

Symptoms of low androgen levels

There are not many obvious symptoms of low androgen in cis-women and people with ovaries. Symptoms might include changes in sex drive and mood, but the research here isn't clear cut (7,9,10).

Procedures, treatments, and conditions that can cause or are associated with unexpectedly low androgen levels include:

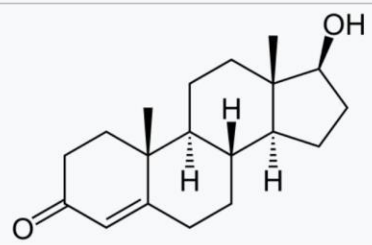
- Primary ovarian insufficiency (i.e. very early menopause)
- Surgically-induced menopause
- Hypopituitarism
- Chemotherapy
- Adrenal insufficiency
- HIV
- Birth control and hormone therapy containing estrogen (7,9,10)

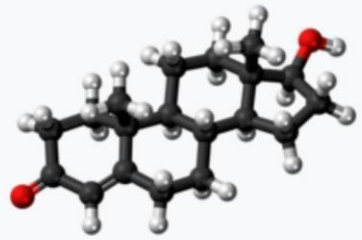
Some of these things can lead to low androgen levels by increasing the amount of *sex hormone binding globulin* (SHBG) (7,9). An increase in SHBG causes a decrease in bioavailable testosterone, so even if your total testosterone levels are normal, the testosterone that's actually available may still be low.

Testosterone

Testosterone is the primary sex hormone and anabolic steroid in males.[3] In humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate, as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair.[4] In addition, testosterone in both sexes is involved in health and well-being, including moods, behaviour, and in the prevention of osteoporosis.[5][6] Insufficient levels of testosterone in men may lead to abnormalities including frailty and bone loss.

Testosterone

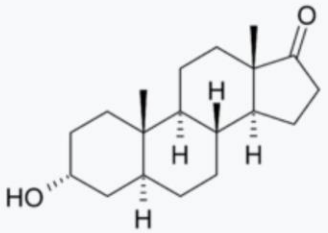


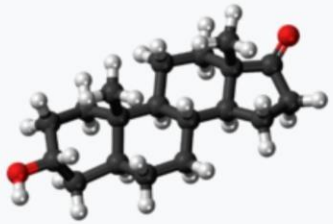


Androsterone

Androsterone, or **3α-hydroxy-5α-androstan-17-one**, is an endogenous steroid hormone, neurosteroid, and putative pheromone.[1] It is a weak androgen with a potency that is approximately 1/7 that of testosterone.[2] Androsterone is a metabolite of testosterone and dihydrotestosterone (DHT). In addition, it can be converted back into DHT via 3α-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase, bypassing conventional intermediates such as androstanedione and testosterone, and as such, can be considered to be a metabolic intermediate in its own right.[3][4]

Androsterone





Biological function

Androsterone has generally been considered to be an inactive metabolite of testosterone, which when conjugated by glucuronidation and sulfation allows testosterone to be removed from the body, but it is a weak neurosteroid that can cross into the brain and could have effects on brain function.[8]

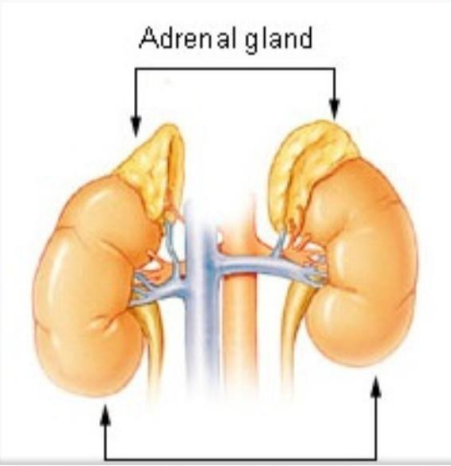
The view of androsterone as generally being of low significance however, seems to need review in the light of 21st century research, which suggests that androsterone significantly affects masculinization in mammalian fetuses. Masculinization of the external genitalia in humans is subject to dihydrotestosterone (DHT) derived via the recognised androgenic pathway and also via a backdoor pathway.[10] Therefore, androstanediol can be used a marker of the backdoor pathway of DHT synthesis.[11] Spectrometric studies identify androsterone as the main backdoor androgen in the human male fetus. Circulating levels are sex dependent, DHT being essentially absent in the female, in which titres of backdoor intermediates also are very low.[10]

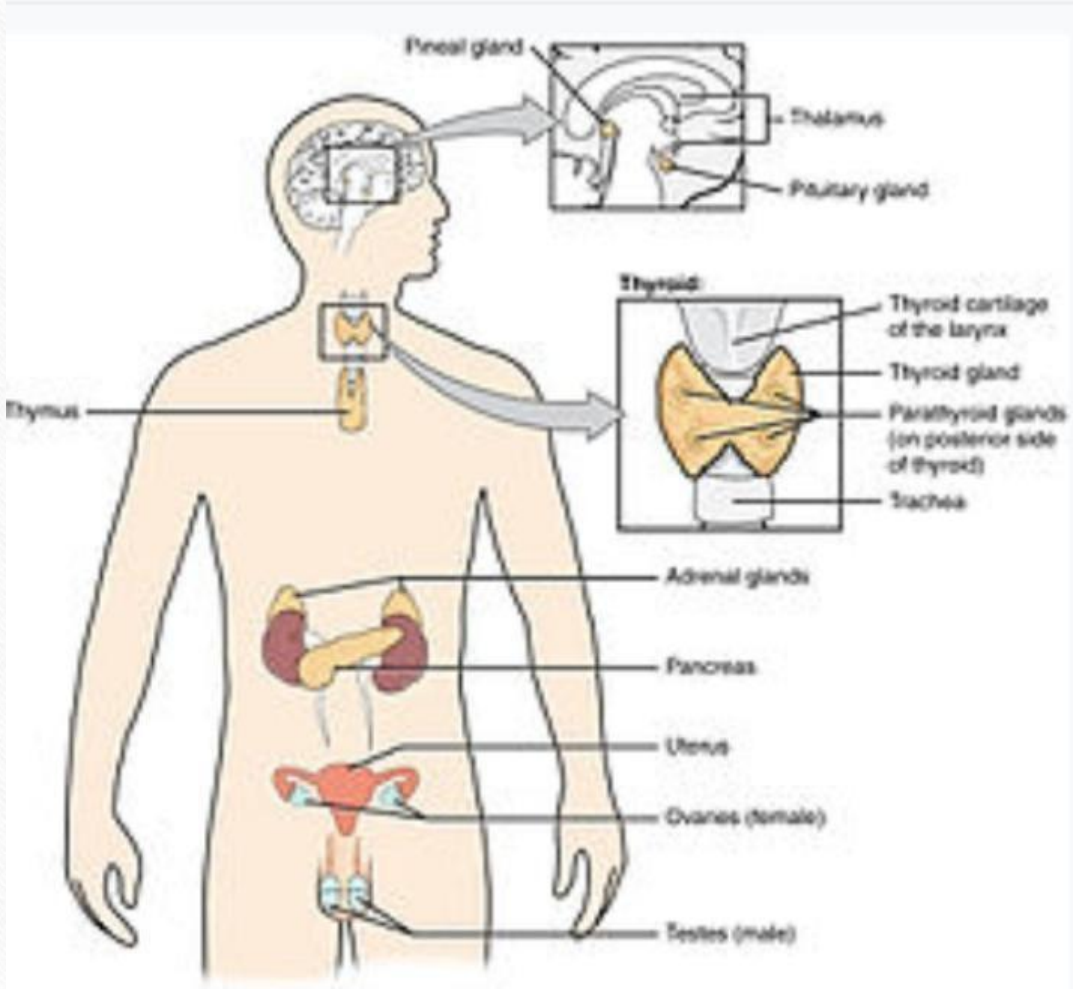
Carbon-21

Adrenal cortical hormones

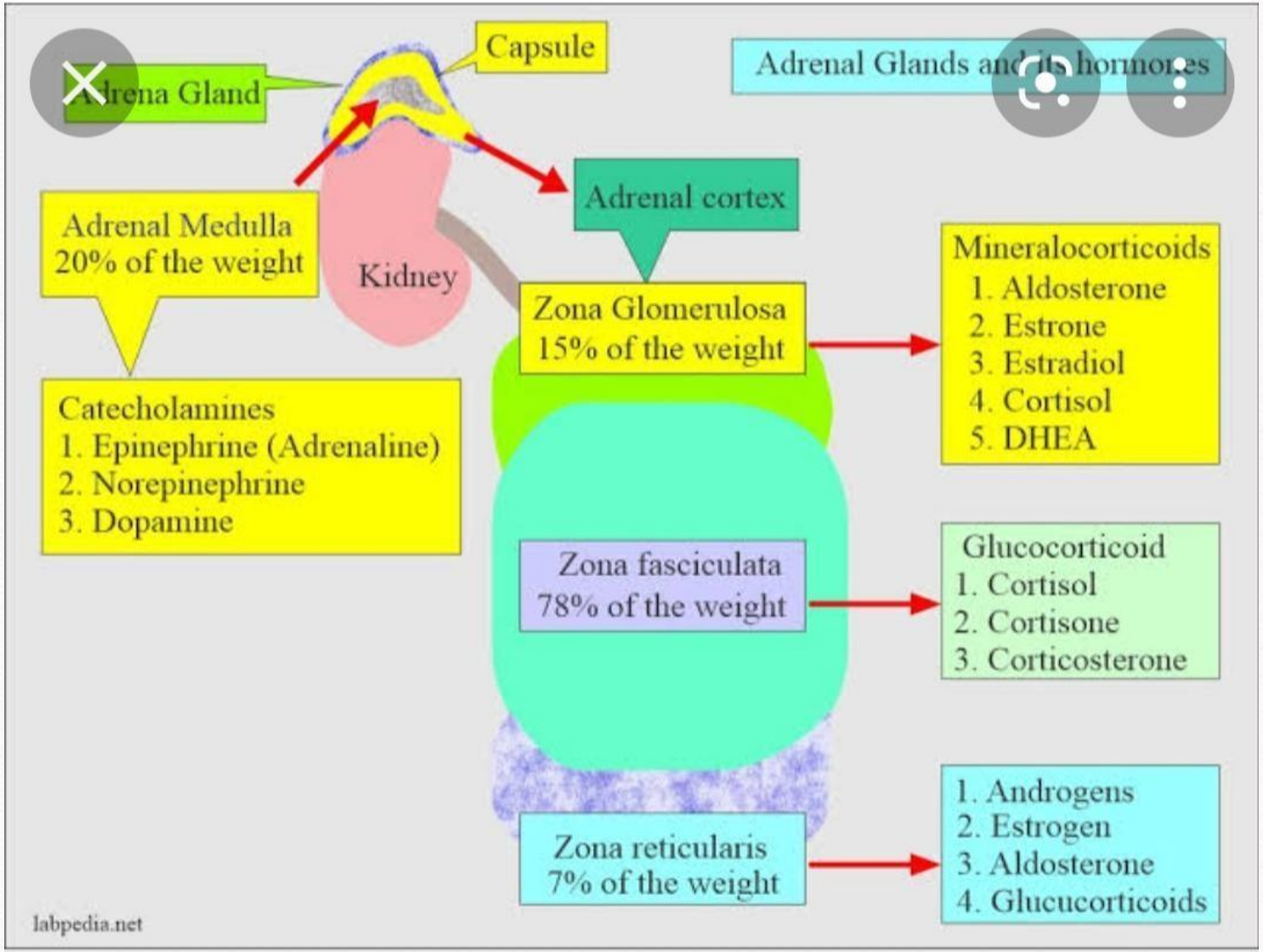
The **adrenal glands** (also known as **suprarenal glands**) are endocrine glands that produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol.[1][2] They are found above the kidneys. Each gland has an outer cortex which produces steroid hormones and an inner medulla. The adrenal cortex itself is divided into three main zones: the zona glomerulosa, the zona fasciculata and the zona reticularis.[3]

Adrenal gland





Endocrine system


Adrena Gland
Capsule
Adrenal Glands and its hormones
Adrenal cortex
Adrenal Medulla
20% of the weight
Kidney
Zona Glomerulosa
15% of the weight
Mineralocorticoids
1. Aldosterone
2. Estrone
3. Estradiol
4. Cortisol
5. DHEA
Catecholamines
1. Epinephrine (Adrenaline)
2. Norepinephrine
3. Dopamine
Zona fasciculata
78% of the weight
Glucocorticoid
1. Cortisol
2. Cortisone
3. Corticosterone
Zona reticularis
7% of the weight
1. Androgens
2. Estrogen
3. Aldosterone
4. Glucucorticoids
labpedia.net

to enable them to function correctly. All adrenocortical hormones are steroid compounds made from cholesterol.

What hormones do my adrenal glands produce?

The adrenal **cortex** produces three hormones:

1. Mineralocorticoids: the most important of which is aldosterone. This hormone helps to maintain the body's salt and water levels which, in turn, regulates blood pressure. Without aldosterone, the kidney loses excessive amounts of salt (sodium) and, consequently, water, leading to severe dehydration and low blood pressure.

2. Glucocorticoids: predominantly cortisol. This hormone is involved in the response to illness and also helps to regulate body metabolism. Cortisol stimulates glucose production helping the body to free up the necessary ingredients from storage (fat and muscle) to make glucose. Cortisol also has significant anti-inflammatory effects.

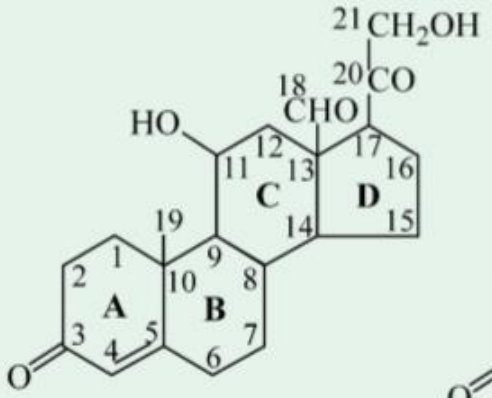
3. Adrenal androgens: male sex hormones mainly dehydroepiandrosterone (DHEA) and testosterone. All have weak effects, but play a role inPrecocious puberty' data-content='1268' > early development of the male sex organs in childhood, and female body hair during puberty.

Adrenocorticotropic hormone (ACTH), secreted by the anterior pituitary gland, primarily affects release of glucocorticoids and adrenal

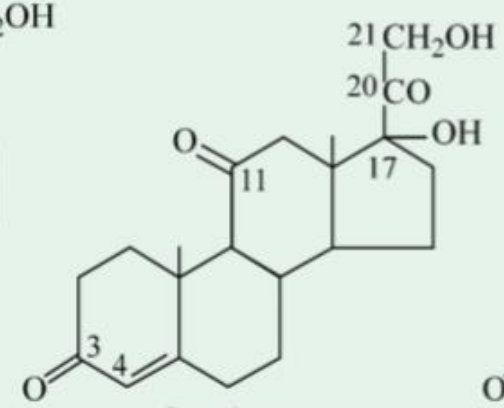
Adrenocorticotropic hormone (ACTH), secreted by the anterior pituitary gland, primarily affects release of glucocorticoids and adrenal androgens by the adrenal gland and, to a much lesser extent, also stimulates aldosterone release.

The adrenal **medulla** produces catecholamines:

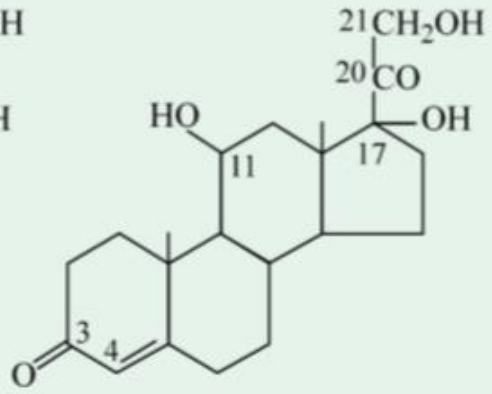
> Catecholamines include adrenaline, noradrenaline and small amounts of dopamine – these hormones are responsible for all the physiological characteristics of the stress response, the so called 'fight or flight' response.



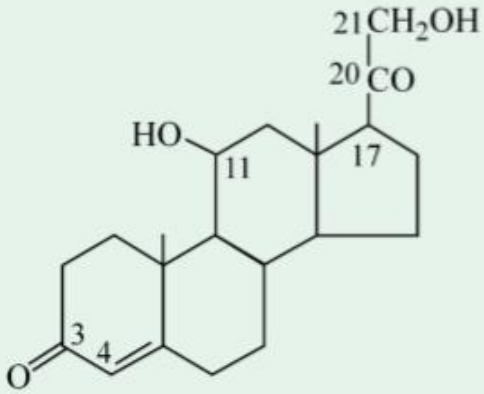
Aldosterone
(Δ^4-pregnene-11[β],
21-diol-3,20-dione-18-a1)



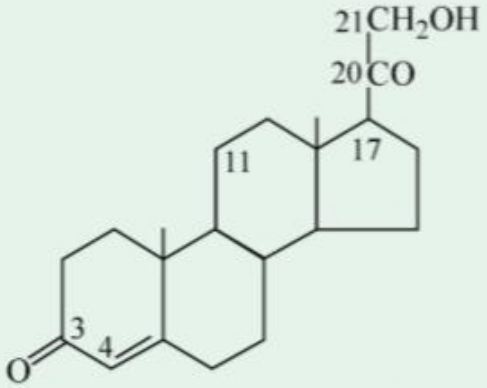
Cortisone
(Δ^4-pregnene-3,11,
20-trione-17[α], 21-diol)



Cortisol or **Hydrocortisone**
(Δ^4-pregnene-3,20 -dione-
11,17[α],21-triol)



Corticosterone
(Δ^4-pregnene-3,20 -dione-11,21-diol)



Deoxycorticosterone, DOC
(Δ^4-pregnene-3,20 -dione-21-ol)

What could go wrong with my adrenal glands?

Commonly, overproduction of aldosterone can occur, which causes a condition known as hyperaldosteronism' data-content='1318' >primary hyperaldosteronism. This causes high blood pressure, which is resistant to conventional blood pressure control tablets, and salt disturbances. High blood pressure may cause headaches and visual problems. Some studies have suggested that hyperaldosteronism may account for up to 5% of all people with high blood pressure and an even higher proportion of those who have treatment-resistant hypertension.

In rare cases, the adrenal glands can become either overactive or underactive. The two main glucocorticoid-related disorders resulting from these are Cushing's syndrome and Addison's disease, respectively.

Cushing's syndrome is due to overactive adrenal glands from excessive production of cortisol. The clinical findings include thinning and bruising of the skin, obesity, diabetes, psychiatric disturbances, high blood pressure, muscle weakness, osteoporosis, excessive facial hair and irregular periods in women. It can result in growth failure in children. Patients with cortisol excess also have impaired wound healing and an increased susceptibility to infection.

Addison's disease or adrenal insufficiency is due to underactive adrenal glands associated with lack of hormones. Adrenal insufficiency may be acute or chronic. Symptoms of chronic adrenal insufficiency include low blood pressure, fatigue, weight loss, anorexia, nausea, vomiting, abdominal pain, salt craving and low blood sugar. Skin and mucous membranes may show increased pigmentation. The loss of secondary sex characteristics is seen only in women with the disease. Acute adrenal insufficiency is a medical emergency and must be identified and promptly treated. The hallmarks of acute adrenal insufficiency are circulatory collapse with abdominal pain and low blood sugar.

Overproduction of androgens is also very rare but may result in excessive hair growth and menstrual period disturbances.

Tumours of the adrenal gland are mostly benign and do not result in over or underproduction of adrenal hormones. Most tumours are discovered incidentally when people undergo scans for various other reasons. Adrenal cancer is very rare. Adrenal tumours may require surgery if they are large or overproduce hormones.

The treatment of each disorder varies according to the specific cause. Patients with any concerns about these conditions should seek advice from their doctor.

Hypoadrenocorticism. A decrease in the amount of corticosteroids in the body (hypoadrenocorticism) leads to the decreased metabolic rate, excessive pigmentation, loss of appetite (anorexia), muscular weakness, deficiency of blood (anemia), eosinophilia and decreased blood sugar (hypoglycemia) with fasting.

Hyperadrenocorticism. The excessive supply of adrenal cortical steroids (hyperadrenocorticism) results from cortical cell tumours which may arise in or outside the adrenal gland. Oversecretion of cortisol in man leads to a rare disease, **Cushing's syndrome** (Fig. 31–19), after its discoverer, Harvey Cushing. The most common cause of the symptoms of Cushing's syndrome is the prolonged administration of glucocorticoids for medical treatment. The syndrome is characterized by profound disturbance of carbohydrate, protein, fat and calcium metabolism. There occurs mobilization of fat from the lower part of the body, with the concomitant extra deposition of fat in the thoracic region. The obesity becomes visible on the neck (buffalo hump) and on the face (moon face). Weakness and muscle wastings with marked osteosis become evident. Hypertension, pigmentation of the hair and excessive growth of hair are other symptoms. In men, there is impotence, and in women, amenorrhea and masculinization. Thus, Cushing's syndrome resembles somewhat adrenogenital syndrome.

Fig. 31–19. Typical findings in Cushing's syndrome
(Adapted from Forsham and Di Raimondo in : Traumatic Medicine and sufery for the Attorney. Butterworth 1960)

Hypersecretion of aldosterone leads to a marked Na^+ and water retention, resulting in edema and hypertension causing heart failure.

The adrenal cortex also produces androgenic steroids known as *adrenosterones*. Their hypersecretion has effects varying according to the age and sex of the patient. In adult female, it leads to **adrenal virilism.** In it menstruation stops, breasts atrophy, hair on breast and face develop and the voice deepens. In all, the adult woman becomes masculine. In adult males, there occurs excessive hair growth, enlargement of the sex organ and increased sexual desire. However, in children excessive supply of adrenosterones results in precocious development of sex organs and the secondary sexual characters.

Adrenal decortication. Removal of adrenal cortex (*adrenalectomy*) leads to a fatal human disease known as **Addison's disease** (Fig. 31–20), named after its discoverer Thomas Addison.

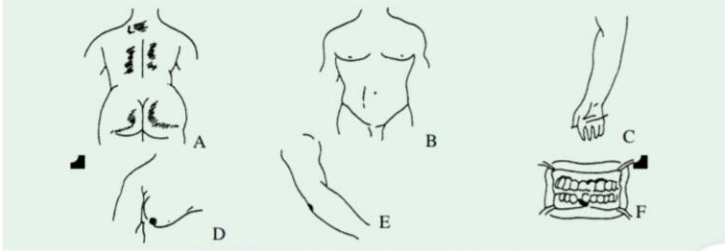


Fig. 31–20. Permentation in Addison's disease

(A) Tan and vitiligo (B) Pigmentation of scars (C) Pigmentation of skin creates (D) Darkening of are
Pigmentation of pressure points (F) Pigmentation of the gums.

(Adapted from Forsham and Di Raimond

also cures the disease.

4. Corpus Luteal Hormones

Structure. The hormones secreted by the ovarian bed, corpus luteum are collectively called as **gestogens** or **progestins**. The principal gestogen is progesterone (the two pregnenolones, 20α-OH and 20β-OH are other hormones secreted by the corpus luteum). Progesterone (Fig. 31–21) is a C_{21} steroid and is secreted by the corpus luteum during the second half of the menstrual cycle. This was first isolated in pure form by Adolf Butenandt *et al* (1934) from corpus lutea of pregnant sows. It has also been isolated from adrenal cortical extracts. But its presence in the adrenal tissue is a consequence of its role as an intermediate in the biosynthesis of the typical adrenal cortical hormones. Chemically, progesterone is one of the pregnane derivatives and lacks the ketol group. Its molecular formula is $C_{21}H_{30}O_2$. It closely resembles deoxycorticosterone in structure. It is, therefore, not surprising to find progesterone with certain adrenocortical properties, *viz*., those influencing salt and water. Indeed, it serves as a procursor of the steroidal adrenocorticoids. It is soluble in most organic solvents and in vegetable oils but is insoluble in water.

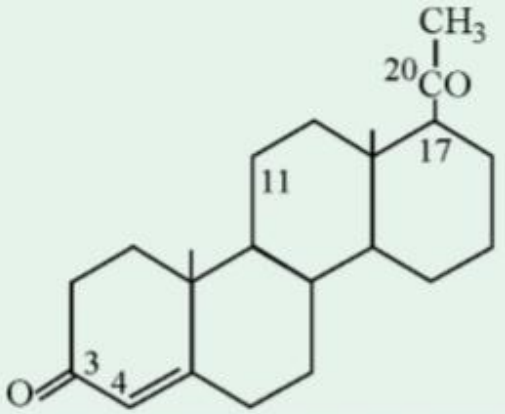


Fig. 31–21. Progesterone or "pregnancy hormone"
(Δ^4 - pregnene-3, 20-dione or 3, 20-diketo-$\Delta^{4,5}$-pregnene, *cis*)

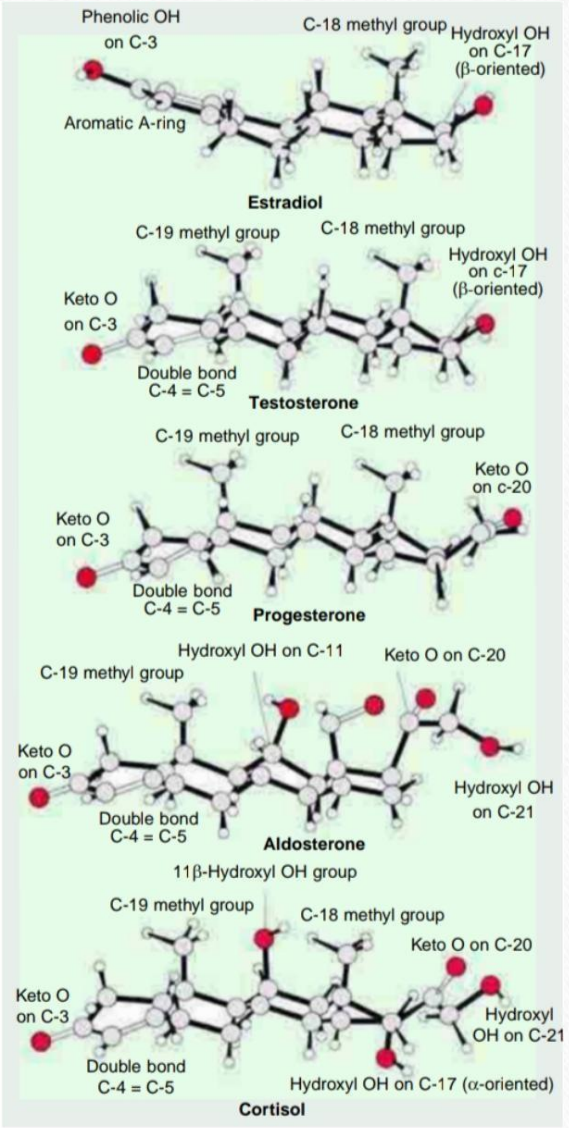
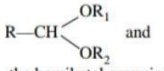
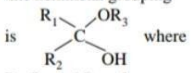


Fig. 31-22. Ball-and-stick representation of some steroid hormones

Details of each structure are labelled. In aldosterone, the acetal grouping is



and the hemiketal grouping



is where R_1, R_2 and R_3 refer to different substituents. *(Courtesy: Glusker JP, 1979)*