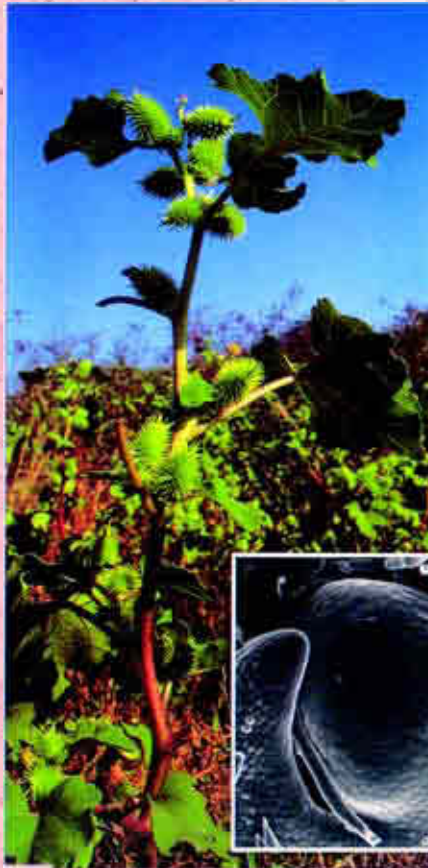


PART

IV

Hormone Biochemistry

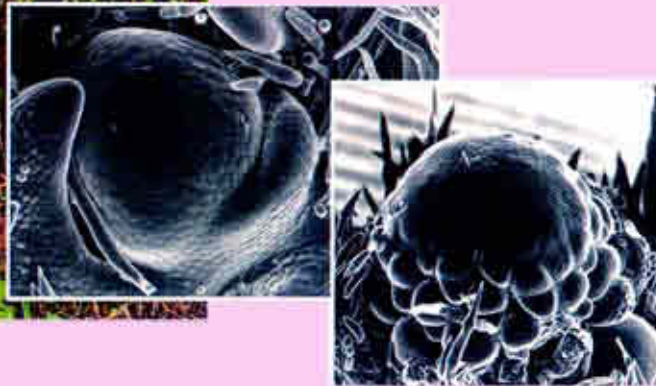


In a flowering apex, sepals, petals, stamens and carpels are produced instead of leaves. The arrangement of these is specific to each species and is determined by hormones and developmental genes.

(Left) The weed cocklebur (*Xanthium strumarium*)

(Middle) A highly magnified shoot tip showing bumplike “initials”

(Right) Shoot tip showing flower production

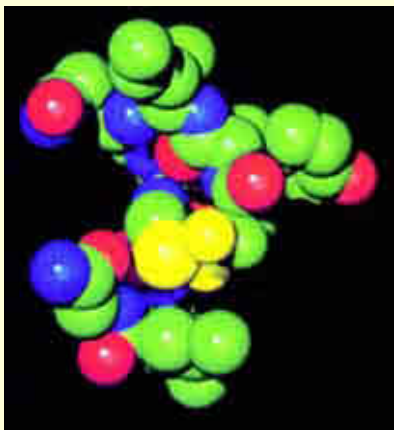


“Life – human life included – is the outcome of an elaborate organization based on trivial ingredients and ordinary forces”

– G.E. Palade : *Nat. Acad. of Sciences, Proceedings, 1964*

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Space-filling model of oxytocin

This hormone stimulates the contraction of smooth muscles, especially those of uterus, thus facilitating childbirth.

CHAPTER

31

Animal Hormones

DEFINITION

The term hormone (*hormao*^G = to excite) was first used by William M. Bayliss and his brother-in-law Ernest H. Starling, both of London University College, in 1904, who showed that a chemical substance (*secretin*) from the intestine could stimulate the action of a pancreatic secretion. These substances were then called as 'chemical messengers'. Went and Thimann (1937) defined a hormone as "a substance which, produced in any one part of an organism, is transferred to another part and there influences a specific physiological process." The tissues or organs where they are produced are called as **effectors** and those where they exert their influence as **targets**. These have low molecular weight and diffuse readily. As they are readily oxidized, their effects do not remain permanent unless these are supplied continuously.

Based on their site of action, the hormones are of two types : local and general. The *local hormones*, obviously, have specific local effects, whence their nomenclature. These may be exemplified by acetylcholine, secretin, cholecystokinin etc. The *general hormones*, on the other hand, are secreted by specific endocrine glands and are transported in the blood to cause physiologic actions at points remote from their place of origin. A few of the general hormones affect almost all cells of the body, e.g., growth hormones (GH) and thyroid hormones ; whereas other general hormones, however, affect specific tissues far more

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than other tissues, *e.g.*, adrenocorticotropin (a hormone secreted from adenohiphophysis and stimulating the adrenal cortex) and ovarian hormones (affecting the uterine endometrium).

Non-specificity and Cross Effects — Hormones are not sepcific for the organisms in which they are produced and may influence bodily processes in other individuals also. Adrenalin, for example, also influences protozoans and crustaceans besides man and other vertebrates. Their cross effects have also been found between plants and animals. For example, auxin, a

growth-promoting plant hormone, can also stimulate a protozoan, *Euglena viridis*. Likewise, some animal hormones also stimulate growth in root tips of many plants after decapping.

Differences with Nutrient Materials and Enzymes — A distinction between hormones and **nutrient materials** may be made, as the former are utilized in extremely minute quantities in comparison to the latter. For example, a 5×10^{-10} molar solution of ocytocin (about 1 mg in 2,000 litres of solution) will cause the contraction of uterine muscles.

They also differ from **enzymes**, which are essential to initiate and continue reactions, in that the hormones cannot initiate reactions but can influence the rate at which they proceed. Furthermore, the hormones are usually consumed in the process of growth, whereas the enzymes are not.

SIR WILLIAM H. BAYLISS

(LT, 1860-1924)



ERNEST H. STARLING

(LT, 1866-1927)



Bayllis and Starling, both of London University, are called 'founders of endocrinology'.

(Courtesy: Fulton JF and Wilson LG, 1966)

GENERAL FUNCTIONS

The hormones conduct a wide variety of functions ranging from growth, vegetative and sexual development, cellular oxidation to thermal production and the metabolism of carbohydrates, proteins and fats. The various functions performed by hormones may, in general, be discussed under following heads :

1. Regulatory or homeostatic function. The hormones have regulatory effects on the composition of the body fluids, the rate of gaseous exchange and the activity of the vascular system and the central nervous system (CNS). There always exists a high degree of precision and constancy in the composition of the body fluids in a normal individual for the conduction of various activities. Such an environment within the cell has been termed the *milieu intérieur* (or internal enivrnoment) in 1857 by **Claude Bernard**, a French physician. Throughout his research, he had been impressed by the way in which organisms were able to regulate physiological parameters, such as body temperature and water content, and maintain them within fairly narrow ranges. This concept of self-regulation leading to physiological stability was summed up by Bernard in the now classic statement, '*La fixité du milieu intérieur est la condition de la vie libre.*' (The constancy of the internal environment is the condition of the free life). In other words, it means that for an organism to function optimally, its component cells must be surrounded by a medium of closely-regulated composition. Bernard went on to distinguish between the *external environment* in which organisms live and the *internal environment* in which the individual cells live (in mammals, this is tissue, or interstitial, fluid). He realized the importance of conditions in the latter being continuously stable. He concluded that an organism is the sum of its constituent cells and the optimum functioning of the whole depends upon the optimum functioning of its parts.

CLAUDE BERNARD

(LT, 1813-1878)

Claude Bernard, a French physiologist, had parents who were vineyard workers. From his early experiences, Bernard retained an enthusiasm for the Beaujolais region of his native country and for the countryside in general, throughout a working life that kept him in a Paris laboratory. He trained as an apothecary, and later as a doctor, but was no more than an average student. He never worked as a medical practitioner, but did make his mark in experimental medicine.



Bernard's work centred on the physiology of mammals. Working with dogs and rabbits he established that :

- (a) an enzyme is present in the gastric juice.
- (b) the digestion of dietary carbohydrates to sugar occurs prior to their absorption.
- (c) the digestion of fat involves bile and pancreatic juices.
- (d) glycogen and sugar are interconverted in the liver.
- (e) respiration produces heat in all body tissues.

Bernard was a 'modern' researcher, combining experimental skills with an appreciation of the theory behind his work.

He believed in the constancy of the *milieu intérieur* ("internal environment"), which is the extracellular fluid bathing the cells. He pointed out that it is through the *milieu intérieur* that foods and wastes and gases are exchanged and through which chemical messengers are distributed. He wrote :

"The living organism does not really exist in the external environment (the outside air or water) but in the liquid *milieu intérieur*... that bathes the tissue elements."

He is best remembered for his idea that animal life is dependent upon a constant internal environment—that cells function best in a narrow range of conditions of solute potential and temperature, and when bathed in a constant concentration of chemical constituents. Truly, Bernard was one of the most influential of nineteenth century physiologists.

For performing various metabolic functions, an organism should maintain a normal, constant internal state or **homeostasis** (*homoios*^G = same or similar ; *stasis*^G = state or standing), a term coined by an American physiologist, **Walter B. Cannon** in 1932. Homeostasis can be defined as the tendency to maintain uniformity or stability in the internal environment of the organism and to maintain the normal composition of the body fluids. In other words, homeostasis is the maintenance of a constant internal environment in the face of changes in the external environment. Hormones play an important and decisive role in homeostatic regulation of internal milieu.

2. Permissive function. Not only does each endocrine gland affect a number of processes, but these glands also affect the functioning of one another. Thus certain hormones require the presence (or 'permission') of another hormone for the expression of their activity. This helps in maintaining a perfect hormonal balance. Derangements of this balance, either clinical or experimental, lead to a variety of metabolic aberrations.

The scientist James Lovelock argues that the Earth with its atmosphere is 'alive', in the same way that the world shares with other living things the capacity to self-regulate (homeostasis). He calls his idea the **gaia hypothesis**. In fact, *gaia is the homeostasis at planet level*.

3. Integrative function. The integrative function of the hormones is reflected in the fact that they support the role of nervous system. However, the integrative properties of the endocrine system are slow and steady whereas those of the nervous system are rapid. This close tie between the two systems has led to the emergence of a new discipline of science called *neuroendocrinology*.

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WALTER BRADFORD CANNON

(LT, 1871–1945)

Cannon, an American scientist, was George Higginson Professor of Physiology, Emeritus at Harvard University Medical School from 1906 till 1942. He introduced the first radio-opaque agent, barium (later, he used barium salts) into the gut of a living animal to create a 'shadow' of the alimentary tract so that the mechanics of digestion could be observed. He devised this technique first in the year 1896, the year after Roentgen discovered x-rays. The technique has been used in diagnostic radiography ever since. He developed the concept originated by French physiologist Claude Bernard. Developed out of his studies of the nervous system and reactions to stress, he described the ceaseless balancing and rebalancing of physiological processes that maintain stability and restore the normal state when it has been disturbed. And he gave it the name, **homeostasis**. He spend his life in the study of homeostatic mechanisms. The term soon flooded the medical literature of 1930s. Physicians spoke of getting their patients back into homeostasis. Even politicians and sociologists saw what they considered to be deep nonphysiological implications. Cannon enjoyed this broadened application of the concept and later suggested that democracy was the form of government that took the homeostatic middle course. Despite the enduring importance of the homeostasis concept, Cannon never received the Nobel Prize – *one of several acknowledged oversights of the Nobel Committee*. In his terminal Year (*i.e.*, 1945), Cannon expressed his ideas about scientific research in his autobiography, *The way of an Investigator*. This absorbing book describes the resourceful career of a homespun man whose life embodied the traits that favour successful research.



(Photo Courtesy : Fulton JF and Wilson LG, 1966)

4. Morphogenetic function. The hormones govern the ontogenetic development of an individual from the embryonic to the adult state.

An account of **animal hormones** is given below.

INVERTEBRATE HORMONES

Among invertebrates, evidence of hormone control is less satisfactory in the acoelomate and pseudocoelomate animals. However, studies of endocrine function of the coelomate vertebrates have been mainly confined to the arthropods, annelids, molluscs and echinoderms; the arthropods (*esp.*, the insects and crustaceans) are the best-studied group.

1. Hormones from Coelenterata

According to Burnett and Diehl (1964), the hypostome of an adult *Hydra* possesses neurosecretory cells in abundance. This is the region of new growth. Buds fail to develop if detached from the parent body prior to the secretion of neurosecretory cells in the hypostome. With the onset of sexual maturity, the neurosecretory cells disappear. Thus, growth and reproduction are antagonistic processes. The *neurosecretory growth hormone*, as it may be called, is credited with the following two functions :

- (a) It activates cell proliferation.
- (b) It causes interstitial cells to develop into somatic structures such as nematocysts.

In the absence of this hormone, growth ceases and interstitial cells form gametes.

2. Hormones from Annelida

Investigations conducted during the past four decades make it clear that neurosecretions play an important role in the regulation of various processes in annelids including seasonal swarming of distinct sexual forms, hermaphroditism and viviparity. In the polychaete worm *Nereis*, many neurosecretory cells have been localized in the brain and other ganglia. These cells govern diverse processes such as growth, metamorphosis, sexual development and reproductive behaviour.

The studies regarding regeneration of *Nereis diversicolor* have been conducted by Clark *et al* in 1962. The worm grows by adding new segments until it has produced about 50 segments; thereafter growth is mostly due to increase in segment size up to 90 segments. Segment proliferation then ensues which is regulated by hormones synthesized in the supra-oesophageal ganglia. Removal of these ganglia in the young ones ceases segment proliferation, which can be resumed after implanting ganglia from other young worms. Besides, old worms, which have stopped growing, can be induced to grow by implanting ganglia from young worms and not from other old worms. Amputation of a part of the worm (with less than 60 segments) activates neurosecretory cells to elaborate hormones which provoke segment proliferation. It is, however, not known whether the growth-promoting and the regeneration-promoting hormones are identical (Jenkin, 1970)

3. Hormones from Arthropoda

Among invertebrates, insects and crustaceans furnish excellent examples of hormone secretion. These hormones govern many metabolic processes including growth, development, reproduction, colour adaptation etc.

A. Hormones from Insecta. In insects, the growth after emergence from the egg is characterized by a process of metamorphosis during which larva passes to the adult phase via pupal stage. During these changes, the insect undergoes a process of moulting or ecdysis (*ekdysis*^G = a getting out). The processes of moulting and metamorphosis are controlled by hormones secreted by the following three organs of endocrine nature (refer Fig. 31-1).

(a) neurosecretory cells of corpus cardiacum

(b) prothoracic gland

(c) corpus allatum.

The neurosensory cells of the corpus cardiacum produce a secretion which stimulates ecdysial or prothoracic gland to secrete a hormone named **ecdysone** or **prothoracic gland hormone, PGH** (Fig. 31-2). This induces moulting. Based on its biological function, this hormone has been variously called as moulting hormone, pupation hormone or metamorphosis hormone. Chemically, it is a steroid.

In the larva, corpus allatum secretes another hormone called **status quo hormone (SQH)** or **neotenin** (Fig. 31-3). This delays metamorphosis of immature insects by maintaining the juvenile

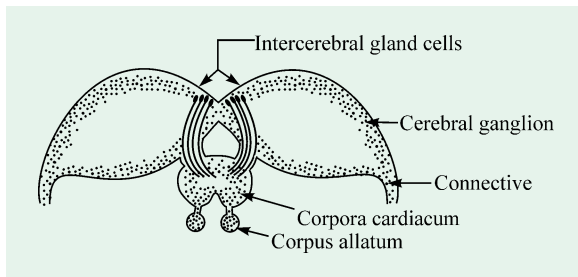


Fig. 31-1. Some of the endocrine glands of an insect

(After Bodenstein)

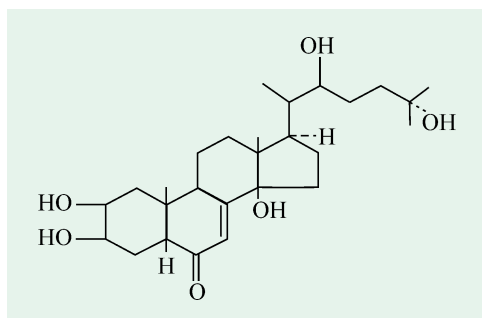


Fig. 31-2. α -ecdysone or moulting hormone, MH

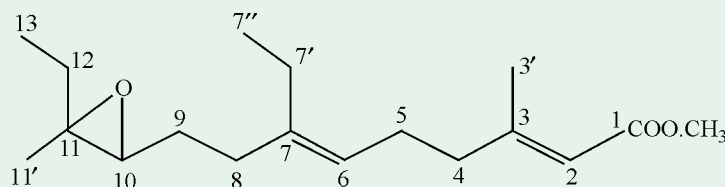


Fig. 31-3. Status quo hormone, SQH or juvenile hormone, JH

(methyl-10-epoxy-7-ethyl,-3, 11-dimethyltrideca-2, 6-dienoate)

(= larval) character of the growing insect for a longer period. Henceforth, this hormone is variously called as juvenile hormone, larval hormone or inhibitory hormone. It was isolated in pure form from

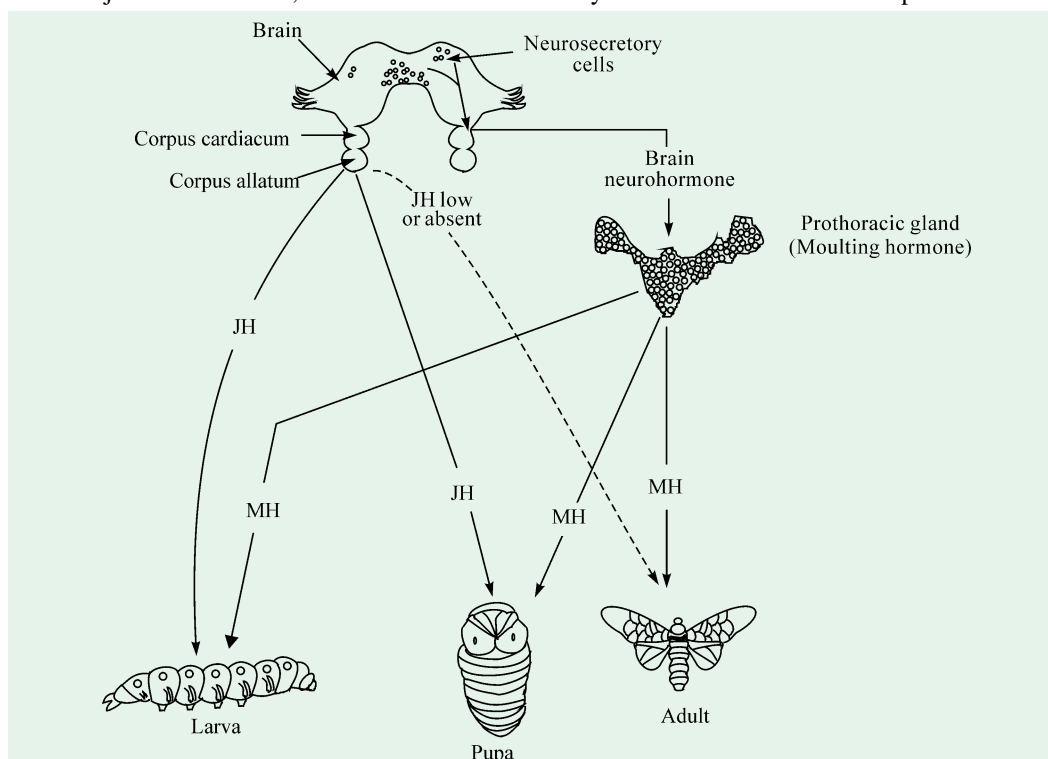


Fig. 31-4. Interrelationship between neural and endocrine secretions controlling growth and moulting in a moth

(Adapted from Turner and Bagnara, 1971)

the giant silkworm moth, *Hyalophora cecropia* by Röller *et al* in 1965. It is a derivative of farnesoic acid, a compound that is related to intermediates in steroid biosynthesis. Juvenile hormone may be regarded as an acyclic sesquiterpenoid type of compound. SQH remains active only in the presence of ecdysone. In later stages, the activity of SQH decreases so that the larva leads to adult stage by ecdysone activity. Besides SQH, the corpus allatum also produces other secretions which control colour changes and reproduction.

The endocrine as well as neural control of growth and moulting in a moth has been diagrammatically represented in Fig. 31-4.

B. Hormones from Crustacea. The hormones in crustaceans are usually produced in the neurosensory cells of the brain and in the central nervous system. The X-organs of these invertebrates produce a **moult-inhibiting hormone** which is stored in the sinus glands found in the eye stalks or in

the head in species without eye stalks. This hormone has been thought to inhibit moulting as in the absence of the X-organs (or the sinus glands), the crustaceans moult more frequently than the normal individuals. The X-organs also secrete another hormone, **moult-promoting hormone** which stimulates the moulting gland or Y-organ.

The chromatophores in crustaceans contain pigments concerned with the body colour. The relative dispersion and concentration of these pigments is controlled by **colour-change hormones**. Two types of colour-change hormones may be recognized :

- (a) *lightening hormones*—induce concentration of the dark pigments (red, black), thereby bleaching the body colour of the animal.
- (b) *darkening hormones*—cause dispersal of these pigments within the chromatophores.

The crustaceans can, thus, change their body colour in harmony with their environment.

4. Hormones from Mollusca

In the cephalopod *Octopus*, which is one of the greatest evolutionary achievements, the brain (subpeduncular lobes) controls a pair of optic glands through the action of inhibitory nerves. The optic glands are located on the optic stalks, one on either side of the central part of the supraesophageal brain (see Fig. 31-5). The brain, in turn, receives environmental hints through the eyes. The optic

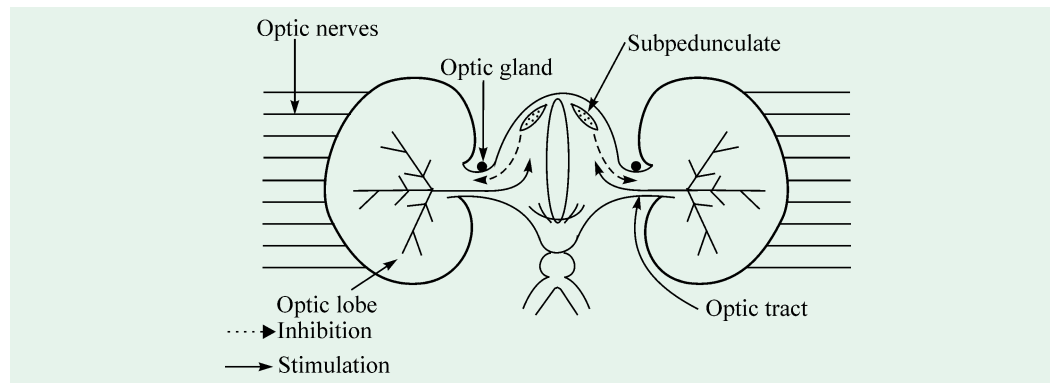


Fig. 31-5. Position of the optic glands in Octopus

glands dominate the reproductive endocrinology in a manner somewhat comparable to the vertebrate pituitary. The secretions from the optic gland promote vitellogenesis in females and spermatogenesis in males. They also govern the differentiation of the female reproductive tract. As a contrast, the male sex differentiation is under direct control of testicular hormones (Wells and Wells, 1969). As a corollary, *the endocrine controls in Octopus parallel the vertebrate pattern* but are much simpler in that the neurosecretions and ovarian hormones seem to be absent.

Among gastropods, *Lymnaea stagnalis* has been most carefully studied. Here the well-established endocrine organs are the dorsal bodies. There are small discrete bodies on the cerebral ganglia and develop from glial cells and the perineurium of the cerebral ganglia. Their secretions stimulate vitellogenesis and the differentiation of the female genital tract. The functions carried out by the dorsal bodies are more diverse than those conducted by the cephalopod optic glands (Bonga, 1972).

5. Hormones from Echinodermata

According to Chaet (1967), in the starfishes, a simple system of hormones regulates sexual maturation and spawning. Two such hormones recognized are :

- (a) *gonad-stimulating substance (GSS)*—It is a low molecular weight (2,000) protein which is synthesized in the radial nerves.
- (b) *maturation-inducing substance (MIS)*—It is 1-methyl adenine and is produced by the ovarian follicles.

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It is well known that spawning reactions of starfishes are synchronized and that the presence of eggs or sperms in the water stimulates other individuals to spawn. The endocrinological explanation of this mass spawning is simple. A neurosecretion released by the radial nerves acts on the follicle cells to induce the synthesis of MIS, which triggers ovulation, release of gametes and reproductive behaviour.

VERTEBRATE HORMONES

Most glands of the body release their secretions by means of ducts. These are called as the **exocrine** (*exos*^G = outside ; *krinein*^G = to separate) **glands** or **duct glands**, e.g., salivary, sebaceous, sweat glands etc. Other glands in the body, on the contrary, produce chemical substances which are

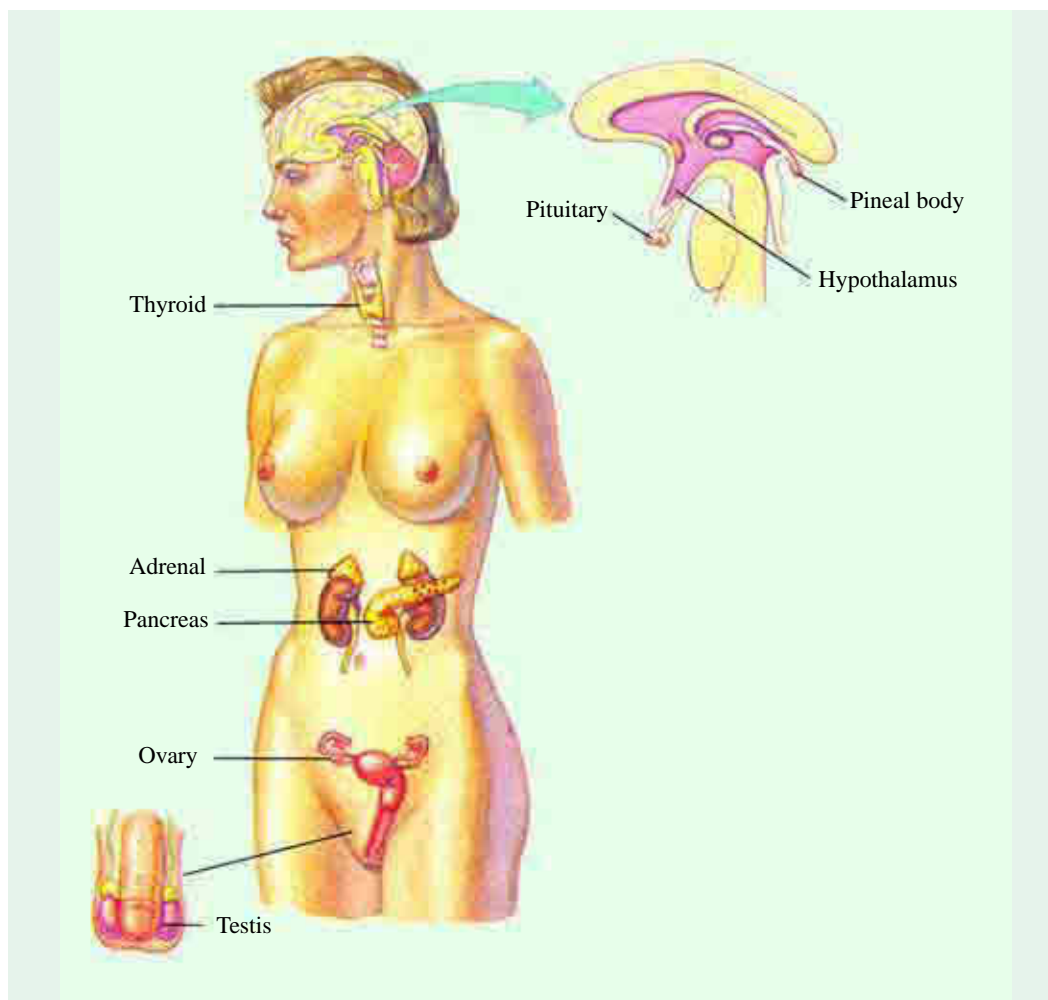


Fig. 31-6. Endocrine glands in human body

Location of major endocrine glands in humans. The hypothalamus regulates the anterior pituitary, which regulates the hormonal secretions of the thyroid, adrenals, and gonads (ovary in the female and testis in the male).

(After Lehinger AL, 1984)

released directly into the nearby blood and lymph vessels which carry them to various organs (target or effector organs) where they exert their characteristic effect. These glands have been termed as the **endocrine** (*endon*^G = within) **glands** or **ductless** glands and their secretions are called as the hormones.

The science of the study of structure and function of these endocrine glands and their secretions (*i.e.*, hormones) is designated as **endocrinology**, a term introduced by Pende.

Vertebrate Hormones		
STEROID HORMONES	PEPTIDE HORMONES	AMINO ACID HORMONES
C₁₈ STEROIDS		
1. Ovarian Hormones β-estradiol Estriol Estrone	1. Hormones of the Pancreas Insulin Glucagon	1. Thyroidal Hormones Triiodothyronine, T ₃ Tetraiodothyronine T ₄
C₁₉ STEROIDS		
2. Testicular Hormones <i>From testes</i> Testosterone Androsterone Dehydroepiandrosterone <i>From adrenal gland</i> Androst-4-ene-3,17,dione Androst-4-ene-3,11,17-trione	2. Hormones of the Hypophysis <i>Pars distalis</i> Thyrotropin, TSH Corticotropin, ACTH Gonadotropins, GTH FSH LH LTH Somatotropin, SH <i>Pars intermedia</i> Intermedins, MSH α-MSH β-MSH <i>Pars nervosa</i> Ocytocin or pitocin Vasopressin or pitressin	2. Adrenal Medullary Hormones Adrenalin Noradrenalin
C₂₁ STEROIDS		
3. Adrenal Cortical Hormones <i>Mineralocorticoids</i> Aldosterone Deoxycorticosterone <i>Glucocorticoids</i> Cortisone Cortisol Corticosterone	3. Hormone of the Parathyroid Parathormone, PTH	
4. Corpus Luteal Hormone Progesterone	4. Hormones of the Gastrointestinal Tract Gastrin Secretin Cholecystokinin Pancreozymin Enterogastrone Enterokrinin Hepatocrinin Duicrinin Villikinin Parotin 5. Hormone of the Corpus Luteum Relaxin	

A noteworthy point about the endocrines is their similarity, except in minor details, in all the vertebrates. They are highly vascular as the blood not only acts as a vehicle for transport of their secretions but also serves as a source of the chemical raw materials from which these hormones are

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synthesized. Ontogenetically, all these glands are derived from the epithelial tissues. The amount of hormones produced by the endocrines in 24 hours measures fractions of a milligram. The principal endocrine glands (refer Fig. 31-6) include :

- (a) two in the head region— the *pineal* and the *pituitary*,
- (b) three in the neck region— the *thymus*, the *thyroid* and the *parathyroid*, and
- (c) four in the abdominal region— the *pancreas*, the *gastrointestinal mucosa*, the *adrenals* and the *gonads*.

Barring the *parathyroid*, all the remaining 8 glands are found in all the vertebrates. There is, however, controversy regarding the endocrinal nature of the two glands, the *pineal* and the *thymus*. But it is customary to include them in the endocrine system.

A gland may be **temporary**, lasting only for a limited period and then dying away, *e.g.*, *thymus*. Some glands are, however, **seasonal** being periodic and recurrent, *e.g.*, *placenta* and *corpus luteum*.

Chemically, a hormone may be any kind of organic molecule. Most known hormones are either **steroids** or **peptides** with usually high molecular weights. A third group of hormones, which is less common, consists of **amino acid derivatives** (or phenolic derivatives) with relatively low molecular weights. Thus, three categories of hormones may be recognized: steroids, peptides and amino acid derivatives. A classification of vertebrate hormones, based on their chemical composition, is outlined on page 843.

The majority of animal hormones are water-soluble, and are derived from amino acids, small peptides, or larger proteins. Because these molecules are hydrophilic, and often large, they cannot easily pass through the hydrophobic lipid layer of the cell membrane. Instead, they interact with receptor molecules on the membrane surface; the hormones themselves do not enter the cell. Other hormones, such as the steroid and thyroid hormones, are hydrophobic in nature, and as such can readily diffuse through the cell membrane and bind to specific receptor inside the cell.

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.

C_{18} STEROIDS

1. Ovarian Hormones

Structure. Mammalian ovary contains ovarian follicles and corpus lutea. Hormones produced mainly in the follicles are known as estrogens (*oistros*^G = a gadfly, hence sting or frenzy). “Estrogen is a generic term for a substance that induces estrus, which is a cyclic phenomenon of the female reproductive system. The stages and timings differ in various species but, in general, first a *proestrus*

period occurs, during which the follicle reopens and the organs of reproduction develop. This is followed by *estrus*, the period of heat, in which the female will receive the male. Ovulation takes place toward the end of estrus, either spontaneously or, as in rabbit, after mating. Then follows a period of retrogression of the accessory reproductive organs and a period of sexual inactivity” (Orten and Neuhaus, 1979).

Chemically, the estrogens are derivatives of a C₁₈ hydrocarbon, estrane (Fig. 31-7).

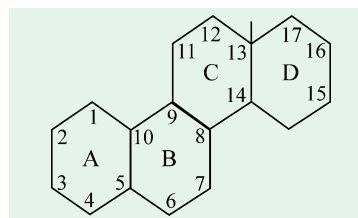


Fig. 31-7. Estrane
(Parent hydrocarbon of estrogens)

The three compounds of this group (Fig. 31-8) with hormonal activity are :

1. β -estradiol (= dihydrotheelin), C₁₈H₂₄O₂
2. Estriol (= theelol), C₁₈H₂₄O₃
3. Estrone (= theelin), C₁₈H₂₂O₂

Estrone is the first known member of the sex hormones and was isolated by Adolf Butenandt and Doisy independently in 1929 from the urine of pregnant women. A year later, the estriol was isolated from human pregnancy urine by Marrian. Later, the estradiol was also isolated.

Adolf Butenandt, a German, shared Nobel prize in Chemistry in 1939 with Leopold Ruzicka for his work on sex hormones. Butenandt's main contributions are : isolation of estrone, isolation and synthesis of progesterone, commercial production of testosterone, and nature and position of the side chain of cholesterol.

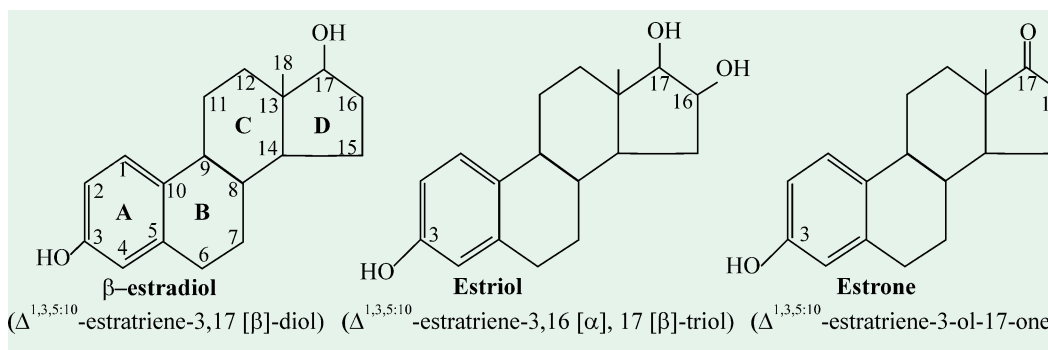


Fig. 31-8. Principal ovarian hormones

All these are characterized by the absence of a CH₃ group at carbon 10 and by the aromatic nature of ring A, making the OH group phenolic in character. Of all these, β -estradiol is most potent physiologically, estrone less potent and estriol is least active. Their relative potencies are 50 : 5 : 1 respectively. Although ovary is the chief source of estrogens, they are in smaller amounts also produced by the testis and the adrenal cortex.

Estrogen production is highest when a woman is young and slows down with age, giving rise to menopausal symptoms. The symptoms vary with each woman. By 40's, women enter perimenopause, when menstruation becomes less regular, skin becomes dryer, hair turn brittle and sparser; women may feel a loss of libido and may suffer fluctuations in mood. Menopause follows, on an average between 45 and 50 years of age. Heavy women have an

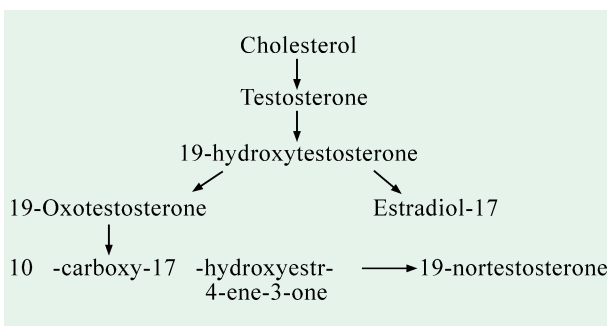


Fig. 31-9. Biosynthesis of estrogen

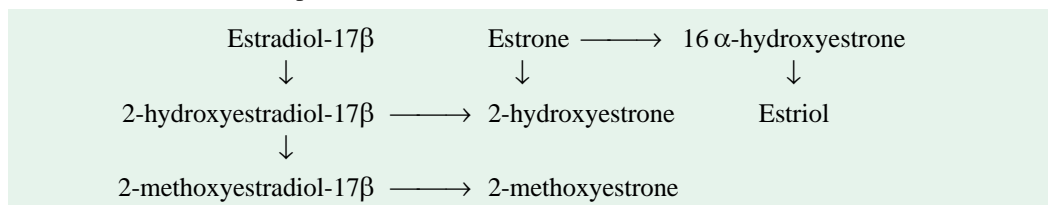
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advantage over the slim ones. Their fat cells manufacture a form of estrogen called estrone, even after estrogen from ovaries shuts off.

Biosynthesis. In nonpregnant females, estrogen is mainly synthesized in the ovary. The estrogen (as well as the androgen) are, in part, transported by binding to a specific plasma protein called sex steroid binding protein SBT. The amount of this protein increases in pregnancy or estrogen therapy which results in reduced androgenic action.

Curiously enough, testosterone, a male hormone, is the precursor of estrogens. Eve was made from more than Adam's rib ! Fig. 31-9 depicts the probable pathway of estrogen synthesis.

Metabolism. Most of the metabolic reactions of the estrogens (*i.e.*, the interconversion reactions of all the three forms) take place in the liver as follows :



Estriol is the principal estrogen found in the placenta and urine of pregnant females. It is produced by hydroxylation of estrone at C₁₆ and reduction of keto group at C₁₇.

Functions. "In women, the follicular hormones (estrogens) prepare the uterine mucosa for the later action of the progestational hormones (produced by the corpus luteum). The changes in the uterine include proliferative growth of the lining of the endometrium, deepening of uterine glands, and increased vascularity; changes in the epithelium of the fallopian tubes and of the vagina also occur. All of these changes begin immediately after menstrual bleeding has ceased." (Harper and Grodsky, 1973).

Estrogen preserves the elasticity of the skin and possibly improves the memory in women at postmenopausal stages. It also protects women from osteoporosis by slowing the rate at which calcium is leached from their bones. Estrogen supplement also preserves the flexibility of blood vessels, thus helping to prevent cardiac diseases. Nowadays, estrogen in combination with the hormone progesterin is considered an important tool for helping women remain healthy. The combination is known as **hormone replacement therapy (HRT)**, which has indeed become the closest in medicine to a woman's elixir of youth. HRT, when used by menopausal women, relieves hot flashes, dry sweats and vaginal dryness. However, the long-term use of HRT or estrogen therapy heightens the risk of ovarian cancer.

Victoria Luine (1997) of the Rockefeller University, New York has clearly shown the effect of estrogen on two brain areas, commonly associated with memory and learning, the hippocampus and cerebral cortex. She found that ovariectomized female rats given estrogen had more of an enzyme called *choline acetyltransferase (ChAT)* in the hippocampus and cerebral cortex than control animals did. ChAT enhances the working of the cells in basal forebrain because ChAT makes acetylcholine (ACh) which helps nervous communication with other nerve cells. In a nutshell, *estrogen enhances brain power*. Estrogens could also protect brain cells from toxins (Simpkins, 1994). Estrogens can also act as an antioxidant soaking up highly reactive molecules called free radicals which can kill a cell by fracturing its membrane lipids, proteins and DNA. Estrogen is also being widely perceived to have a significant effect (of improving verbal memory) on patients with Alzheimer's disease.

The estrogens are also effective in the development of *secondary sex characters in females*. These are listed in Table 31–1.

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 enlargement. The 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.

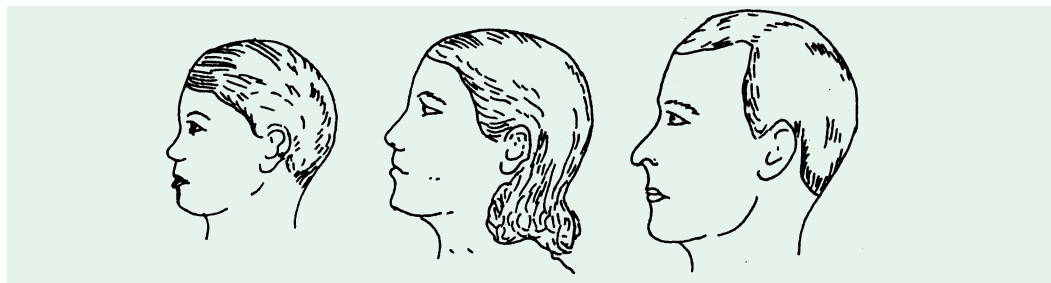


Fig. 31–10. Hair line pattern of child, woman and man

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.

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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.

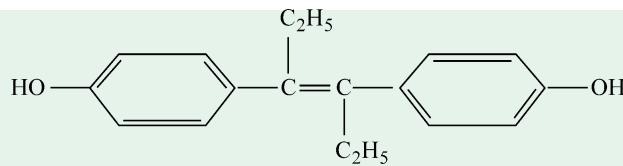


Fig. 31–11. Diethylstilbesterol

C₁₉ 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 C₁₉ 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, C₁₉H₂₈O₂
2. Androsterone, C₁₉H₃₀O₂
3. Dehydroepiandrosterone, C₁₉H₂₅O₂

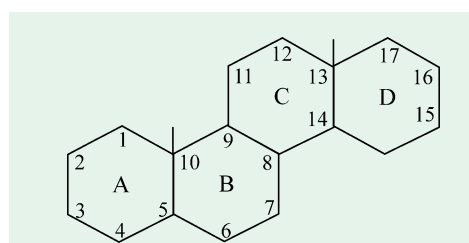
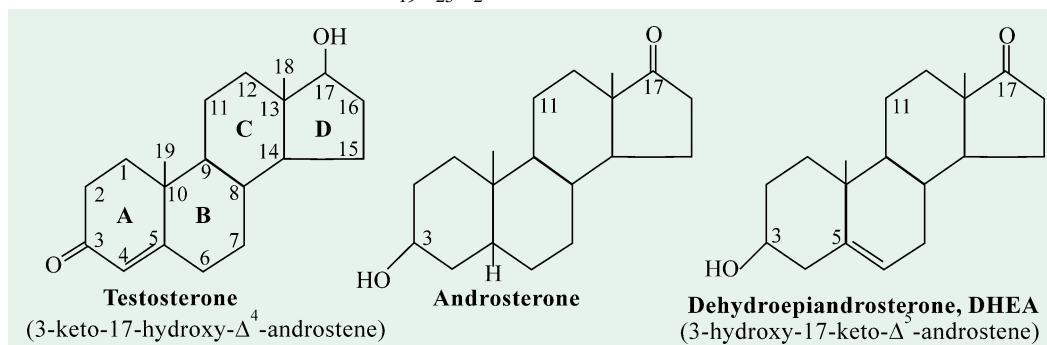
Fig. 31–12. Androstane
(parent hydrocarbon of androgens)

Fig. 31–13. Principal testicular hormones

Androsterone was first isolated by Adolf Butenandt *et al* in 1931 from male urine (about 15 mg from 15,000 litres of urine).

Testosterone is most potent of all these and dehydroepiandrosterone is least active. The relative potency ratio of these three forms is 20 : 7 : 1. Testosterone has a tendency to rise during late summer and early fall to peak in September. DHEA production peaks between ages 25 and 30 and wanes with age. Restoring DHEA levels to peak is said to boost the immune system.

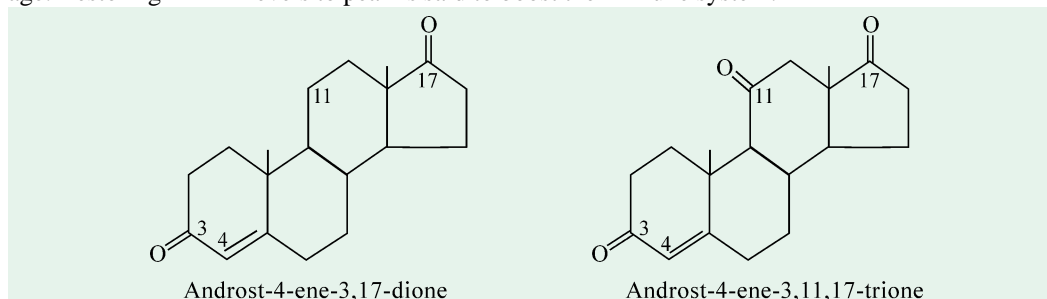


Fig. 31–14. Two testicular hormones produced from adrenal cortex

A few testicular hormones are also produced by the adrenal gland. The structure of two such hormones is given in Fig. 31–14.

Biosynthesis. In Fig. 31–15, biosynthesis of testosterone from cholesterol has been depicted.

The principal male hormone, testosterone, is synthesized by the Leydig cells of the testes from cholesterol through pregnenolone, progesterone and hydroxyprogesterone. The latter is then converted to a C_{19} ketosteroid called androstenedione which is the immediate precursor of testosterone. It is presumed that the same sequence of events also takes place in the adrenal gland, ovary and placenta.

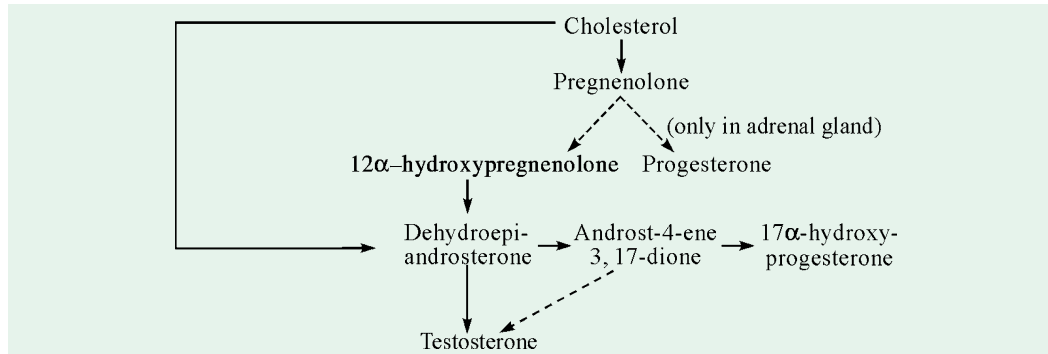


Fig. 31–15. Biosynthesis of testosterone

In addition to testosterone, androstenedione and DHEA are also synthesized in the testes, although in amounts far less than that of testosterone.

In normal male, 4 to 12 mg of testosterone are secreted each day. The amount of DHEA secreted is, however, greater than that of testosterone (approximately 15 to 50 mg/day).

Metabolism. Most of the metabolic transformations of androgens takes place in the liver. In some mammals like rats, these reactions occur mainly in the bile and urine. Two major reactions occurring in the liver are :

- (a) Conversion of testosterone to androst-4-ene-3,17-dione.
- (b) Interconversion of 3-hydroxy and 3-keto derivatives.

Functions. Testosterone has often been considered to be a 'youth hormone', because of its effects on the musculature, and it is occasionally used for treatment of persons who have poorly developed muscles. Because of the ability of testosterone to increase the size and strength of bones, it is often used in old age to treat osteoporosis. Like estrogens, the androgens are also responsible for the development of secondary sex characters in males. These are listed in Table 31.2.

Androgens regulate the activities of the male reproductive system; estrogens stimulate the growth, maturation and maintenance of the female reproductive system and accessory sex tissues. However, both androgens and estrogens also have significant effects on the non-reproductive tissues of the body. For instance, androgens stimulate the growth of skeletal muscles. Androgens and certain androgen derivatives (collectively called as **anabolic steroids**) are often used by weight lifters, wrestlers and football players to increase muscle mass and strength. Anabolic steroids are also used by female athletes, probably with advantage ; however, they produce other masculinizing effects as well.

The androgens constitute one factor in the production of baldness. Age and inheritance are other factors involved in causing this condition. But baldness does not ensue without androgenic stimulation.

In cases where the testes fail to descend in a normal manner (cryptorchidism), the testosterone is of considerable value. But the long usage and higher dosage of testosterone (*e.g.*, 25 mg per day for 4–6 weeks) in individuals often leads to atrophy of the sperm. The effect can, however be reversed by discontinuing the treatment for a similar period. Testosterone also controls the libido, and also the development of muscle mass and bone density.

Table 31–2. Body changes at puberty in boys
(= Secondary sex characters in males)

Characters	Changes
1. External genitalia	Penis increases in length and width; Scrotum becomes pigmented and rugose.
2. Internal genitalia	Seminal vesicles enlarge and secrete– they also begin to form fructose ; Prostate and bulbourethral glands also enlarge and secrete.
3. Voice	Larynx enlarges and the vocal cords increase in length and thickness; Voice becomes deeper.
4. Hair growth	General body hair increases; Hair line on scalp recedes anterolaterally (Fig. 31–10); Hair appear in axillae (axillary hair) and around anus; Pubic hair have a characteristic male pattern, i.e., triangle with apex up; Hair on face grow as beard.
5. Mental	More aggressive; Active attitude; Interest in opposite sex more pronounced.
6. Body conformation	Shoulders broaden and hips remain unaltered, i.e., narrow; Thighs that diverge and arms that converge, i.e., a narrow carrying angle; No distribution of body fat in the chests and buttocks; Muscles enlarge, leading to a muscular body contour.
7. Skin	Sebaceous gland secretion thickens and increases (predisposing to acne).
8. Weight gain	Tend to gain weight in the abdominal region.

Castration. Prepubertal castration in males results in :

1. Ossification of long-bone epiphyses
2. Increased adiposity
3. Lipid deposition leading to slight extrusion of the chest *i.e.*, enlargement of the male breast (gynecomastia)
4. Depressed growth of hair on the face and chest
5. Suppressed male organ (penis)
6. Diminished muscular growth.

Castration after puberty, leads to almost similar changes described above but less intensified.

C₂₁ STEROIDS

3. Adrenal Cortical Hormones

Secretory gland. The adrenals (*ad* = at; *renal* = pertaining to kidneys) or suprarenal glands in all tetrapods are a pair of glands, so named because of their position very close to or at the top of the kidneys. Each of the two adrenals among mammals is actually a 'double gland' and is composed of 2 distinct parts : namely an outer barlike covering called the cortex, surrounding an inner corelike dark-coloured mass called the medulla. The cortex is derived from the mesodermal glandular tissue and the medulla originates from the cells of neural crest. Both these parts secrete hormones which differ from each other chemically as well as physiologically. Hence, these 2 components are discussed separately. In man, the adrenals are two small structures sitting like 'cocked hats'

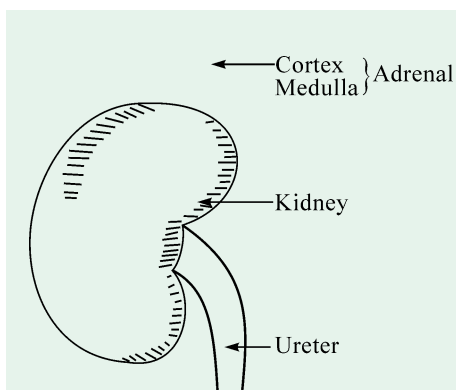


Fig. 31–16. The adrenal gland in man
(After D. Marsland, 1964)

over the apical end of the kidneys (refer Fig. 31–16) and each gland weighs about 3 grams.

Histologically, the adrenal cortex is made up of three layers (Fig. 31–17) :

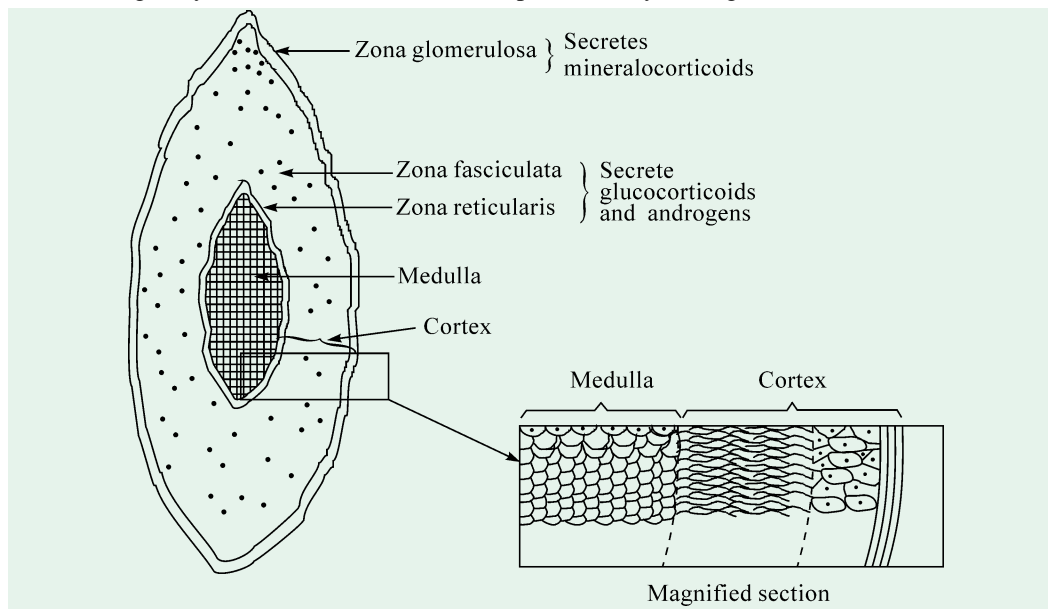


Fig. 31–17. Microscopic structure of the adrenal gland

- (a) an outer narrow *zona glomerulosa*, believed to be the site of biosynthesis of the mineralocorticoid hormones.
- (b) a middle, comparatively broader *zona fasciculata*, responsible for the production of glucocorticoid hormones and the adrenal androgens.
- (c) an inner narrow *zona reticularis*, secreting glucocorticoids along with the middle zone.

When there is prolonged stimulation of the adrenal cortex by adrenocorticotrophic hormone (ACTH), the middle and inner zones both hypertrophy; but a total lack of ACTH causes these two zones to atrophy almost entirely, leaving the outer *zona glomerulosa* partially intact. On the other hand, enhanced aldosterone production causes hypertrophy of the *zona glomerulosa*, while the other two zones remain almost unaffected.

Structure. Adrenal cortex secretes some 40-50 closely related C_{21} steroids, collectively called as corticosteroids (refer Fig. 31–18). From physiological viewpoint, the corticosteroids may be grouped under two categories :

- A. *Mineralocorticoids*. — concerned primarily with the transport of electrolytes and the distribution of water in tissues, *e.g.*, aldosterone and deoxycorticosterone.
- B. *Glucocorticoids*. — concerned primarily with the metabolism of carbohydrates, proteins and fats, *e.g.*, cortisone (= compound E), cortisol (= hydrocortisone) and corticosterone.

The estimated 24-hour production of major compounds of human adrenal gland is :

Cortisol	8-24 mg
Corticosterone	1.5-4 mg
11-deoxycortisol	0.5 mg
11-deoxycorticosterone	0.2 mg
Aldosterone	0.04-0.2 mg
18-hydroxycorticosterone	0.15-0.45 mg
18-hydroxy-11-deoxycorticosterone	ca 0.1 mg

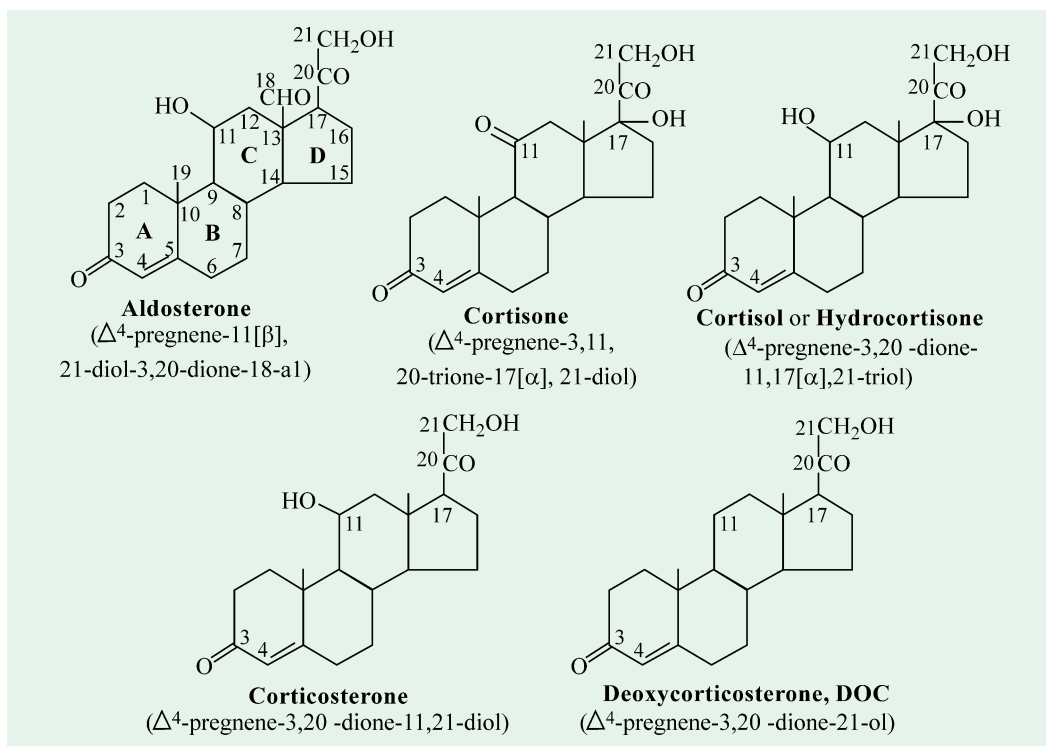


Fig. 31–18. Principal corticosteroids

However, during periods of stress, the amount of cortisol released during 24 hours may increase even up to 300 mg. The release of cortisol by the adrenal cortex has a diurnal rhythm. More is released during the day than during the night. Their structure is given in Fig. 31–18.

Aldosterone is 30 times more active than deoxycorticosterone. Deoxycorticosterone, in its turn, is 4 times more potent than cortisone and cortisol in maintenance of life. Corticosterone is least active in this regard.

Functions. A *mineralocorticoid*, aldosterone is chiefly concerned with water-salt balance of the body. It stimulates the reabsorption of Na^+ ion from the kidney tubules and as such regulates NaCl contents of the blood. This also causes excretion of K in the urine. Aldosterone is also more potent in maintaining the life of adrenalectomized animals.

Glucocorticoids, on the contrary, govern many other processes. They perform the following physiological functions :

1. Influence the carbohydrate metabolism firstly by increasing release of glucose from the liver and secondly by promoting the transformation of amino acids to carbohydrates.
2. Inhibit protein synthesis in muscle tissues.
3. Control eosinophil cells of the blood.
4. Regulate lipogenesis.
5. Reduce the osteoid matrix of bone, thus favouring osteoporosis (weak bones) and heavy loss of calcium from the body.
6. Decrease immune responses associated with infection and anaphylaxis (immunosuppressive effects).
7. Cause increased secretion of hydrochloric acid and pepsinogen by the stomach and that of trypsinogen by the pancreas (exocrine secretory effects).
8. Cause retention of sodium (and water) and loss of potassium to some extent. In this respect, it resembles aldosterone in action.

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.

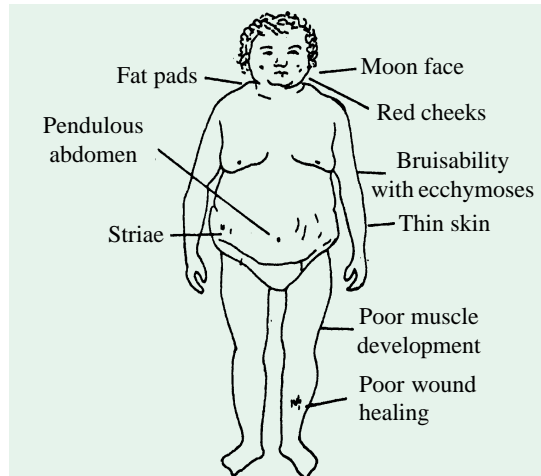


Fig. 31-19. Typical findings in Cushing's syndrome

(Adapted from Forsham and Di Raimondo in : *Traumatic Medicine and surgery for the Attorney*. Butterworth 1960)

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.

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.

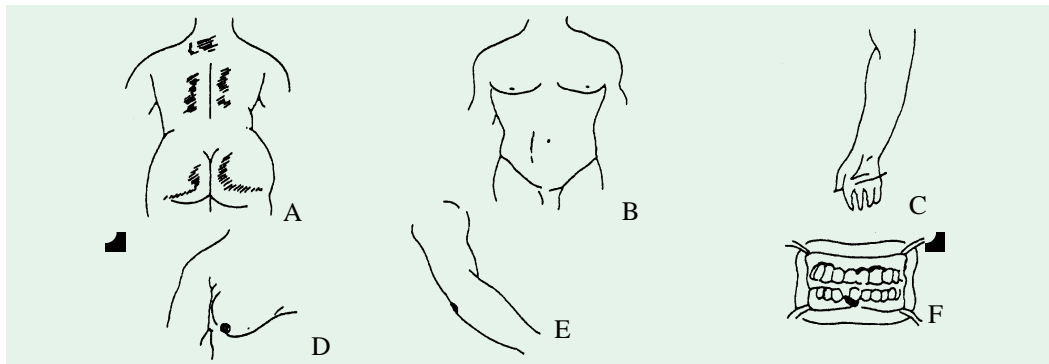


Fig. 31-20. Permentation in Addison's disease

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

(Adapted from Forsham and Di Raimondo, 1960)

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Many of the symptoms of this syndrome resemble those of adrenalectomized animals. Addison (1855) described these in his own words as follows :

“The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of the heart’s action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a *diseased* condition of the ‘supra-renal’ capsules”.

Other symptoms now attributed to this disease are low blood pressure, lowered basal metabolic rate (BMR), subnormal temperature and a disturbed water and electrolyte balance. This includes loss of sodium and chloride ions and a loss of body water. The person develops hyperkalemia and acidosis because of failure of potassium and hydrogen ions to be secreted in exchange for sodium reabsorption. The patient becomes hypoglycemic. The kidneys are also affected, resulting in urea retention. Skin pigmentation occurs in areas of greatest normal pigmentation. Frequently, the face and neck and backs of the hands are so deeply bronzed as to cause the afflicted individual to look like a mulatto. The melanin is not always deposited evenly but occasionally in blotches and especially in the thin skin areas such as the mucous membranes of the lips and the thin skin of the nipples. Thus, the chief symptoms of this syndrome are: anorexia, emesis (= vomiting), diarrhea, anemia, deep pigmentation of the buccal cavity and nipples, rapid loss of weight, excessive loss of NaCl in the urine and low blood pressure. As the extracellular fluid becomes depleted, the plasma volume falls, the concentration of R.B.C. rises markedly, the cardiac output lowers down and the patient dies in shock. The grip of Addisonian patients on their life is tenuous and any stress, infection, cold or even noise can precipitate a crisis leading to death.

Addisonian patients may be cured by giving extracts of the adrenal cortex. This has been very successful since its beginning in about 1929. Because this is substitution therapy, like most endocrine therapy, the constant administration of potent extracts is essential. Loeb (1939) has, however, demonstrated that NaCl is of immense value to Addisonian patients as it corrects the electrolyte and water imbalance in them. The administration of deoxycorticosterone (usually as acetate) or aldosterone 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, 20 α -OH and 20 β -OH are other hormones secreted by the corpus luteum). Progesterone (Fig. 31–21) is a C₂₁ 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 C₂₁H₃₀O₂. 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 precursor of the steroidal adrenocorticoids. It is soluble in most organic solvents and in vegetable oils but is insoluble in water.

The 3-dimensional structures of some steroid hormones determined by x-ray crystallography is presented in Fig. 31-22.

Biosynthesis. Progesterone is synthesized in the corpus luteum, placenta and the adrenal cortex from its immediate precursor, pregnenolone by a combined dehydrogenase and isomerase reaction.

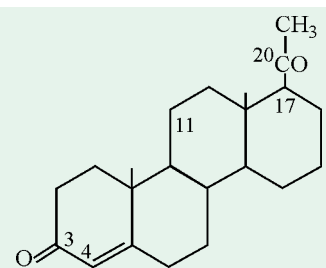


Fig. 31–21. Progesterone or “pregnancy hormone”

(Δ^4 - pregnene-3, 20-dione or 3, 20-diketo- $\Delta^{4,5}$ -pregnene, *cis*)

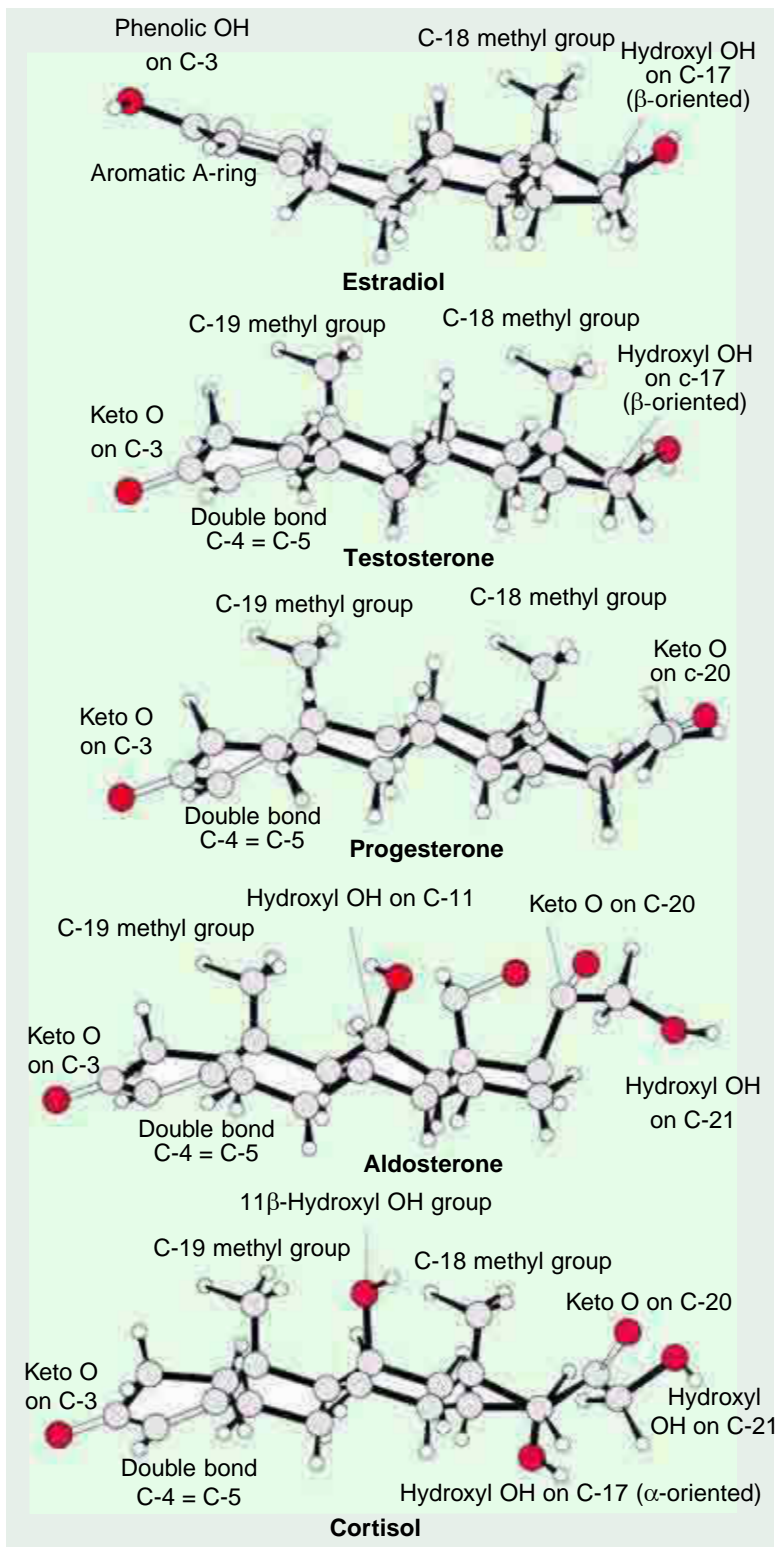
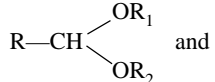
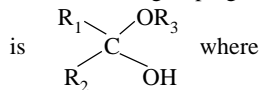


Fig. 31-22. Ball-and-stick representation of some steroid hormones

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



the hemiketal grouping is



R_1 , R_2 and R_3 refer to different substituents.

(Courtesy: Glusker JP, 1979)

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Unlike testosterone and estradiol, the progesterone is bound in plasma to the corticosteroid-binding globulin (CBG).

Metabolism. The metabolic fate of progesterone has been studied by injecting C^{14} - labelled hormone. About 75% of the injected progesterone is translocated to the intestine *via* bile and passed out in feces. A 20-hydroxy compound, pregnanediol, is the main urinary product of progesterone metabolism in human beings and rabbits. Such a conversion of progesterone into pregnanediol is not carried out in rat liver.

Functions. Progesterone has manifold functions :

1. The primary function of progesterone is to promote the proliferation of uterine mucosa so that the latter may receive the fertilized ovum. It, thus, serves for implantation of the fertilized ovum. If pregnancy ensues, continued secretion of progesterone is essential for completion of term.
2. It brings mammary glands to full maturity during gestation (pregnancy) for their onward use in breast-feeding by the newborn (Fig. 31–23)
3. It also maintains the uterus quiescent during pregnancy (*i.e.*, inhibits contraction of the uterus).
4. If given between 5th and 25th day of the normal menstrual cycle, progesterone exerts an antioviulatory effect. This is the basis for the use of certain progestins as oral contraceptive agents.
5. It serves as precursor of cortisol and corticosterone in the adrenal glands.

[Relaxin. Corpus luteum also secretes another hormone (or group of hormones) called relaxin or uterine-releasing factor (URF). It was discovered by Hisaw in 1926. Relaxin is a polypeptide of molecular weight about 9,000. It has not yet been obtained in pure form and, consequently, its structure has remained undetermined as yet. It is produced during pregnancy. The hormone is active only when injected into an animal which is in normal estrus (sexual heat). A wide variety of mammals including pregnant women, cows, rabbits and dogs secrete this hormone. Relaxin causes relaxation (hence the name) of the ligaments of the symphysis pubis in the estrus rat and guinea pig. This effect is, however, least pronounced in pregnant woman. It performs two other functions :

- I. softening of the cervix of the pregnant woman at the time of delivery.
- II. inhibition of the uterine motility.]

We, thus, see that many aspects of sexual reproduction in humans are controlled by hormones, including gamete production, puberty, pregnancy, birth and lactation (Fig. 31-24).



Fig. 31–23. A mother breast-feeding her baby

Progesterone brings mammary glands to full maturity and oxytocin helps in the ejection of milk which is suckled by the baby during infancy.



Fig. 31–24. The effect of hormones on sexual reproduction in humans
Hormones control gamete production, puberty, pregnancy, birth and lactation in humans.

Prohormones or Hormogens

Some polypeptide hormones, like certain enzymes, are synthesized in an inactive form, *i.e.*, as prohormones or hormogens. Prohormones are examples of proteins with extracellular functions, such as the enzymes chymotrypsin and trypsin, whose biological activities are dormant until activated by *peptidases*. Table 31–3 lists some of the known prohormones.

Table 31-3. Some prohormones

Prohormone	Source
Proinsulin	Pancreas– β cells
Proparathormone	Parathyroid
Angiotensinogen	Liver
Progastrin	Stomach

PEPTIDE HORMONES

1. Hormones of the Pancreas

Secretory gland. The pancreas (from pankreas : *pan*^G = all, *kreas*^G = flesh ; referring to the fleshy nature of the tissue) is both an exocrine and endocrine gland. It is situated transversely below and behind the stomach between the curve of duodenum and spleen. It is a compact and lobulated organ. It weighs about half a pound and resembles an elongated cone lying on its side. The broad end or ‘head’ of the pancreas is located next to a curve of the duodenum, the part of the small intestine just beyond the stomach. The gland tapers off to the left in the direction of the spleen and left kidney and ends in a portion called ‘tail’ (Fig. 31-25).

Barring cyclostomes, the pancreas in all the vertebrates is composed of two types of cells (Fig. 31–26).

- the glandular cells or *acinar* or *acini* (exocrine), which make up the bulk of the pancreatic tissues and secrete digestive juices into the duodenum by the pancreatic duct.
- the polygonal cells or *islets of Langerhans* or *islet tissue* (endocrine), which do not have any means for emptying their secretions externally but instead pour their secretions (*i.e.*, insulin and glucagon) directly into the blood. These were discovered by Langerhans in 1867, hence so named.

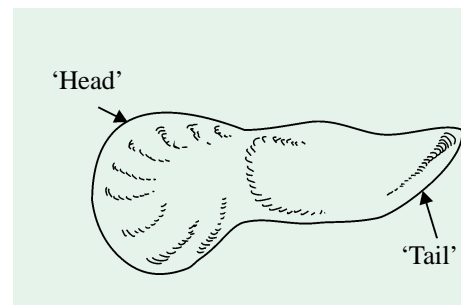


Fig. 31–25. Morphologic structure of pancreas

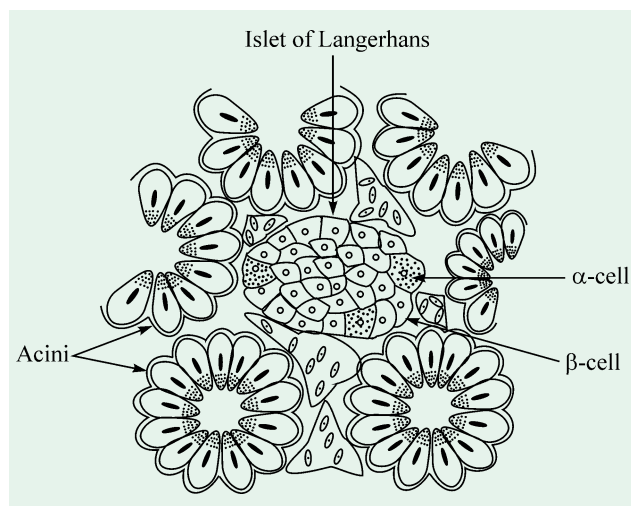


Fig. 31–26. Histologic structure of pancreas

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Each pancreas has about 1,00,000 islets of Langerhans, which are clusters of various types of cells. These islets in mammals contain 3 major types of cells: α cells, β cells and δ cells. Each islet contains between 1,000 and 2,000 **β cells**, which were first described in 1869. The β cells contain granules which are insoluble in alcohol and manufacture a hormone insulin, store it and eventually release it directly into the bloodstream at the appropriate times. These amazing cells (*i.e.*, β cells) are also capable of measuring the blood glucose level within seconds to within a range of 2 mg %. Using this information, they can determine how much insulin is needed, and, within a minute or so, secrete the precise amount of required insulin. The **α -cells** contain granules which are soluble in alcohol and produce another hormone, glucagon. The α -cells tend to be arranged about the periphery of the islets. The existence of α -cells is dubious in cyclostomes and urodeles. Of the two cell types, the α -cells predominate in the reptiles and birds, whereas in amphibians and mammals, the β -cells are more abundant. Teleost fishes, however, often exhibit seasonal variations between the two cell types. However, a 3rd cell type **δ cells** secrete another hormone, *somatostatin*.

The islets of Langerhans are also known to contain one more type of cells designated as **D** or **α_1 -cells**. These cells probably secrete *gastrin* which is a recognized gastrointestinal hormone and is derived from pyloric mucosa.

FREDERICK SANGER (Born, 1918 at Rendcombe, England)

Sanger, a British chemist, received his doctorate in 1943 on the metabolism of lysine from Cambridge University, where he has worked for his entire career. During his service tenure, he preferred working in a laboratory with his own hands to teaching and administrative jobs. Sanger has been responsible for two of the most important technical advances of the past 45 years first, in the early 1950s, he developed a method for determining the amino acid sequence of a polypeptide, and put it to use by working out the sequence of amino acids in insulin. This work, completed in 1955, provided the first real proof that the amino acids in a protein are present as a constant, genetically determined sequence. This gave molecular biologists the confidence to tackle other problems such as the genetic code. Then, in 1977, Sanger perfected a rapid method for sequencing DNA, opening the door to precise examination of gene structure and organization. Both advances have been invaluable and both were recognized by Nobel Committee. Sanger is *one of the two scientists to have ever won Nobel Prizes twice in the same subject* : **First in 1958** for determining the amino acid sequence of insulin on his own, and **later in 1980** for determining the base sequences in nucleic acids, along with **W. Gilbert**, thus both times in chemistry [the other being an American physicist John Bardeen-in 1956 and 1972, both time jointly]. Sanger has spent his career at the University Department of Biochemistry and the Medical Research Council Laboratory for Molecular Biology at Cambridge, U.K. The Principle behind his success, in his own words, is : "If the planned experiment doesn't work, don't worry, start planning the next experiment"

**Insulin**

Structure. Insulin (*insula*^L = island) was first isolated in 1922 from the pancreas of dogs by Banting and Best, both of the University of Toronto, Canada. They also demonstrated the curative effect of pancreatic extract in dogs ailing with diabetes mellitus. Abel and his associates (1926) obtained insulin in crystalline form (Fig. 31–27) and also demonstrated its protein nature. *Insulin is, in fact, the first hormone to be recognized as a protein.* The chemical structure of insulin has been determined by Sanger and his coworkers at Cambridge, England in a painstaking 10-year (1944–54) study. It has a molecular formula, $C_{254}H_{377}O_{75}N_{65}S_6$ (consult Chapter 9 for structure). Just to recall, bovine insulin consists of 51 amino acid residues dispersed in two chains. The two polypeptide chains are held together by cross linkages of two disulfide bonds. The acidic chain A contains 21 residues and the peptide chain B having 30 residues. It has a molecular weight of 5,733 and is isoelectric at pH 5.4. Human insulin, however, has a molecular weight of 5,808. Insulin is destroyed by alkali but is relatively stable in acid solutions. Reduction of the disulfide bond results in a loss of biologic activity. Zinc is always found with this hormone but is not a part of the insulin molecule.

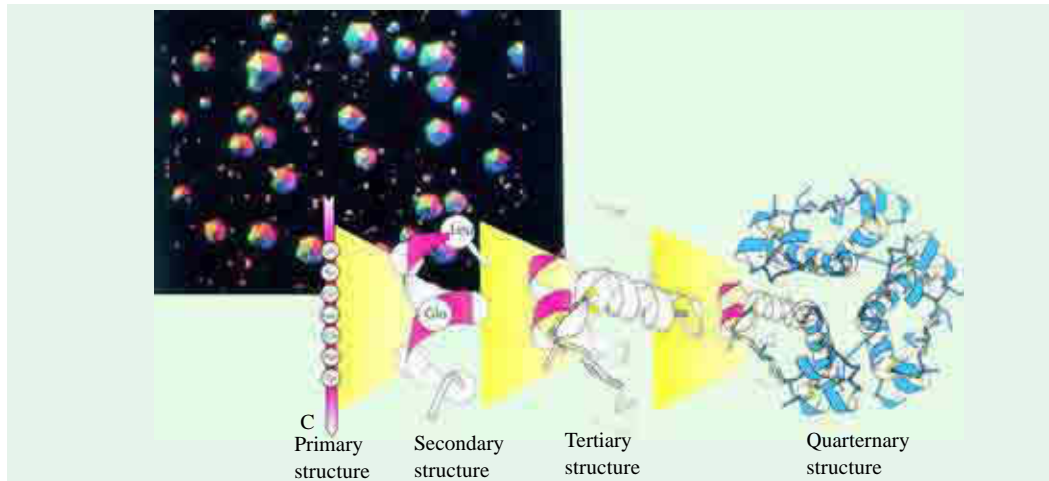


Fig. 31-27. Crystals of human insulin

Insulin is a protein hormone, crucial for maintaining blood sugar at appropriate levels. (Above) Chains of amino acids in a specific sequence (the primary structure) define a protein like insulin. These chains fold into well-defined structures (the tertiary structure)—in this case a single insulin molecule. Such structures assemble with other chains to form arrays such as the complex of six insulin molecules shown at the far from right (the quarternary structure). These arrays can often be induced to form well-defined crystals (photo at left), which allows determination of these structures in detail,

[Courtesy: (left) Alfred Pasieka/Peter Amoild]

It has been established that the insulins from various species differ only slightly, although their biologic activities are identical. Sanger and Smith (1957) have determined the amino acid sequence of insulins from 5 different species. They found the sequence to be identical except the identity and sequence of only three amino acids at positions 8, 9 and 10 in the chain A (refer Table 31-4).

SIR FREDERICK GRANT BANTING (LT, 1891–1941)
AND

CHARLES HERBERT BEST (LT, 1899–1978)

Banting and Best were both Canadian physicians who are credited with curing dogs ailing with diabetes mellitus by giving them pancreatic extract containing insulin. Later, insulin purified from pig or cow pancreas was successfully tried on humans but it produced immunogenic reactions in them. However, in 1982, using genetic engineering (recombinant DNA technology), insulin was manufactured and marketed for human use. Thus, *insulin became the first hormone product of genetic engineering*. The new recombinant insulin has the exact structure of human insulin and hence will not produce immunogenic reactions.

Sir Banting (and not Best) was awarded the **1923 Nobel Prize in Medicine or physiology** for demonstrating the curative effect of insulin, along with his physiology professor JJR Macleod, also of the University of Toronto.



Best (left) and **Banting** with their dog, which they experimented upon, on November 19, 1921

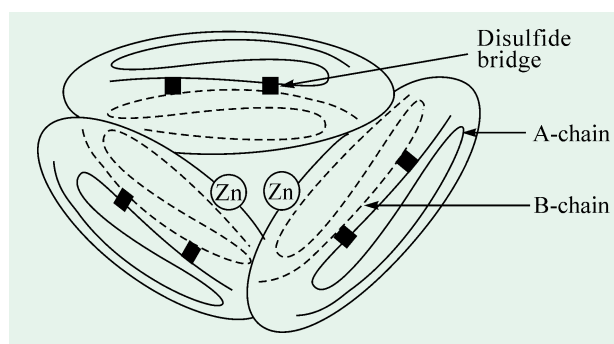
The dog was depancreatized prior to administration of the pancreatic extract. Following injection, the blood sugar fell from 330 mg per cent to 170 mg per cent in one hour. This experiment demonstrated that the active principle could be extracted from the fetal pancreas with acetone and alcohol and that it was not destroyed by chloroform and ether.

(Photo from Fruton JF and Wilson LC, 1966)

Table 31-4. Differences in amino acid sequences in insulin of various species

Species	Amino acid present in chain A at position		
	8	9	10
1. Beef or Cattle	Ala	Ser	Val
2. Pig or Hog	Thr	Ser	Ile
3. Sheep	Ala	Gly	Val
4. Horse	Thr	Gly	Ile
5. Whale	Thr	Ser	Ile

Dorothy Crowfoot Hodgkin and coworkers of Oxford have shown that porcine and presumably also bovine insulin (the types used for injection in man) are hexameric molecules composed of three subunits (Fig. 31-28). Each subunit, in turn, is a dimer composed of two polypeptide chains, A and B. This multicomponent molecule of insulin, thus, is a triangular ring like structure consisting of three tilted, football like dimers around two central zinc atoms in the core. The hexamer is held together by a variety of forces. The ends of the overlapping dimers are apparently joined by interlocking phenylalanine groups. There is also a hydrogen bonding between dual glutamic acid groups midway in the dimer. The two chains of the monomers are linked by hydrogen and hydrophobic interactions and by two disulfide bridges between the chains. The role of two zinc atoms in the quaternary structure is yet to be ascertained.

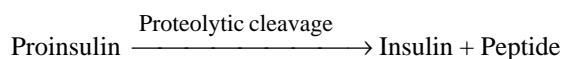
**Fig. 31-28. Schematic representation of the three-dimensional structure of insulin**

[The zinc atoms are apparently involved in the formation of the quaternary structure]

(Adapted from Orten and Neuhaus, 1970)

Biosynthesis. β -cells of the pancreas synthesize insulin by the ribosomes of the endoplasmic reticulum. Previously, it was suggested that the two chains of insulin are synthesized independently and later these combine by disulfide bonds. But now Donald F. Steiner *et al* (1967) have shown that it is formed from its precursor, *proinsulin*. Proinsulin has been isolated and purified from pancreatic extracts. It is a linear protein with 84 amino acid residues and has a molecular weight of about 9,100.

The transformation of proinsulin to insulin takes place in the granules and not in the endoplasmic reticulum where synthesis of proinsulin takes place. The conversion, which is brought about by lysosomal proteolytic enzymes, consists in cleavage of a 33 amino acid-connecting peptide chain from the proinsulin molecule leaving behind insulin (Fig. 31-29).



As proinsulin comprises only 5% of the total insulinlike protein of the islets of Langerhans, it is not a storage form of insulin. It rather appears essential in the formation of the disulfide bonds which are indispensable for the biological activity of insulin. The formation of proinsulin has been demonstrated in the pancreatic tissues of bovine, porcine, rat and man as well.

Functions. Insulin has a profound influence on carbohydrate metabolism. It facilitates entry of glucose and other sugars into the cells, by increasing penetration of cell membranes and augmenting

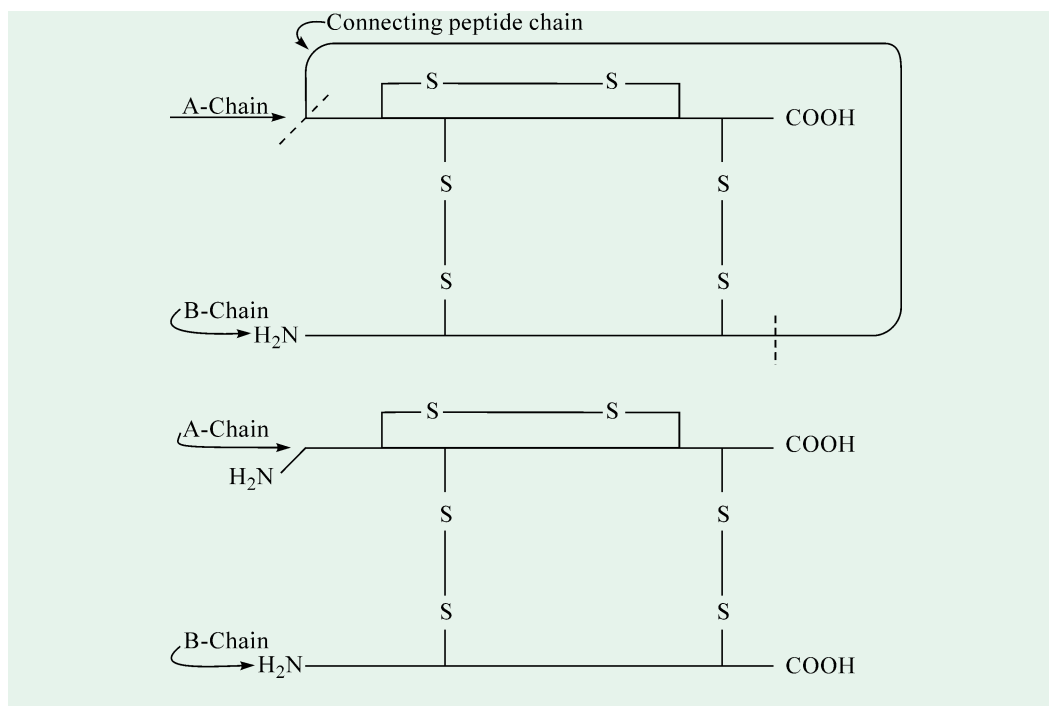


Fig. 31–29. Formation of insulin from its precursor, proinsulin

DOROTHY CROWFOOT HODGKIN (LT, 1910-1994)

Dorothy Hodgkin was one of the outstanding British scientists of the 20th century, endowed with a brilliant mind and an iron will to succeed and in many ways proved herself a trendsetter. One of her students is Margaret Thatcher, the 'Iron Lady' and ex Prime Minister of Great Britain. Born on 12 May, 1910 in Cairo, Dorothy Mary Crowfoot (her name before she married) was educated at Sir John Leman School, Beccles, Suffolk and later at Somerville College at Oxford where she also taught. She was elected a fellow of the Royal Society at age 37 (in 1947) and was also awarded the Gold Medal of the Royal Society in 1956. She took to x-ray crystallography and elucidated the x-ray diffraction patterns of pepsin and insulin. Insulin's structure was the one she laboured with perseverance of a hedgehog. She also researched on the structure of a number of antibiotics including penicillin and cephalosporins. In 1957, she established the unusually distinct structure of the complex molecule of vitamin B₁₂ and was awarded the **Nobel Chemistry Prize in 1964** for the same. In 1960, Hodgkin became the Royal Society Wolfson Professor. She was made a member of the Order of Merit in 1965. She remained the President of the International Union of Crystallography from 1969 to 1975. Dorothy was the founding mother of the "Pugwash" movement, which helped scientists maintain communication with the countries behind the 'Iron Curtain'. She remained the President of the Pugwash Movement of scientists for peace between 1976-1988. (Pugwash Organization later got Nobel Peace Prize in 1995). A 14-year-old boy (Leonard Thompson) in Canada was treated with insulin, the first-ever diabetic patient to be so treated (along with Joseph Rotblat, a scientist turned antinuclear weapon compaigner, who nursed the Organization for about 4 decades by the time he got the award.) She held the Sir C.V. Raman Professorship of the Indian Academy of Sciences, of which she was an honorary fellow. During the last few years, she was bodily crippled by arthritis but this affliction had had no debilitating effect on her indomitable will. Only a year before her death on 29 July, 1994, although she was wheelchair-bound, she flew to China to attend an International Crystallography Conference. Such was Hodgkin ! Once she helped her three-year-old son search for a lost toy when she said : "It must be somewhere; it can't be nowhere."



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phosphorylation of glucose. This results in lowering the sugar content of the blood – a fact leading to its common name, **hypoglycemic factor**, which may be abbreviated as **hG-factor**.

Insulin administration promotes protein synthesis (proteogenesis) by assisting incorporation of amino acids into proteins. This effect is not dependent on glucose utilization. At the same time, it also acts as an *antiproteolytic agent*, i.e., discourages excessive breakdown of tissue protein. This action is similar to that of GH and testosterone.

Synthesis of lipids (lipogenesis) is also stimulated by administration of insulin. Insulin also influences the inorganic metabolism *esp.*, that of phosphate and potassium. Insulin administration lowers the blood phosphate level and facilitates absorption of inorganic phosphate by the cells. This phosphate appears within the cells as ATP. A similar mechanism operates in potassium uptake.

It may be said, in general, that insulin promotes anabolic processes (synthesis of glycogen, fatty acids and proteins) and inhibits catabolic ones (breakdown of glycogen and fat).

Insulin deficiency. The deficiency of insulin caused either by inadequate insulin production or by accelerated insulin destruction, leads to *diabetes mellitus** in man. This disease is characterized by :

1. an increase in blood sugar or glucose (hyperglycemia) from a normal value of 80 mg/100 ml of plasma to abnormal value ranging between 150—200 mg/100 ml of plasma.
2. the appearance of sugar in the urine (glycosuria); with the result, the victim's urine tastes sweet.
3. an increase in concentration of ketone bodies in the blood (ketonemia) and in the urine (ketonuria).
4. the excretion of large quantities of urine (polyuria), frequently at night (nocturia), leading to dehydration.
5. the excessive drinking of water (polydipsia) on account of an unrelenting thirst.
6. the excessive eating (polyphagia) due to feeling constant hunger. This is because the tissues cannot utilize glucose normally, even though they need fuel.
7. the lack of energy (asthenia) which is apparently caused mainly by loss of body protein.

One of the present authors (JL Jain) proposes the abbreviation '**hG-factor**' for the hypoglycemic factor insulin, where the small letter 'h' justifiably denotes 'small' or hypo function. It should, however, not be abbreviated as 'HG-factor', which is aptly kept reserved for the hyperglycemic factor glucagon, where the capital letter 'H' signifies 'big' or hyper function.

CLINICAL IMPLICATIONS

DIABETES MELLITUS

The Greek physician Arteus (ca A.D. 200) apparently was the first to call insulin deficiency disease as **diabetes** (to follow through; urine), referring to a large volume of urine passed in it. Later, the Latin term **mellitus** (sweetened or honey-like) was added to it and dates from the time when urine was tested by tasting, and the urine in this condition is sweet to the taste. Used alone, diabetes is taken to mean diabetes mellitus, by far the most common (80–90%) of the two types of diabetes (*diabetes mellitus* and *diabetes insipidus*). Normally, some sugar (glucose) is in the blood at all times. These terms, glucose and sugar, are used interchangeably, although with regard to diabetes we almost always mean glucose. The level of glucose is usually between 60 and 120 milligrams per cent (mg %), which means that there are 60 to 120 milligrams of glucose in each 100 cubic centimeters (cc) of blood. Milligrams per cent is sometimes expressed as milligrams per deciliter (mg/dL). *Diabetes mellitus* is characterized by a level of glucose in the blood that is above normal, most of the time.

Glucose is the major fuel of the body. We ingest a great deal of glucose each day, as carbohydrates
(Cont'd)

(starches) are made of glucose. When we eat glucose, it gets into the bloodstream and ultimately into each of the individual cells of the body to provide them with energy. Glucose cannot just flow into the cells, however. Cells are enclosed in membranes that separate what is inside the cell from what is outside. Somehow, the cells must be told that the glucose waiting outside the cell should be allowed in. That is what insulin does. It is needed to signal to the cells that they should allow the glucose, that normally is in the blood, to penetrate their outer layer. If the glucose cannot enter the cells, it “backsup” in the blood. The level of glucose in the blood increases and a state of diabetes is produced. Such a condition occurs if there is a lack of insulin for whatever reason. Perhaps the pancreas cannot produce enough insulin.

Diabetes mellitus is of 2 types : type I (insulin-dependent) and type II (noninsulin-dependent). The use of Roman numerals probably dignifies the importance of this classification.

Type I (Insulin-dependent diabetes mellitus, IDDM) : IDDM occurs because the insulin producing β -cells are destroyed and there is not enough insulin produced. In the past, there was treatment that had some measure of success. This was *relative starvation*. People with IDDM had very short careers. The former synonyms for this disease are *brittle diabetes* or *juvenile diabetes*.

Type II Noninsulin-dependent diabetes mellitus, NIDDM) : NIDDM is caused by a relative insulin insufficiency due to insulin resistance– the inability of the insulin to tell the cells to use glucose– plus insufficient insulin to overcome this resistance. Patients with NIDDM often lived for many years, if they heroically reduced their weight to live with the small amount of insulin that might be available. In a sense, this was *organised starvation*. NIDDM is also known by the former names, *stable diabetes* or *adult-onset diabetes*. In case of type II diabetes, it may be said that heredity may load the cannon, but stress or obesity pulls the trigger.

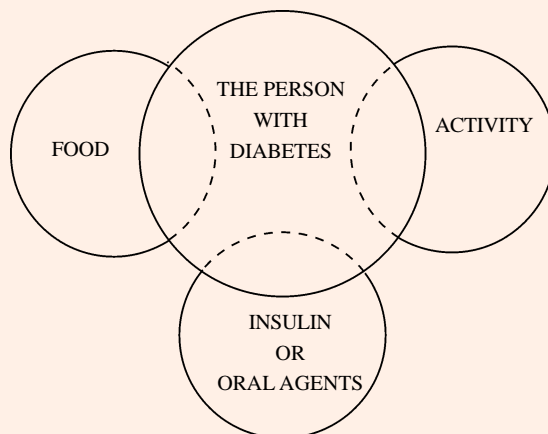
Table given below draws comparison between type I and type II diabetes.

Comparison of two types of diabetes mellitus

Item	Type I (IDDM)	Type II (NIDDM)
1. Percentage of all people with diabetes	20%	80%
2. Dependence on insulin	Dependent	Not dependent
3. Age of discovery	In children or in adults, usually under 40	In adults, usually over 40
4. Cause of diabetes	Reduced or none insulin production	Insulin resistance and relative or absolute deficiency of insulin
5. Pancreatic insulin content	0	> 5% of normal
6. Weight	Often underweight or normal weight	Usually overweight but 20% are normal weight
7. Primary insulin resistance	Minimal	Marked
8. Anti-islet antibodies	85%	> 5%
9. Concordance rate of identical twins for diabetes mellitus	25–50%	~ 100%
10. Condition when discovered	Usually moderately to severely ill	Often not ill at all or having mild symptoms
11. Acute complications	Ketoacidosis	Nonketotic, hyperosmolar, hyperglycemic comma, not usually prone to ketoacidosis.
12. Usual treatment	Insulin, eating plan, exercise	Diet, exercise, insulin, if needed oral agents

The control of diabetes, however, depends on the triad of food, activity and insulin or oral agents. All of these, however, must be balanced properly by the person with diabetes.

(Cont'd)



Diabetes and its controlling triad

The diabetic person gradually becomes weaker and loses weight due to the failure of glucose utilization by the body despite a voracious appetite. Diabetic coma ensues, the plasma volume decreases and the kidney fails. This eventually leads to death. In England, the disease for centuries was approximately called the “*pissing evil*”.

Since insulin is a protein, it is not amazingly digested and thus inactivated by the proteolytic enzymes, pepsin and trypsin. Hence, insulin has no effect when taken orally and must be, therefore, administered parenterally in diabetic patients.

Hypoglycemic agents. There are many hypoglycemic drugs, effective when taken orally, that control diabetes. Certain of these drugs, which belong to the group sulfonamide, are tolbutamide (orinase), chlorpropamide (diabinese) and tolazamide (tolinase).

Parenteral is any route outside the gastrointestinal tract, including subcutaneous, intramuscular, intraperitoneal and intravenous injections or infusions. In practice, parenteral feeding is done intravenously.

In 1978, Riggs and his collaborators of the City of Hope National Medical Centre, California, have been able to produce human insulin by using artificial genes which make bacteria produce it. The scientists first synthesized a gene that dictates insulin production. This gene was then inserted into molecules of a harmless laboratory strain of human bacteria called *Escherichia coli*. These bacterial molecules are called **plasmids** or **DNA rings**. In the plasmids, the genes were joined to clusters of regulatory genes called **lac operons** which react to the presence of milk sugar (lactose) by switching on the bacteria's protein-making apparatus. When an experimental colony of *E. coli* was salted with the new genes and plasmids, it obeyed the command to make protein. The protein in this case was obviously insulin since that was the DNA blueprint in the bacteria's doctored genetic material. This finding, however, might benefit the world's 100 million diabetics by providing them better and probably cheaper insulin. Besides, about 5% of the diabetics are allergic to the animal insulin now in use and the man-made carbon copy of human insulin will be a boon to them. The greatest achievement of this new research, however, is that it has opened up large vistas in a new era of biology since any protein can be *tailor-made* by this process. The cell proteins include hormones, antibodies, enzymes etc., and these can now be produced at will.

Glucagon

Structure. Glucagon was first isolated in crystalline form by Behrens and others. This peptide hormone has a molecular weight of 3,485 and is isoelectric at pH 8. It has 29 amino acid residues (of 15 different types) arranged in a linear row. Histidine is the N-terminal amino acid and threonine, the C-terminal amino acid. Unlike insulin, it contains no cystine, proline or isoleucine, but possesses

either intramuscularly or intravenously. Response may be observed within 10–15 minutes after administration of 0.5 to 1.0 mg of glucagon.

2. Hormones of the Hypophysis or Pituitary Gland

Secretory gland. Hypophysis (meaning undergrowth) is so named because of its location below the brain as an undergrowth. Its synonym pituitary gland is, however, misleading as the gland is not concerned with the secretion of mucus or phlegm (*pituita*^L = phlegm), as was thought previously. This is an unpaired small ovoid gland and is no larger than the end of the little finger. It is located at the base of the brain and lies below the diencephalon in a depression of basisphenoid bone of the skull called sella turcica. It is a complex structure formed of ectodermal outgrowth of the mouth cavity and downgrowth of the infundibulum.

The human hypophysis is a reddish-grey oval structure and measures about 10 mm in diameter. Its average weight varies in the two sexes : 0.5–0.6 g in males and 0.6–0.7 g in females. It consists of 3 lobes (Fig. 31–32) :

- an anterior richly vascular largest lobe, pars distalis or adenohypophysis.
- an intermediate relatively avascular smallest lobe, pars intermedia.
- a posterior neural lobe, pars nervosa or neurohypophysis.

While all the three parts are important, it is the anterior lobe that seems to be essential to life.

This gland plays perhaps the most dominant role as it secretes hormones which govern the secretion of other endocrine glands (like thyroid, adrenal and gonads) and also its secretions have a direct effect on the metabolism of nonendocrine tissues (refer Fig. 31–33). It has, therefore, aptly been described as the ‘*master gland*’ of the system or the ‘*master (= conductor) of endocrine orchestra*’. However, the view held by some biochemists is that since the hypophysis is subservient to the nervous system and some of the other endocrine glands, it is erroneous to call this gland as the master gland of the body.

Pars distalis or Adenohypophysis

The anterior lobe is the largest and shares about 70% of the total weight of hypophysis. The adenohypophysis originates from an embryonic invagination of the pharyngeal epithelium called Rathke’s pouch. This explains the epithelioid nature of its cells. It consists of glandular epithelial cells of varying shapes and sizes, arranged in columns separated by sinusoids containing blood. In general, there is one type of cell for each type of hormone that is produced in this gland. These various cell types can be differentiated from one another on the basis of special staining techniques (the only likely exception to this is that the same cell type may secrete both luteinizing hormone and follicle-stimulating hormone). Using acid-base histological stains, only 3 types of cells may be differentiated in this region :

- acidophils or α cells*—these stain strongly with acidic dyes (acid fuchsin) and secrete growth hormone and prolactin.
- basophils or β cells*—these stain strongly with basic dyes (aniline blue) and secrete luteinizing hormone, follicle-stimulating hormone and thyroid-stimulating hormone.
- neutrophils or chromophobe cells*—these do not stain with either and are believed to secrete adrenocorticotrophic hormone.

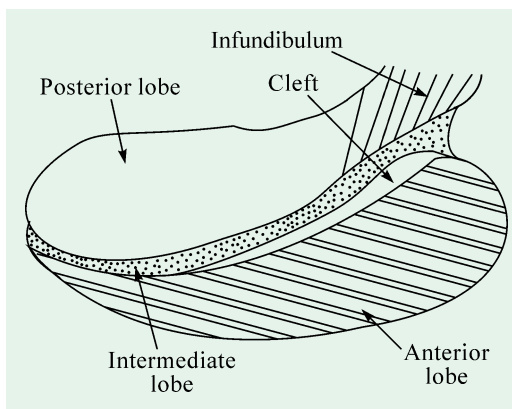


Fig. 31–32. The hypophysis in man
(After D. Marsland, 1964)

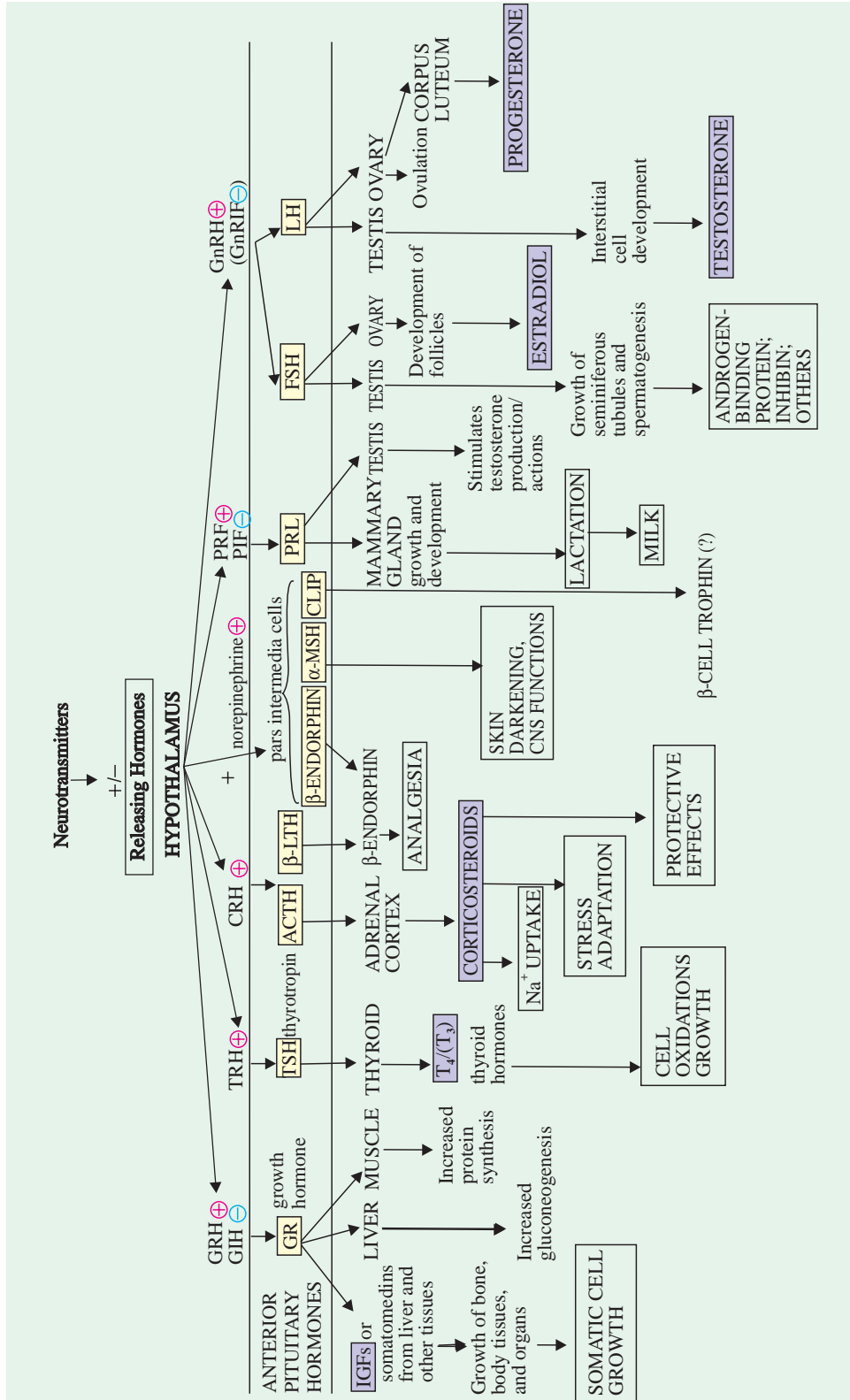


Fig. 31-33. Overview of anterior pituitary hormones with hypothalamic releasing hormones and their actions

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The anterior lobe produces hormones which govern the production of hormones secreted by other glands. These hormones are called as **tropins** (*tropos*^G = turning) or **trophic** (*trophikos*^G = nursing) **hormones**. Evidences available indicate that the rate of secretion of a trophic hormone is inversely proportional to the concentration, in the blood, of the hormone with which it is related. For example, a high blood level of thyroid hormone tends to inhibit the secretion of TSH from the adenohypophysis and a low level causes an increased production of it.

Neurohormones— The secretion of thyrotropin (as of almost all other pituitary hormones) is controlled by the hormones (or factors) released from hypothalamus, a region of the brain immediately proximal to the pituitary. These hormones are called as **hypothalamo-releasing hormones** or **hypothalamic factors**. These have been classified as *neurohormones*, *i.e.*, those produced by the nerve cells. These are unlike *neurohumors* (*e.g.*, acetylcholine, serotonin, norepinephrine etc) which are released at nerve endings and activate the adjacent nerve bodies. The neurohormones, on the contrary, are released into the blood and activate cells a little far from their point of release. These are introduced into the capillary of the hypothalamo-hypophyseal portal system at the floor of the hypothalamus called median eminence. In addition, the release of anterior pituitary hormone may be inhibited by a *release inhibiting* factor which passes down the same hypothalamo-hypophyseal portal veins.

The various hypothalamic factors controlling the release of pituitary hormones have been listed in Table 31–5.

Table 31–5. Pituitary hormones and the hypothalamic factors controlling their secretion

S.N.	Pituitary Hormones	Hypothalamic Releasing Factors*
1.	Thyrotropin, TSH	Thyrotropin-releasing factor, TRF
2.	Corticotropin, ACTH	Corticotropin-releasing factor, CRF
3.	Follicle-stimulating hormone, FSH	Follicle-stimulating hormone-releasing factor, FSH-RF
4.	Luteinizing hormone, LH	Luteinizing hormone-releasing factor, LH-RF
5.	Prolactin, PL	Prolactin-releasing factor, PRF
6.	Growth hormone, GH	Growth hormone-releasing factor, GH-RF
7.	Melanocyte-stimulating hormone, MSH	Melanocyte-stimulating hormone-releasing factor, MRF

* Also, sometimes called hormones, so in some books, the abbreviations may have an H instead of an F at the end.

(After Schally *et al*, 1973)

Some 30 tropins are secreted from the anterior lobe. The four important tropins are described below.

1. Thyrotropin or thyroid-stimulating hormone, TSH. It is a glycoprotein with molecular weight about 30,000. Each molecule has 8-9 cystine residues and the disulfide groups are present as intrachain linkages rather than interchain linkages.

In general, it stimulates the activity of thyroid gland and enhances the rate of certain reactions such as :

- (a) removal of iodide from blood by thyroid
- (b) conversion of iodide to thyroid hormones
- (c) release of hormonal iodine from thyroid.

The release of thyrotropin is controlled by another hormone from hypothalamus called thyrotropin-releasing factor, TRF.

2. Corticotropin or adrenocorticotrophic hormone, ACTH. Corticotropin (Fig. 31–34) is a straight chain polypeptide with a molecular weight of about 4,500 and consists of 39 amino acid residues in mammals like man, ox, sheep and pig. The most potent segment of activity is from residue 15 to 18. ACTH molecule in these species differs from each other only in the constituents present from residue 25 to 33. Thus far, no differences in residues 1–24 and 34–39 have been reported.

ACTH, in general, has a stimulatory effect on the hormone-producing capacity of the adrenal cortex. ACTH administration leads to accelerated gluconeogenesis (= neoglucogenesis) with accompanied retardation of protein synthesis in all tissues except liver. It also possesses an intrinsic melanocyte-stimulating activity, causing darkening of the skin in a manner similar to that of another hormone, MSH.

Oversecretion of ACTH results in Cushing's disease, already described earlier.

Certain peptides found in hypothalamus and also in neurohypophysis have ACTH-releasing activity. These have been termed as corticotropin-releasing factor, CRF.

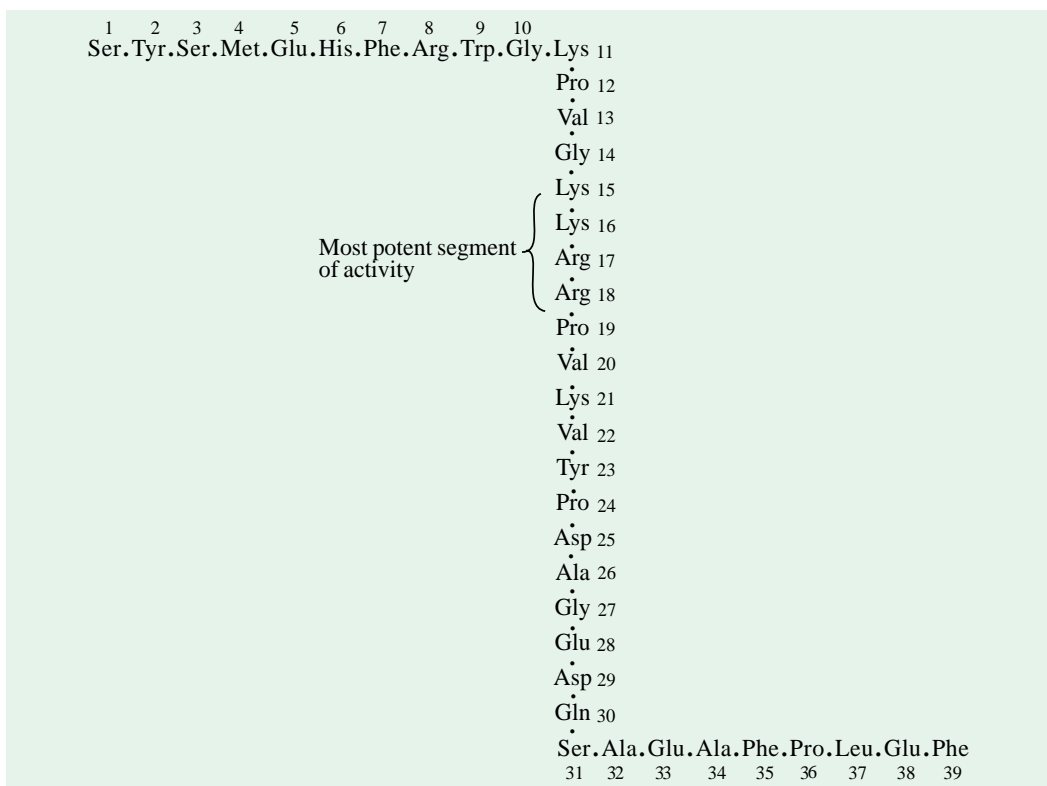


Fig. 31–34. Structure of human adrenocorticotropin

3. Gonadotropins or gonadotrophic hormones, GTH. These hormones control the development and functioning of the gonads which remain dormant until the age of 12–14 years in the human beings. Damage to certain areas of the hypothalamus greatly decreases the secretion of gonadotrophic hormones by the anterior pituitary. If this occurs prior to puberty, it causes typical eunuchism. The damage often causes simultaneous overeating because of its effect on the feeding centre of the hypothalamus. Consequently, the person develops severe obesity along with the eunuchism. This condition is called **adiposogenital syndrome** or **Frohlich's syndrome** or **hypothalamic eunuchism**. Three gonadotropins are known.

A. Follitropin or follicle-stimulating hormone, FSH. It is a glycoprotein that contains galactose, mannose, galactosamine, glucosamine, sialic acid, fucose and uronic acid. It has a molecular weight of about 30,000 in man. In human females, it induces the growth of graafian follicles resulting in

an increased weight of the ovary. In males, however, FSH promotes spermatogenesis by stimulating the development of seminiferous tubules, thus leading to the formation of a large number of spermatocytes.

The release of this hormone is controlled by another hormone from hypothalamus called follicle-stimulating hormone-releasing factor, FSH-RF.

B. Luteinizing hormone, LH or interstitial cell-stimulating hormone, ICSH. It is a peptide hormone with molecular weight of about 26,000 (in man) or 100,000 (in swine). It lacks tryptophan but has a high content of cystine and proline. Each molecule contains 10 glucosamine and 3 galactosamine residues. In females, LH is concerned with the ripening and rupturing of ovarian follicles, which later transform into corpus lutea. It also induces the development of interstitial cells of both the ovaries and the testes—a fact responsible for its nomenclature.

The secretion of LH is controlled by luteinizing hormone-releasing factor, LH-RF, a secretion from hypothalamus. The long-acting analogue of LH-RF has been found useful in the treatment of precocious puberty in females by Florence Comite et al (1983), the American researchers at the National Institute of Health. Puberty is initiated by pulsed nocturnal secretions of gonadotropins that result from the release of the hormone LH-RF by the hypothalamus gland in the brain. The administration of LH-RF analogue “initially stimulated but subsequently inhibited” the release of LH and FSH, the two sex hormones that initiate puberty.

C. Luteotropin or luteotrophic hormone, LTH. Because of its broad spectrum of effects on vertebrates in general, *luteotropin is the most versatile of all the adenohipophyseal hormones*. It is also the first anterior pituitary hormone to be obtained in pure form. This is also a peptide hormone with 198 amino acid residues and a molecular weight of about 23,500. It has 3 disulfide bonds between

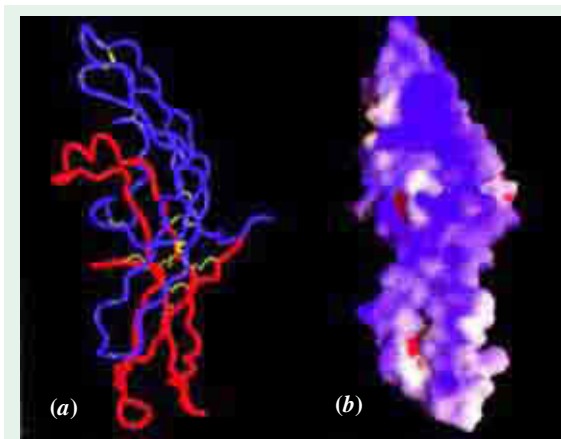


Fig. 31–35. The x-ray structure of human chorionic gonadotropin (hCG)

(a) A C_{α} diagram showing the α subunit in red and the β subunit in blue with disulfide linkages in yellow. The pseudo-twofold axis relating the two subunits is horizontal.

(b) The surface electrostatic potential of the hCG as viewed towards its receptor-binding surface. The surface is coloured according to its electrostatic potential, with the most positive regions dark blue and the most negative regions dark red. The view is related to that in Part a by a 60° rotation about the vertical axis.

[Courtesy : Hao Wu and Wayne Hendrickson]

cysteine residues at 4-11, 58-173 and 190-198 (Li *et al*, 1971). It differs from FSH and LH in that it contains no carbohydrate. It is thermolabile and is destroyed by tryptic digestion. In pure form, it has no growth-promoting, thyrotropic, diabetogenic, adrenotropic or gonadotropic activities. However, in association with estrogen, luteotropin promotes the growth of the mammary glands (mammogenesis) and also induces secretion of milk (lactation) at the time of child birth (parturition). Henceforth, this hormone is variously called as *prolactin*, PL or *lactogenic hormone or mammotrophic hormone*, MH. It also stimulates glucose uptake and lipogenesis. Along with androgens, it causes the development of secondary male sex characters. In rat, at least, prolactin also has gonadotropic activities in that it maintains functional corpora lutea in hypophysectomized animals. It also acts as an anabolic agent mimicking the effects of growth hormone, although it is less active in this respect. In pigeons, however, it stimulates enlargement of crop glands and formation of ‘crop milk’.

In fact, prolactin is credited with performing some more than 80 functions and it is for the same reason that it has been jocularly termed as a “*jack-of-all-trades*.” According to Nicoll and Bern (1971), these various functions of prolactin fall under 5 major categories : reproduction, osmoregulation, growth, integument and synergistic effect with the steroid hormones.

[N.B.]—A hormone chorionic gonadotropin, although of placental origin, resembles hypophyseal hormones in its biological effects. It was previously recognized as anterior pituitary like factor (APL factor). *Human chorionic gonadotropin, hCG* (Fig 31–35) is a glycoprotein with molecular weight of about 30,000. The carbohydrate moiety contains some 6 components, viz., D-galactose, D-mannose, *N*-acetylglu-cosamine, *N*-acetylgalactosa-mine, L-fucose and *N*-acetylneuraminic acid. Their sequence is not fully known. *N*-acetylneuraminic acid is essential to the biologic activity of this hormone. Apparently, all the common amino acids are present in the protein moiety, proline being especially high (about 20%).

As to its biological role, hCG factor supplements hypophysis in maintaining growth of the corpus luteum during pregnancy. This hormone, when administered, stimulates Leydig tissue and hence the male accessory organ.

The hormone appears sharply after pregnancy in the urine. This fact has become the basis for a pregnancy test known as *Aschheim-Zondek test*. This involves injecting urine or an alcoholic precipitate of urine from a woman into immature female rats. Urine from a pregnant woman containing this hormone will cause rupturing (hemorrhage) of ovarian follicles within 48 hours.

In another pregnancy test known as *Friedman test*, a virgin rabbit is used and the test urine is injected into an ear vein. After 24 hours, the ovaries are examined for ruptured or hemorrhagic follicles.]

4. Somatotrophin or somatotrophic hormone, STH or growth hormone, GH.

Somatotropin obtained from human hypophysis (Fig. 31–36) is a protein with molecular weight 27,000 (41,600 in pig) and an isoelectric point 4.9. It has 190 amino acids and consists of 2 disulfide bridges between adjacent cysteine residues at 53-164 and 181-188 (Niall, 1971 ; Li, 1972). The N-terminal and C-terminal residues are both phenylalanine.

Unlike other adenohipophyseal hormones, the various effects of somatotropin are not due to its influence on other endocrine glands. It acts rather directly upon various tissues to produce diverse effects. *It is, therefore, not a true tropic hormone*. The various metabolic activities particularly attributed to this hormone are listed below.

- (a) It affects the rate of skeletal growth and gain in body weight. In adult animals with closed epiphyses, SH stimulates chondrogenesis followed by ossification.

The name **anterior pituitary like factor** is, however, inaccurate because the hormone is not effective in hypophysectomized rats whereas the hypophyseal hormones are.

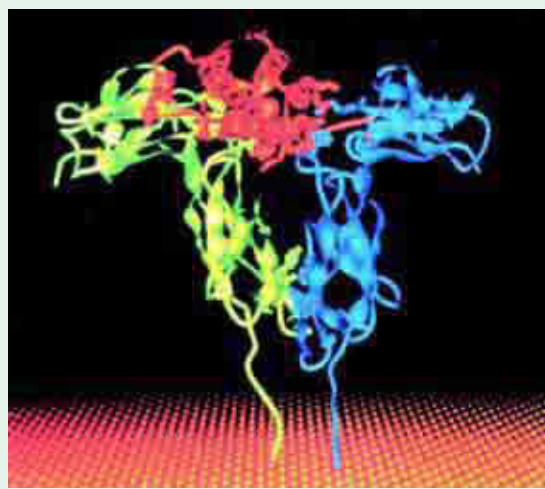


Fig. 31–36. The x-ray structure of human growth hormone (hGH) in complex with two molecules of its receptor’s extracellular domain (hGHbp)

The proteins are shown in ribbon form, with the two hGHbp molecules, which together bind one molecule of hGH, *green* and *blue* and with the hGH *red*. The side chains involved in intersubunit interactions are shown in *space-filling* form. The *yellow pebbled surface* represents the cell membrane, through which the C-terminal ends of the hGHbp molecules are shown penetrating as they do in the intact hGH receptor.

[Courtesy : Abraham de Vos and Anthony Kossiakoff, Genentech Inc., South San Francisco, California.]

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- (b) It causes abnormal increase in blood sugar by producing degenerative changes in islets of Langerhans (*diabetogenic effect*).
- (c) It stimulates the growth of the islets of Langerhans (*pancreatotropic effect*).
- (d) It controls the production of fat in the body and its deposition in the liver (*ketogenic effect*).
- (e) It prevents the fall of muscle glycogen in fasting and hypophysectomized animals.
- (f) It also stimulates milk secretion in cows and also the growth of mammary glands in hypophysectomized rats (*galactopoietic effect*).
- (g) STH is also known to cause adrenal enlargement (*corticotropic effect*). The adrenal enlargement can be greatly augmented by simultaneous treatment with low doses of thyroxine, thus indicating the participation of thyroid gland along with the hypophysis in this action.

It is now recognized that as people live to their 70s and beyond, the effect of declining hormones may contribute significantly to chronic, debilitating and costly illnesses. Among the well-known **attributes of ageing** that hormone loss may bring about are loss of muscle mass and strength, an increase of body fat, particularly fat around the abdomen, a weakening of the bones, a decline in immune responses and a general loss of energy. In 1990s, attention has now been diverted to the study of growth hormone and other trophic hormones, substances that promote growth or maintenance of tissues. They may, at least, have a promise for halting or reversing degenerative changes in bones, muscles, nerves and cartilage.

Pituitary diabetes— A general increase in the secretion of all the adenohipophyseal hormones causes elevated blood glucose concentration. This condition is clinically designated as pituitary diabetes. It, however, differs from diabetes mellitus, which results from insulin deficiency, in the following respects :

- I. In pituitary diabetes the rate of glucose utilization by the cells is only moderately depressed whereas in diabetes mellitus almost no utilization of glucose takes place.
- II. Many of the side effects that result from reduced carbohydrate metabolism in diabetes mellitus are, however, lacking in pituitary diabetes.

Pars Intermedia

In human beings, the intermediate lobe is poorly developed but is much larger and much more functional in some lower animals. It is, however, absent in certain mammals such as whale, Indian elephant and armadillo.

The intermediate lobe secretes **melanocyte** (or melanophore)-**stimulating hormones, MSH** or **melanotrophins**. These are also known as intermedins. In chicken and whales, where intermediate lobe is absent, MSH function is taken over by adenohipophyseal hormones. In mammals, MSH is a vestigial hormone. The structure of 2 types of intermedins, α -MSH and β -MSH is given in Fig. 31–37.

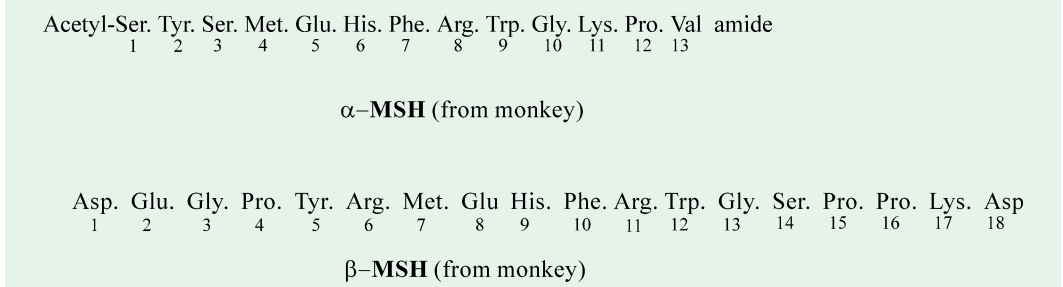


Fig. 31–36. Two types of intermedins

[Note that the structure of α -MSH is identical with the first 13 residues of ACTH except that in α -MSH terminal serine residue is acetylated.]

α -MSH contains 13 amino acid residues with N-terminal residue acylated and the C-terminal valine is in the amide form. β -MSH has been found to possess 18 amino acid residues with aspartic

acid residue at both N- and C-terminals. Thus, in α -type the terminal groups are blocked whereas the β -type has both the end groups free. *The α -MSH has greater biologic activity than β -MSH.*

MSH causes dispersal of black pigment (melanin) in melanophore cells of certain lower vertebrates. This leads to darkening of the skin. This hormone is particularly used in colour adaptation in lower vertebrates. The animal becomes pale on a light background and dark on a dark background. Its function in higher vertebrates including man is not known but it is, however, thought to participate in darkening the areas already pigmented.

Pars Nervosa or Neurohypophysis

The neurohypophysis develops from an outgrowth of the hypothalamus. This explains the presence of glial type cells in the gland. The posterior pituitary secretes 2 hormones : oxytocin and vasopressin. These were separated by Kamm and others.

1. Oxytocin (*ocy*^G = quick ; *tokos*^G = birth) or **pitocin**. It is a nonapeptide amide. A disulfide bond (—S—S—) is present to link the two cysteine residues present in the molecule (refer Fig. 9–15). Oxytocin preparations from man, cow and pig are identical. Besides mammals, it is also found in chondrichthyes, lung fishes, amphibians and aves.

Oxytocin stimulates the contraction of smooth muscles, *esp.*, those of uterus, thus facilitating childbirth. Commercial form of oxytocin is frequently used to induce 'labour'. In general, it also causes contraction of other smooth muscles like those of intestine, urinary bladder and the ducts of mammary glands resulting in milk ejection. It is, therefore, also called as *milk-let-down-ejection factor*. Oxytocin levels are increased by suckling which is necessary for the continued formation of milk by the breasts. Optimum milk secretion lasts for about 8 to 10 months after which it gradually falls and ultimately ceases.

2. Vasopressin or **pitressin**. It is also a cyclic nonapeptide amide and resembles oxytocin except that isoleucine is replaced by phenylalanine and leucine by arginine (Fig. 31–38). The hormone was synthesized, in 1953, by V. du Vigneaud and colleagues from U.S.A. and du Vigneaud received the Nobel Prize in 1955 for the first synthesis of a polypeptide hormone.

Oxytocin is often called oxytocin. However, the name oxytocin is preferred since its Greek origin (meaning quick birth) tallies with it and also it avoids confusion with the prefix *oxy* = oxygen-containing, as the hormone refers in no way to oxygen.

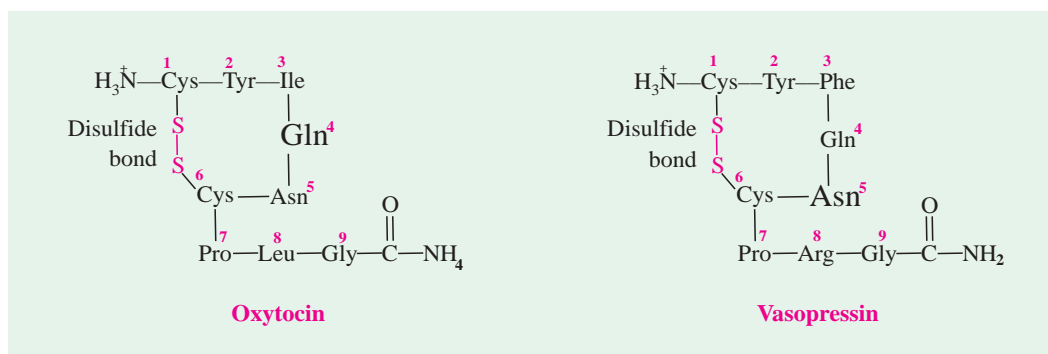


Fig. 31–38. Structure of the two neurohypophyseal hormones

Vasopressin (VP), obtained from pig, differs from that of human beings (shown above) in arginine being replaced by lysine at position 8. It is, therefore, better called as *lysine vasopressin* and that from human beings as *vasopressin*.

Vasopressin regulates many functions :

I. Circulatory or pressor action. Vasopressin causes a rise in blood pressure by contraction

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of peripheral blood vessels. It is, thus, a vasopressor substance and for this reason it is termed 'vasopressin'. It has been used in surgical shock as an adjuvant in elevating blood pressure. It may also be used at the time of delivery to overcome uterine inertia. The effect is similar to that caused by adrenalin. However, the rise in blood pressure caused by vasopressin lasts much longer than that caused by adrenalin which wears off in a few minutes.

II. Antidiuretic action. It brings about a reduction in the urine volume by causing renal tubules to withhold more water. Consequently, the urine passed is rich in sodium chloride, phosphate and total nitrogen. It was earlier thought that this antidiuretic effect was due to a different hormone called *antidiuretic hormone, ADH*. But it is now established that the two hormones (vasopressin and ADH) are one and the same. Vasopressin, therefore, finds use against persons suffering from **diabetes insipidus**, a disease characterized by excretion of large quantities of urine (polyuria) and a marked thirst (polydipsia). The urine specific gravity remains almost constant between 1.002 and 1.006. The urine output becomes 4 to 6 litres a day but can be sometimes as high as 12 to 15 litres a day, depending mainly on the amount of water taken by the patient. Furthermore, the rapid loss of fluid in the urine creates a constant thirst which keeps the water flushing throughout the body. The patient, thus, has a tendency to become dehydrated. But this tendency is quite well offset by the increased thirst. The disease may be controlled by administration of posterior pituitary extracts subcutaneously or even by nasal instillation.

The term '**insipidus**' (= tasteless) dates from the time when the only method of testing urine was to taste it after diluting, and in this condition the urine is tasteless.

Table 31–6. Summarizes the biological effects of the two neurohypophyseal hormones.

Table 31–6. Comparison of the biological effects of oxytocin and vasopressin

S. N.	Biological Effect	Oxytocin	Vasopressin
1.	Water diuresis	no effect	inhibits
2.	Blood pressure	slightly lowers	raises
3.	Coronary arteries	slightly dilates	constricts
4.	Intestinal contractions	?	stimulates
5.	Uterine contractions	stimulates	stimulates
6.	Ejection of milk	stimulates	slightly stimulates

Hypopituitarism. Insufficient secretion of pituitary hormones (or hypopituitarism) may occur as a result of pituitary tumours or atrophy of the gonad. Hypoactivity of this gland may lead to the following disorders :

1. **Dwarfism.** It refers to the arrested growth of the individuals (Fig 31–39). It is of 2 types :

- (a) Lorain type— short statured individuals with a head large in comparison to the rest of the body ; usually intelligent but unattractive.



Fig. 31–39. Two physiologic conditions arising from abnormal pituitary secretion. Here we see dwarfism and gigantism both.

Obesity is “that state in which the accumulation of reserve fat becomes so extreme that the functions of the organism are interfered with”. It can be quantitated by measuring skinfold thickness with calipers. Obesity may arise from either overeating or diminished utilization or a combination of both. Obesity results from a low basal metabolic rate (BMR) in obese and therefore, even with a normal intake of food, an excess of calorie is available. The BMR diminishes slightly as the individuals grow older but often the food consumption is not decreased proportionally. As a consequence, obesity may result. Obesity is usually due to an excess intake of food. Appetite may be influenced by a variety of factors such as psychologic disturbances; hypothalamic, pituitary, or other brain lesions; and hyperinsulinism. Obesity may also develop from an increase in number or in size of fat cells, adipocytes. Adipocytes increase in number when caloric intake is increased, especially in the gestational months and during the first year of life. The obese may become resistant to insulin, resulting in an increase in the levels of circulating insulin. Insulin decreases lipolysis and increases fat synthesis and uptake.

Obesity may become evident at any stage, but it appears most frequently in the first year of life, at 5 to 6 years of age, and during adolescence. The adiposity in the mammary regions of **boys** is often indicative of breast development and hence an embarrassing feature. The abdomen tends to be pendulous, and white or purple striae are often present. The external genitalia of boys appear disproportionately small but actually are most often of average size; the penis is often embedded in the pubic fat. Puberty may occur early, with the result that the ultimate height of the obese may be less than that of their slower-maturing peers. The development of external genitalia is normal in the majority of **girls**, and menarche is usually not delayed. The obesity of the extremities is usually greater in the upper arm and thigh and is sometimes limited to them. The hands may be relatively small and the fingers tapering. Obesity remains an enigma today as it has for many centuries – the earliest recorded case of human obesity dating back to the Willendorf Stone Age Venus of about 22,000 B.C.

(b) Fröhlich type—obesity and arrested sexual development ; men-tally below normal and usually lethargic.

2. **Panhypopituitarism.** It is caused because of the destruction of the gland, thus leading to cessation of all hypophyseal functions.

3. **Pituitary myxedema.** It is caused due to the lack of TSH and produces symptoms similar to those described for primary hypothyroidism.

Hyperpituitarism. It refers to the overproduction of hypophyseal hormones. Hypersecretion of this gland leads to **gigantism** during childhood or adolescence, *i.e.*, before closure of the epiphyses. The disease is characterized by overgrowth of the bones, especially at joints, leading to a tall individual with 2 to 2.5 M height. The limbs usually become disproportionately large.

In human adults with closed epiphyses, excessive secretion of pituitary hormones causes **acromegaly** (*acron*^G = extremity). The chief symptoms of this disease are (Fig. 30–40) :

1. consistent overgrowth of the bones of face, hands and feet (*acral* parts ; hence the term acromegaly) so that the patient often complains of having have to change globes and shoes frequently as they no longer fit.
2. protrusion of the lower jaw (prognathism). Overgrowth of the malar, frontal, and basal bones combines with prognathism to produce the coarse facial features called *acromegalic facies*.
3. bowing of the spine (kyphosis)
4. overgrowth of the body hair
5. thickening of the soft tissues of nose, lips and forehead
6. enlargement of the visceral organs such as lungs, heart, liver and spleen
7. increased sexual activity in the beginning which is ultimately followed by atrophy of the gonads. This leads to impotence in man and amenorrhea in woman.

A classical example of acromegaly is that of Akhenaton (Fig. 31–41), the Pharaoh who ruled Egypt in the years 1379–1362 BC. His predominant facial features strongly suggest that he suffered from acromegaly. Acromegalic persons usually have enlarged facial & chiral features (Fig. 30-42).

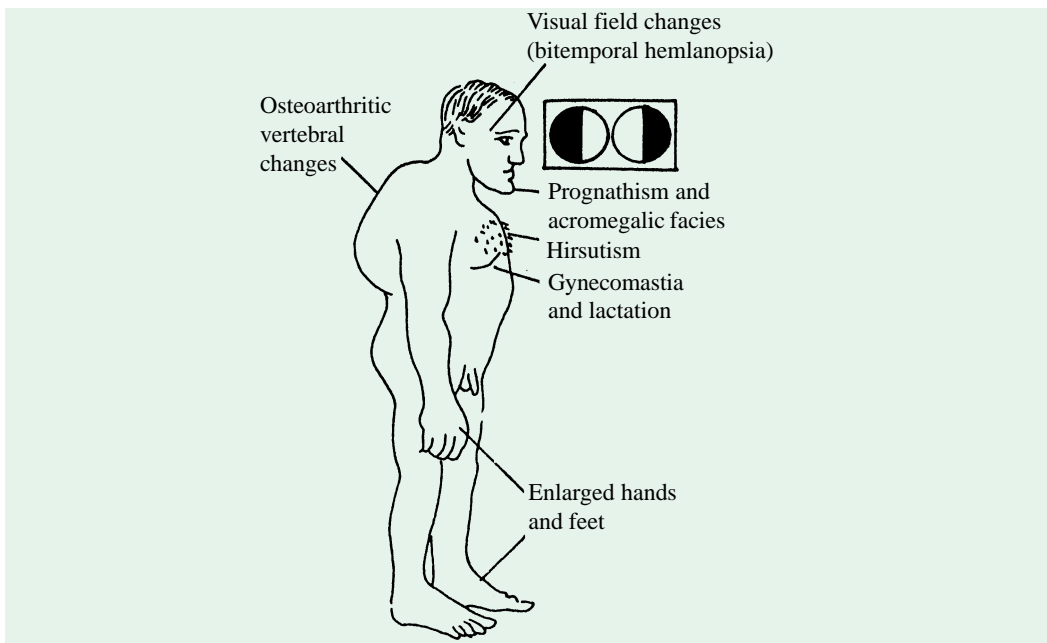


Fig. 31-40. Typical finding in a acromegaly



Fig. 31-40. The ancient carving of the Egyptian Pharaoh Akhenaton, who ruled from 1379-1362 B.C. His characteristic enlarged features strongly suggest that he suffered from acromegaly. It may be the oldest known case.

[Courtesy: Agyptisches Museum. Staatliche Museen Preussischer Kulturbesitz, Berlin, Germany]



Fig. 30-42. An acromegalic person

Sudden increases in the production of growth hormone after maturity produce growth in only certain body parts, such as those of the face and hands. The condition is called acromegaly.

Hypophysectomy. The effects of hypophysectomy (removal of hypophysis) appear to be almost entirely due to the loss of adenohypophysis. Removal of only the neurohypophysis exerts no striking dysfunctions. Hypophysectomy, in general, leads to:

1. gonadal atrophy in either sex
2. atrophy of the thyroid
3. atrophy of the adrenal cortex
4. loss of body tissue with some reversion to younger characters, *i.e.*, appearance of juvenile hair.

3. Hormone of the Parathyroid

Secretory gland. The parathyroids were first discovered by Sandström in 1880. In the human beings, there are usually four small parathyroid glands so closely associated with the thyroid gland that they remained undiscovered for some time. Each parathyroid gland is a reddish or brownish, oval body, measuring about 5—7 mm in length, 3—5 mm in width and 1—2 mm in thickness. The four glands together weigh only 0.1 to 0.2 gm. The glands have a macroscopic appearance of dark brown fat, therefore these are difficult to locate and hence often removed during thyroidectomy (removal of the thyroid). Of the four parathyroids, two lie embedded in the thyroid and are called as *internal parathyroids*; the other two lie close and behind the thyroid and are known as *external parathyroids*. There may be fewer than four or as many as eight parathyroids. The extra ones are scattered along the trachea and are called as accessory parathyroids. Occasionally, the parathyroids are located in the anterior mediastinum or, rarely, in the posterior mediastinum. The parathyroids are, however, lacking in the fishes.

Histologically, the parathyroid of the adult human being consists mainly of chief cells (= principal cells) and oxyphil cells (refer Fig. 31–43). The oxyphil cells are usually absent in young human beings. The chief cells are concerned with the secretion of the parathyroid hormone. The oxyphil cells are rich in mitochondria but lack glycogen. Their function is uncertain. They are regarded as probably aged chief cells that still secrete some hormones.

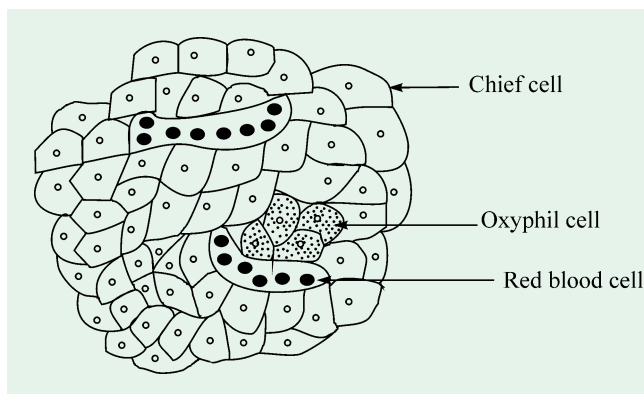


Fig. 31–43. Macroscopic structure of a parathyroid gland

Structure. Parathyroids secrete a hormone called parathyroid hormone (parathormone, PTH) or **Collip's hormone**. PTH has been isolated in pure form. It is a linear polypeptide consisting of 84 amino acid residues and has a molecular weight of about 7,000 to 8,500. Potts and others (1971) have, however, indicated that the physiologic activity of this hormone on both skeletal and renal tissues is contained within the first 34 amino acids from the N-terminal of the chain. As is also true for many other hormones (such as α -MSH and corticotropin), the PTH can be cleaved to form smaller but still active units. Oxidation inactivates the parathormone rapidly.

Functions. The principal sites of parathyroid action are bones, kidney and gastrointestinal tract. Following physiological functions are attributed to this hormone :

1. **Bone resorption**— It exerts a direct influence on the metabolism of bone, leading to an increased release of bone Ca^{2+} into the blood. The exact mechanism behind this phenomenon is not truly known. It has, however, been suggested that the hormone stimulates the production of citric acid in the bone tissues and an increased concentration of citrate ions leads to the removal of phosphate from calcium phosphate, the bone material. The bone is, thus, made soluble.

2. **Renal reabsorption of calcium**— In the kidney, parathormone affects renal tubular reabsorption of calcium and reabsorption or secretion of phosphate. It increases the elimination of calcium and phosphorus in the urine.

It is interesting to note that the secretion of this hormone is controlled by Ca^{2+} ion concentration of the blood itself. As the Ca^{2+} ion concentration increases, PTH secretion decreases tending to preserve the original condition. This affords an excellent example of feedback mechanism of metabolic control.

3. **Increase in osteoelastic activity**— Parathormone increases osteoelastic activity with augmented growth of the connective tissue.

4. **Calcium homeostasis**— An optimum Ca^{2+} concentration is necessary for various functions

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of the body, *viz.*, normal transmission of impulses, the contraction of the muscles, the formation of the bones, the coagulation of the blood etc.

Henceforth, a precise endocrine mechanism has been evolved so as to ensure a stable concentration of this ion. The three hormones of importance in this process of calcium homeostasis, as it is called, are vitamin D, PTH and calcitonin. The vitamin D can be classified as a hormone since it is manufactured in the skin (which is an organ) which it is exposed to light. An interesting finding is the observation that in the presence of vitamin D, the parathormone stimulates the release of calcium accumulated by mitochondria.

Hypoparathyroidism. Undersecretion of PTH causes a decrease in Ca contents of the blood from the normal 10 mg per 100 ml to 7 mg per 100 ml (hypocalcemia) which leads to excessive contraction of the muscles (convulsions). In fact, convulsions occur when the calcium is further decreased to 4 mg per 100 ml of plasma. As the calcium decreases in the blood, there is a decrease in the urine. However, during this period, the phosphorus in plasma increases from a normal 5 mg per

100 ml to 9 mg per 100 ml and even higher (hyperphosphotemia). These changes develop into a fatal disease called **muscular twitchings** or **tetany**. It is characterized by locking up of the jaw, rapid breathing, increased heart beat, rise in temperature and ultimately death due to asphyxia. The signs of tetany in man include **Chvostek's sign**, a quick contraction of the ipsilateral facial muscles elicited by tapping over the facial nerve at the angle of the jaw; and **Trousseau's sign**, a spasm of the muscles of the upper extremity that causes flexion of the wrist and thumb with extension of the fingers (Fig. 31–44). Tetany can be relieved either by the administration of a soluble calcium salt or of PTH.

Hyperparathyroidism. An increase in PTH production is usually due to a tumour of the gland (parathyroid adenoma). Oversecretion of PTH in man results in a cystic bone disease variously called

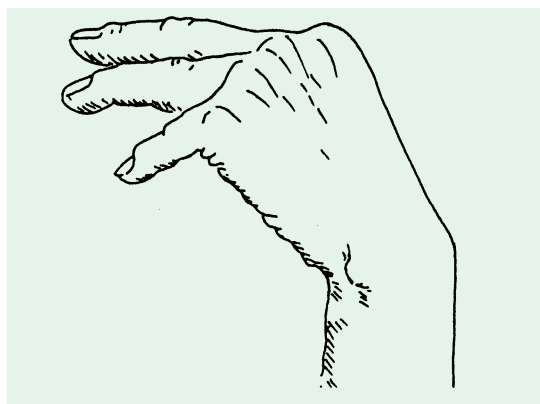


Fig. 31–44. Position of the hand in hypocalcemic (Trousseau's sign)

(After Aub. Drawn from a photograph in Adams : *Physical Diagnosis*, 14th edition, Williams and Wilkins, 1958)

CLINICAL IMPLICATIONS

Neurofibromatosis is one of the most common autosomal dominant genetic disorders. It occurs roughly in 1 of 4,000 live births. It is seen equally in every racial and ethnic group throughout the world. There is virtually a complete dominant penetrance of the gene localized at the centromeric region of chromosome 17. The gene responsible for the disease, isolated in 1990, is huge and actually includes 3 smaller genes. This is only the second time that *nested genes* have been found in humans. This is a tumour-suppressor gene active in controlling cell division. When it mutates, a benign tumour develops. At birth or later, the affected individual may have 6 or more large tan spots on the skin. Such spots may grow in size and number and become darker. Small benign tumours (or lumps), called *neurofibromas*, may occur under the skin or elsewhere. Neurofibromas are made up of nerve cells and other cell types. This genetic disorder shows *variable expressivity*. In most cases, the symptoms are mild and patients live a normal life. In some cases, however, the effects are severe. Skeletal deformities, including a large head, become evident; eye and ear tumours can lead to blindness and hearing loss. Many children with neurofibromatosis have learning disabilities and are hyperactive. In the most extreme form of neurofibromatosis, the connective tissue of the bones and the lining of the nerves produce disfiguring tumorous growths. A devastating expression of the gene occurred in Joseph Merrick, a severely deformed late 19th century Londoner, whose tragic life became the subject of a contemporary play and movie, *The Elephant Man*. However, researchers today believe that Merrick actually suffered from a much rare disorder called *Proteus syndrome*.

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4. Pancreozymin, PZ. It is another polypeptide hormone elaborated by the intestinal mucosa. Along with secretin, it functions to stimulate the release of pancreatic juice, which is rich in enzymes or their zymogens as well as in bicarbonate. The enzymes or zymogens include trypsinogen, lipase, carboxypeptidase etc. The release of pancreozymin is believed to be brought about in the presence of any one of a variety of compounds such as peptone, casein, dextrin, maltose, lactose, saline water and also even distilled water. Pancreozymin has been obtained in pure form. It is thermostable and is not destroyed by acid but it is destroyed by alkali. Like cholecystokinin, it also contains 33 amino acid residues. The 5 C-terminal amino acid residues are the same as those of gastrin and cholecystokinin. Jorpes (1968) believes that the two gastrointestinal hormones, cholecystokinin and pancreozymin are identical. They are now thought to be a single factor and represented as CCK-PZ.

5. Enterogastrone. It is present in duodenal mucosa and is secreted from it only when fat (derived from food) reaches the duodenum. The hormone reaches the stomach where it inhibits gastric secretion and motility of the stomach. There is secretion of lesser volume of juice with a lower concentration of HCl and a smaller amount of pepsin. The effect is to permit digestion to be more completely accomplished.

6. Enterokrinin. It is also isolated from intestinal mucosa and controls the intestinal secretion. It does not influence pancreatic secretion but may increase the volume as well as the enzyme concentrations of succus entericus. It is distinct from secretin in that it stimulates the secretion of both fluid and enzymes by the intestinal mucosa. It is also proteinaceous in nature.

7. Hepatocrinin. It is related to enterokrinin and is believed to stimulate the secretion of dilute, low-salt type of bile juice.

8. Duicrinin. It controls the secretion of Brunner's glands which are located in the submucosa of the upper duodenum.

9. Villikinin. It is secreted by the intestinal mucosa. It stimulates movements of the intestinal villi and hence accelerates intestinal absorption.

10. Parotin. Ito (1953) has claimed that the salivary glands elaborate parotin, a protein hormone. It has multifarious effects : stimulates calcification of the teeth, decreases the calcium content of the blood and increases the phosphorus level of the serum.

Although evidences exist to indicate the presence of all the humoral agents mentioned above, yet gastrin, secretin and cholecystokinin are the only three gastrointestinal hormones which have been fully established with regard to their biochemical and physiological behaviour.

AMINO ACID DERIVATIVES

1. Thyroidal Hormones

Secretory gland. *The thyroid is the largest endocrine gland in the body.* It was first described by Wharton in 1659 who gave it the descriptive name, thyroid because of its resemblance to a shield (*thyreoides*^G = shield-shaped). In man, the gland consists of two lobes on either side of and anterior to the trachea just below the larynx. The two lobes are connected across the ventral surface of the trachea with a narrow bridge called isthmus, making the entire gland more or less H-shaped in appearance (refer Fig. 31–48). The isthmus crosses in front of the 2nd, 3rd and 4th tracheal ring. In the adult, the gland weighs about 25 to 30 gm. The thyroid gland receives blood flow about 5 times its own weight per minute. It has a blood supply as rich as that of any other area of the body barring probably the adrenal cortex. The thyroid is presumed to be homologous with the endostyle of the early vertebrates.

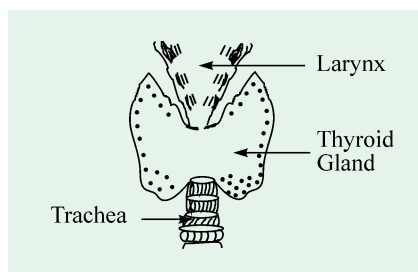


Fig. 31–48. The thyroid in man
(After D. Marsland, 1964)

Histologically, the thyroid gland (refer Fig. 31–49) is composed of a large number of tiny closed vesicles called *follicles*, 150 to 300 microns in diameter. The follicles are held together by areolar tissue and are surrounded by a rich network of capillaries. Each follicle is lined with a single peripheral layer of columnar or cuboidal *epithelioid cells* that secrete into the interior of the cells. Its lumen is filled with a secretory substance called colloid. The major constituent of

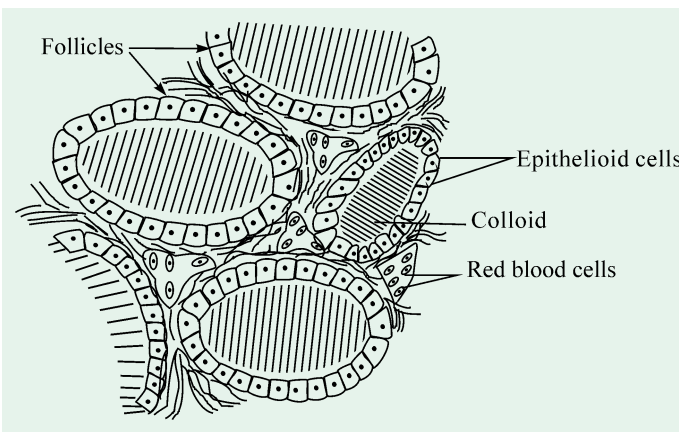


Fig. 31–49. Histologic structure of thyroid gland

colloid is a large protein called thyroglobulin, which contains the thyroid hormones. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can perform its function in the body. The thyroid gland is, thus, unique amongst the endocrine glands in that *it stores its hormone as a colloid in small vesicles in the gland*. The other endocrine glands, however, store their hormones in the cells themselves.

As age advances, the thyroid activity tapers off. That's why elderly persons feel colder, since their body does not produce sufficient heat.

Structure. Thyroid contains large amounts of elemental iodine which is bound to a protein named iodothyroglobulin or simply thyroglobulin. It is a glycoprotein with a molecular weight of about 650,000 and iodine content from 0.5 to 1.0%. This protein represents the storage form of the hormone in the gland.

Evidences available at present indicate that thyroglobulin is hydrolyzed, in the presence of thyrotropin, to release thyroxine (= 3, 5, 3',5'-tetraiodothyronine) in the blood (Fig. 31–50). The release of thyrotropin is, in turn, controlled by the level of thyroxine in the blood.

Thyroxine is one of the earliest recognized hormones. It was so named and isolated first by Kendall in 1915. Harington and Barger (1925) established its chemical formula. It is an iodine-containing aromatic amino acid and closely resembles tyrosine in structure. Diiodotyrosine is believed to be the precursor of thyroxine.

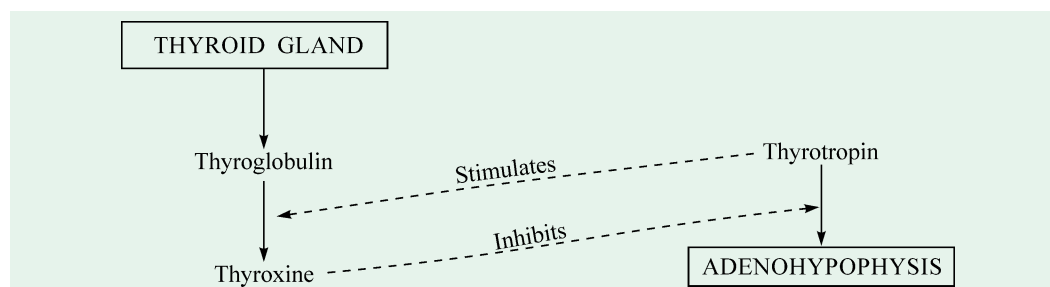


Fig. 31–50. Interdependence of thyroxine and thyrotropin

Besides thyroxine, 3,5,3'-triiodothyronine is also produced from enzymatic hydrolysis of thyroglobulin. It is 5 to 10 times more potent in biologic activity than thyroxine. This may, possibly, be due to the fact that triiodothyronine is bound loosely by serum proteins and hence diffuses much more rapidly into the tissues. It is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine. The structure of triiodothyronine and tetraiodothyronine is given in Fig. 31–51.

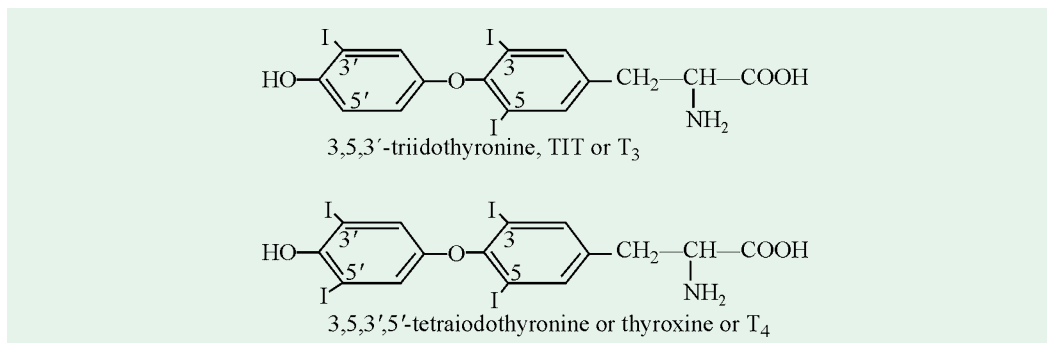


Fig. 31-51. Thyroidal hormone

Functions. Thyroid hormones have widespread effects on the ossification of cartilage, the growth of teeth, the contours of the face and the proportions of the body. They also carry out following functions :

1. They bring about deamination reactions in the liver.
2. They also carry on deiodination in the extrahepatic tissues.
3. These influence oxidative phosphorylation by altering the permeability of the mitochondrial membrane.
4. Their presence accelerates metamorphosis in amphibians. This is so a sensitive test that tadpole has been widely used for the assay of the potency of these hormones.
5. These may increase the level of cytochrome *c* in the tissues.

It is, thus, apparent that these hormones affect the general metabolism, regardless of the nature of its specific activity. It is for this reason that the thyroid gland has rightly been called as the '*pace setter*' of the endocrine system.

Thyroid inhibitors or goitrogens. Certain substances act as antithyroid agents by inhibiting the production of thyroxine. This is explained by the fact that these compounds prevent the oxidation of iodide, which means that the iodine cannot be used for the synthesis of thyroxine. Some important thyroid inhibitors (Fig. 31-52) are 6-propyl-2-thiouracil, 2-thiouracil, thiourea and the sulfonamides. Thiouracil itself is relatively toxic ; less so are propylthiouracil and thiourea. Of these, propylthiouracil has been used most extensively. It is 3 to 5 times more active than thiouracil. The antithyroid drugs or the goitrogens, as they are also called, are also found in common foods such as cabbage, turnips, spinach, peas etc.

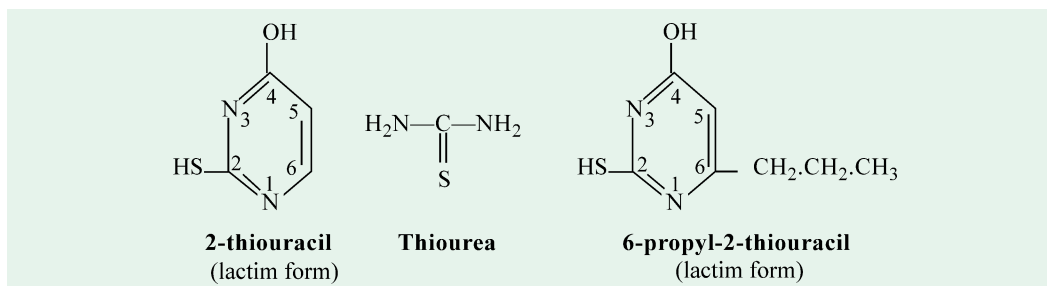


Fig. 31-52. Some thyroid inhibitors

Hypothyroidism. Underactivity of the thyroid may result from two causes : a degeneration of thyroid cells or a lack of sufficient iodide in the diet. The disease that results from thyroid cell degeneration is cretinism in children and myxedema in adults. **Cretinism** (=feeble-mindedness) is characterized by dwarfism and mental suppression. The cretinic children have infantile features

(Fig. 31–53). They possess a large head and an apathetic face ; their teeth erupt late and the speech is retarded. Early treatment with thyroid-active compounds partially prevents this disease.

Myxedema is characterized by an abnormally low basal metabolic rate (BMR). In it, the adults become mentally lethargic and possess thick puffy skin (edema) and dry hair. The patient shows bagginess under the eyes and swelling of the face. The hair thin on the eyebrows and scalp. As there is deposition of semi-fluid material under the skin, the name myxedema (*myxa*^G = mucus; *oidema*^G = swelling) is given to this condition. Myxedema also responds well to administration of thyroid-active compounds. *Myxedema is less severe than cretinism.*

Lack of sufficient iodide in the diet results in thyroid gland enlargement, known as **simple goiter**. It is also associated with a low BMR. This type of goiter is also known as **endemic goiter**, since it is prevalent in areas where the soil and drinking water lack iodide. Simple goiter was once fairly common in some mountainous parts of Switzerland and the United States, where soil and water are deficient in iodine compounds.

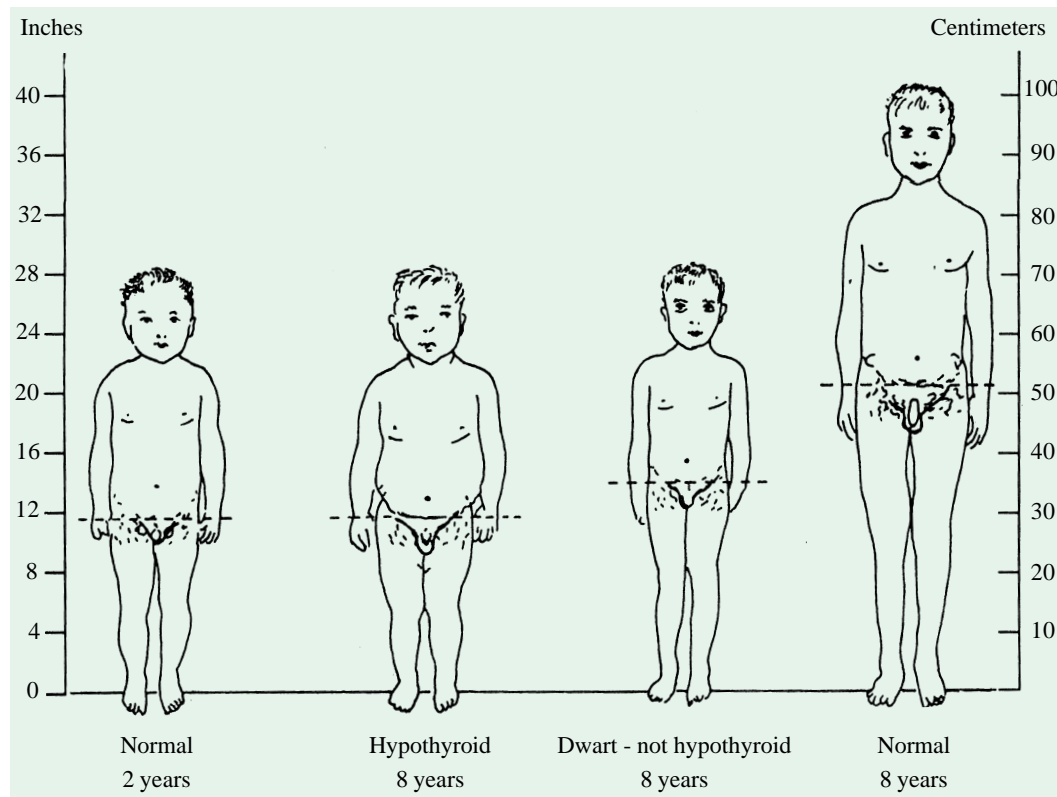


Fig. 31–53. Normal and abnormal growth

Hypothyroid dwarfs retain their infantile proportions, whereas dwarfs of the constitutional type and of the hypopituitary type have proportions characteristics of their chronologic age.

(Adapted from Wilkins : *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence*, 34d ed., Thomas, 1966)

Hyperthyroidism or Thyrotoxicosis. Abnormally high activity of this gland may occur due to either oversecretion of the gland or an increase in size of the gland. Swelling of the gland results in an **exophthalmic goiter** (Fig. 31–54), characterized by protrusion of the eye balls. In it, the BMR increases considerably above the normal figures ; 80% above normal is not unusual. Consequently, appetite is increased in hyperthyroid individuals. In spite of this, they lose weight and often feel hot because of the increased heat production. Their pulse rate is also increased and excessive sweating occurs. Other

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symptoms of this disease are dilated pupils, mental excitement, irritability and cardiac dilatation. Hyperthyroid individuals are, in general, characterized by an above-normal rate of many physiological activities. The clinical syndrome is generally termed **Graves' disease**, after its discoverer Robert James Graves. **Basedow's disease** and **thyrotoxic exophthalmos** are other names of this disease. Not surprisingly, people with hyperactive thyroids (*i.e.*, with Graves' disease), thus, show many symptoms opposite those in hypothyroidism.

Hyperthyroidism can be cured by surgical removal of the thyroid (thyroidectomy), treatment with x-rays, injection of radioactive iodide (^{131}I) or by treating with antithyroid drugs or with agents like thiocyanate or perchlorate which compete with iodide for the uptake mechanism. Propylthiouracil is being particularly used against the Graves' disease.



Fig. 31–54. Graves' disease

Note the goitre and exophthalmos.

(Courtesy of PH Forsham)

Thyrocalcitonin or Calcitonin

A quite different type of hormone which has effects of decreasing calcium ion concentration in the blood has been discovered by Copp et al in 1961 as an impurity in the commercial parathyroid extracts. They termed this hypocalcemic factor as calcitonin (CT). *Later researches revealed that this factor originated in the thyroid, rather than in the parathyroids.* This substance was, henceforth, also named as thyrocalcitonin (TCT). It is secreted by the parafollicular cells or C-cells in the interstitial tissue between the follicles of the human thyroid gland. Later, it was discovered that CT is secreted by the ultimobranchial glands of fishes, amphibians, reptiles and birds. In mammals, however, these glands do not exist as such but have become incorporated into either the parathyroids or the thyroid. The parafollicular cells of human thyroid glands are remnants of the ultimobranchial glands of lower animals.

Thyrocalcitonin (Fig. 31–55) is a large, unbranched polypeptide containing 32 amino acids and has a molecular weight of about 3,600. It is unique in having no isoleucine and lysine residues. Its amino acid sequence has been determined by Foster in 1968.

Thyrocalcitonin acts by causing a transfer of calcium from blood into bone either by increasing calcification of the bones or by diminishing decalcification or by both processes. In other words, it

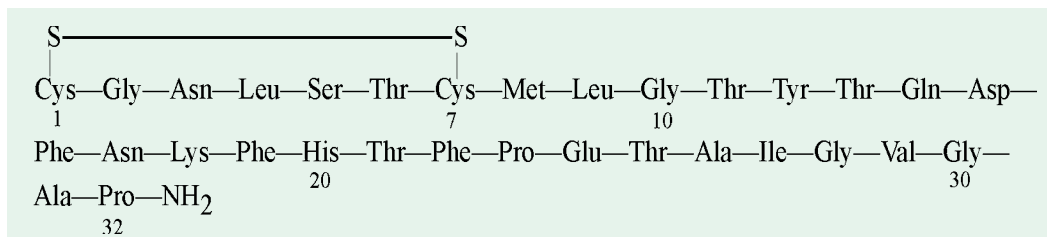


Fig. 31-55. Human calcitonin

Note the presence of an intrachain disulfide bond between two cysteinyl residues placed at positions No. 1 and No. 7.

rapidly inhibits calcium withdrawal from bones. This characteristic property, however, promises it to be a therapeutic agent for the treatment of certain types of bone diseases. This action of thyrocalcitonin is counterbalanced by the hypercalcemic hormone, the parathormone which is secreted by the parathyroids. *TCT, thus, aids in the maintenance of calcium homeostasis.*]

Effect of thyroid hormones on the gonads:

For the normal sexual activity to occur, the secretion of thyroidal hormones needs to be almost normal—neither too little nor too more. In the male, deficiency of the thyroid hormones may cause complete loss of libido whereas their hypersecretion, on the contrary, leads to impotence. Similarly, in the female also, the lack of thyroid hormones leads to greatly diminished libido and often results in menstrual bleeding which may be excessive (menorrhagia) and frequent (polymenorrhea). A hyperthyroid female exhibits greatly reduced bleeding (oligomenorrhea) and sometimes, amenorrhea.

2. Adrenal Medullary Hormones

As already stated, the adrenal medulla forms the central core of adrenal gland and originates from the neural canal. It is composed of densely packed polyhedral cells containing chromaffin granules. It is highly vascular and receives 6—7 ml of blood per gram of tissue per minute. The chromaffin granules store large quantities of adrenal medullary hormones.

Adrenalin and noradrenalin are also spelt as adrenaline and noradrenaline respectively (J.H. Green, 1978)

Structure. Adrenal medulla, whose secretion is under nervous control, produces two hormones (Fig. 31-56): (a) epinephrine or adrenalin ($C_9H_{13}O_3N$) and (b) norepinephrine or noradrenalin ($C_8H_{11}O_3N$). *Epinephrine was the first hormone to be isolated in the crystalline form.* The isolation was, however, done by Abel. It has been produced synthetically by Stoltz. Chemically, these two hormones are catecholamines (= dihydroxy-phenylamines) and are closely related to tyrosine and phenylalanine. Norepinephrine[†], however, differs from epinephrine structurally in having a hydrogen atom in place of the methyl group. The commonly available epinephrine, therefore, is a mixture of these two hormones (usually 10—20% norepinephrine) and its effects are a resultant of the combined actions of these two hormones.

The word 'nor' in norepinephrine (and noradrenalin) was originally coined to indicate nitrogen (N) without (O-Ohne) a radical (R), in this case a methyl group

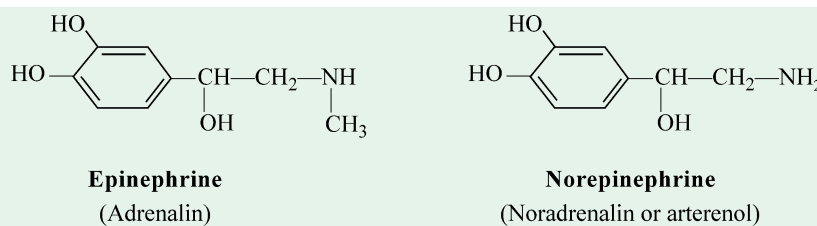


Fig. 31-56. Adrenal medullary hormones

Since these hormones possess an asymmetric carbon atom, two stereoisomers are possible for each one of them. The naturally-occurring epinephrine is the L-isomer and is levorotatory. It is 15 times

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more active than the D-form. Similarly, the natural D(-) form of norepinephrine is about 20 times more potent than the unnatural isomer. Their relative proportion in the adrenal medulla differs from species to species (refer Table 31-7).

Table 31-7. Percentage composition of the two adrenal medullary hormones in various organisms

S.N.	Organism	Epinephrine (Adrenalin)	Norepinephrine (Noradrenalin)
1.	Man	75-90	25-10
2.	Cat	50	50
3.	Whale	10	90

Functions. In general, the adrenal medullary hormones reinforce the functions performed by the sympathetic nervous system. Although both these hormones exert similar effects in regulating carbohydrate metabolism and blood pressure, yet epinephrine is more closely related to carbohydrate metabolism and norepinephrine to blood pressure.

Epinephrine conducts a wide variety of functions, which are as follows :

1. It promotes glycogenolysis in muscles and liver, resulting in an increase of blood glucose level and an increased lactic acid formation in muscles. These changes are then followed by an increase in oxygen consumption.
2. It causes an increase in blood pressure because of arteriolar vasoconstriction of the skin and splanchnic vessels.
3. It brings about an increase in the heart rate and in the cardiac output.
4. It causes dilation of vessels (= vasodilation) of skeletal muscles, corona and the viscera. This results in an increase of blood flow in these areas.
5. It relaxes the muscles of gastrointestinal tract and bronchials of the lungs but causes contraction of the pyloric and ileocecal sphincter muscles.
6. It also serves in cases of emergency. Under emotional stress, fear or anger, it is secreted in the blood stream and the blood is shifted from the viscera to the brain and the muscles so that the individual becomes ready for fight. It is for this reason that the adrenals are frequently referred to as the '*emergency glands*' or the '*glands of flight, fright and fight*' and the two adrenal medullary hormones as '**emergency hormones**'.

Norepinephrine, on the other hand, does not relax bronchiolar muscles and has little effect on cardiac output. It augments both systolic and diastolic blood pressure.

The physiological activities performed by these two hormones have been compared in Table 31-7.

Table 31-7. Comparison of the effects of intravenous infusion of epinephrine and norepinephrine

S.N.	Physiological Activities	Epinephrine* (Adrenalin)	Norepinephrine (Noradrenalin)
1.	Heart rate	+	-
2.	Cardiac output	+++	-, 0
3.	Systolic blood pressure	+++	+++
4.	Diastolic blood pressure	+, -, 0	++
5.	Total peripheral resistance	-	++
6.	Blood glucose	+++	+, 0
7.	Blood lactate	+++	+, 0
8.	Central nervous system action	-	0

* + = increase ; - = decrease ; 0 = no change.

(Modified from Goldenberg, 1951)

Adrenal demedullation. Despite the varied and definite physiologic effects of its characteristic hormones, the adrenal medulla does not appear to be essential to life. Hence, removal of only the medullary portion of the adrenal gland leads to no specific physiologic disorder. This is because the autonomous nervous system may take over in its absence. Consequently, the exact importance of the adrenal medulla is really undetermined. However, certain tumours of the medullary cells result in **pheochromocytoma**, characterized by hypertension and ultimately leading to death due to coronary insufficiency and pulmonary edema. Treatment is to remove the tumour surgically.

PARAHORMONES OR TISSUE HORMONES

In addition to the hormones discussed in the preceding pages, a number of others have been found to possess hormonal properties. These compounds are effective at low concentrations; unlike global hormones, they are not transported between tissues in the blood, but act on the tissue in which they are produced. They are, hence, also called as **tissue hormones**. They are at best local hormones because they are short-lived and are *paracrine* rather than endocrine in nature, but they fit the definition of hormone. They alter the activities of the cells in which they are synthesized and of adjoining cells. The nature of these effects may vary from one type of cell to another, in contrast with the more uniform actions of global hormones such as insulin or glucagon. Four such hormones (or groups of hormones), whose hormonal function has been established, are : *melatonin*, *renal hormones*, *eicosanoids* and *opiate peptides*.

1. Pineal Hormone or Melatonin

Secretory gland : The pineal gland or epiphysis (*epi*^G = upon ; *phyein*^G = to grow) is a tiny conical or pine-like organ (hence its nomenclature, pineal) on the dorsal side of brain in vertebrates, lying deep in the groove between the cerebellum and cerebral hemispheres. The gland was long associated with the folklore of a mysterious “third eye”. As the gland works round the clock, Bruce Fellman (1987) calls this as a ‘*clockwork gland*’. Pineal has a back-dated history. Herophilus (4th century BC) called this as the ‘**sphincter of thought**’ the mind’s valve. Rene Descartes, a 17th century French physiologist called it as ‘**the seat of the rational soul**’. Scientists of the early 20th century, wearied by a vain search for the gland’s function, cast it as a neurological vestige, an appendix of the brain. The pineal, however, was not easily relegated to the cerebral scrap heap. In the early 1960s Richard Wurtman of the Massachusetts Institute of Technology (MIT), USA, aptly coined a phrase to describe the gland’s function, “**a neurological transducer**” : a system that converts a nerve-type signal—one set off by dark and light—into an endocrine signal—that of a hormone whose levels rise and fall in the bloodstream.

Nearly all modern fish, amphibians reptiles, birds and mammals have a pineal. Even the few exceptions—notably alligators crocodiles and armadillos—have cells that act like the gland. And the organ itself has occupied most vertebrates’ skulls since the first backboned creatures joined the earth’s fossil record 500 million years ago. A structure as this ubiquitous and ancient is surely not just going along for the evolutionary ride. In man, this gland is very well developed in children and shrinks after the 7th year and is reduced to a little knot after puberty. It weighs less than a button. Many functions have been attributed to this gland but they, however, remain to be verified.

Structure. Pineal secretes a hormone called **melatonin** which inhibits the secretion of an adenohypophyseal hormone called luteinizing hormone. Melatonin is synthesized (Fig. 31–57) from its precursor, *serotonin* under the influence of two enzymes, N-acetyltransferase (NAT) and hydroxyindole-o-methyltransferase (HIOMT) which are present in rich quantity in the pineal gland. Serotonin was first isolated and crystallized by Page and others in 1948. In fact, like the clockwork, the pineal manufactures melatonin only in the night. However, during daytime, it does not sit idle and converts the amino acid tryptophan (Trp) into serotonin which accumulates and is stored in an inactive form until night. Neurotransmitters (such as norepinephrine) are released by the nerve cells connected

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to the pineal and cause increased concentration in the gland of the enzymes NAT and HIOMT. These enzymes convert serotonin into melatonin which then flows into the bloodstream. Thus, exposure to light slows while exposure to darkness stimulates the production of melatonin in the pineal gland.

David Klein argues that the pineal is a slave and it is under the control of a master clock. The master clock is a concentration of specialized nerve cells found in the hypothalamus, close to where the optic nerve crosses. Called the suprachiasmatic nuclei (SCN), this structure was also identified late, like the pineal gland but its function was a mystery. Klein has found that the SCN turns melatonin production on and off in the pineal by directing the nightly increase in NAT.

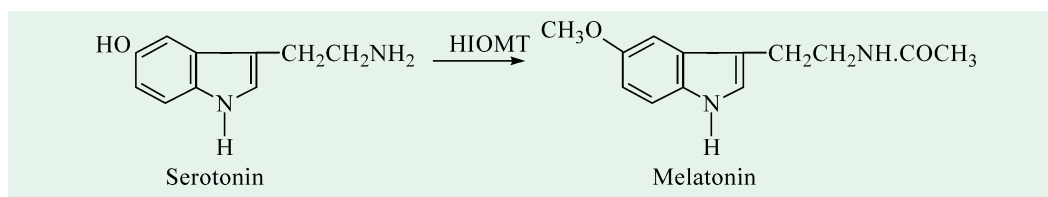


Fig. 31-57. Synthesis of melatonin

Functions. In humans, the gland's rhythm may affect the sleep cycle. Lieberman and Vollrath demonstrated that melatonin makes people drowsy. Hence, nowadays melatonin is being consumed as a sleep aide by insomniacs and people suffering from jet-lag, and also by those having trouble in adaptation to work at odd hours. The hormone is also being used for prevention of cancer and for strengthening the immune system. This '*miracle hormone*' keeps a person using it, away from growing old. As melatonin production diminishes naturally with age, it has been linked to the onset of puberty. Studies have also indicated that melatonin may regulate menstrual cycles in women and sperm production in men.

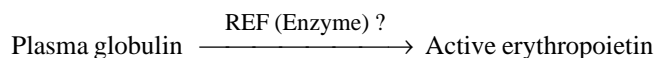
The removal of pineal gland (pinealectomy) in animals causes the gonads to regress. Many animals tie their breeding activities to the seasons, but after a pinealectomy they suffer from reproductive asynchrony, losing touch with nature's calendar. Birds also abandon daily activity rhythms, some eventually losing the urge to migrate.

2. Renal Hormones

The kidney secretes two hormones, erythropoietin and renin.

Erythropoietin or erythrocyte stimulating factor, ESF. It is secreted by the kidney. Its secretion is stimulated by tissue anoxia and also by androgenic hormones and cobalt. In fact, erythropoietin is secreted as an inactive protein called renal erythropoietin factor (REF) which is enzyme like in behaviour. The REF converts a plasma globulin to the active erythropoietin.

Erythropoietin is also spelt as erythropoetin (W.S. Hoar, 1975).



Erythropoietin has been prepared from the plasma of anemic sheep and also from the urine of anemic human beings. It is a glycoprotein with 8-12% total hexose and has a molecular weight of about 60,000. Its molecule contains all the common amino acids except methionine. Its activity is much retarded by proteolytic enzymes and also by the antibiotic actinomycin-D.

Erythropoietin stimulates the differentiation of the stem cell (hemohistioblast) of the bone marrow into the erythroid series, increasing the numbers of proerythroblasts in the bone marrow. This is followed by increases in other nucleated erythrocytes and finally, by increases in reticulocytes (erythrocyte precursor cells) and mature erythrocytes, in the peripheral circulation. Recent studies indicate that the earliest effect of erythropoietin is stimulation of the synthesis of a very large RNA (150 s) by bone marrow cells.

Renin. It catalyzes the synthesis of angiotensins which cause vasoconstriction in the kidneys, thereby causing electrolyte and water retention in the body. This system has been referred to as the *renin-angiotensin system*. An increase in the renal pressure and the levels of plasma Na^+ and angiotensins cause a decrease in renin production.

3. Eicosanoid Hormones

A. Structure and Metabolic Roles

Eicosanoid hormones (or simply eicosanoids) are fatty acid derivatives with a variety of extremely potent hormonelike actions on various tissues of vertebrates. Eicosanoids, in general, are known to be involved in reproductive function ; in the inflammation, fever and pain ; in the formation of blood clots and the regulation of blood pressure ; in gastric acid secretion ; and in a variety of other human processes.

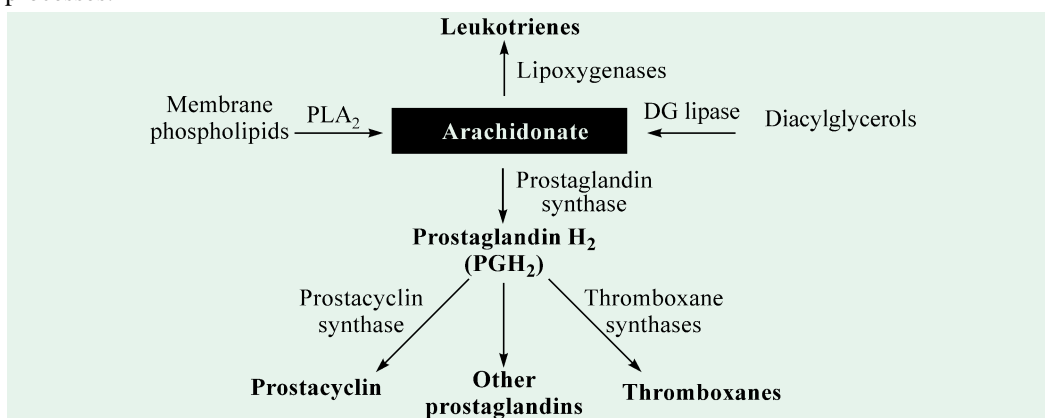


Fig. 31–58. Arachidonic acid and some of its eicosanoid derivatives

In response to certain hormonal signals, *phospholipase A₂* releases arachidonic acid (arachidonate at pH 7) from membrane phospholipids. Arachidonic acid then serves as a precursor of various eicosanoids. *Prostaglandin synthase* catalyzes the first step in a pathway leading to prostaglandins, prostacyclins and thromboxanes. *Lipoxygenase* catalyzes the initial step in a pathway leading to leukotrienes.

Eicosanoids are all derived from 20-carbon polyunsaturated fatty acid, **arachidonic acid** (20 : 4; 5, 8, 11, 14), from which they take their general name (*eikosi*^G = twenty). There are 3 classes of eicosanoids (or the *signal molecules*, as they are also called) : prostaglandins, prostacyclins and thromboxanes, and leukotrienes (Fig. 31–58).

Prostaglandins

Kurzrok and Lieb (1930), for the first time, observed that the human semen is able to bring about strong muscular contraction or relaxation when placed in the uterus. This is due to the presence in the semen of a number of structurally-related compounds collectively termed prostaglandins. The name prostaglandin

ULF SVANTE VON EULER (LT, 1905-1983)



Von Euler was born in Stockholm and received an M.D. from the Karolinska Institute, where he remained as a member of the faculty after receiving his degree. He first identified prostaglandin—from semen—in the early 1930s, and named them for their source, the prostate gland. By the time it was realized that all cells except red blood cells synthesize prostaglandins, their name had become entrenched.

He discovered noradrenaline and identified its function as a chemical intermediate in nerve transmission. For this work, he shared the **1970 Nobel Prize in Medicine or Physiology** with Julius Axelrod and Sir Bernard Katz.

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(abbreviated as PG) was first given by a Swedish chemist U.S. von Euler in 1935 to this lipid-soluble acidic substance. Although prostaglandins were originally found in the seminal fluid of man and other species (hence the nomenclature) but now these have been found to occur in a wide variety of mammalian tissues including brain, spinal cord, thymus, lungs, pancreas, kidneys, menstrual fluid and placenta. However, *semen remains one of the richest sources of prostaglandins as yet.*

Chemically, the prostaglandins resemble prostanic acid (Fig. 31–59). They are hydroxy derivatives of the polyunsaturated C-20 cyclic fatty acids. In its molecule, the carbon atoms 8 to 12

are involved in the formation of a 5-carbon ring called cyclopentane ring. Variations in the double bonds and in the hydroxyl and ketone groups give rise to prostaglandins that can be divided into 9 groups designated as A through I (and accordingly, the prostaglandins are designated as PGA through PGI). The PG, obviously, stands for prostaglandin and the third capital letter, in most cases, indicates the type of the substituents found on the hydrocarbon chain. In fact, two groups of prostaglandins were originally recognized : **PGE** which is ether-soluble (hence the nomenclature, E from ether) and has a keto group at C₉, and **PGF** which is phosphate-buffer-soluble (hence the nomenclature, F from *fosfat* in Swedish) and has a hydroxyl group at C₉. There are 3 compounds from each of these two groups, arising from eicosanoic (*i.e.*, C₂₀) fatty acids with 3, 4 or 5 double bonds. These are the 6 primary prostaglandins and are

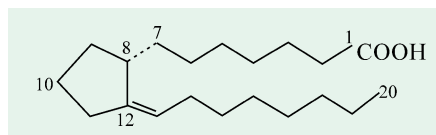


Fig. 31–59. Prostanic acid

abbreviated as PGE₁, PGE₂, PGE₃, PGF_{1α}, PGF_{2α} and PGF_{3α}. In the abbreviations of the prostaglandins, the number 1, 2, 3 is added as subscript to indicate the number of carbon-carbon double bonds outside the ring. When there is more than one member, the group is subdivided into α, β, γ etc. These occur in most cells. Their structure appears in Fig. 30–60 along with their biosynthetic origin. In addition to these, there are several secondary prostaglandins that are derived from PGE types through enzymic conversions. The x-ray structure of PGH₂ synthase from sheep seminal vesicles is presented in Fig. 31–61.

Prostaglandins have a half life of 5 minutes or less, hence they are destroyed very rapidly in the body. They have, therefore, a *high turnover rate*. The short half-life of these tissue hormones is thought to ensure their transient and limited response at the intermediate site of production. From a medical viewpoint, they are potentially the most revolutionary therapeutic substances yet discovered. Prostaglandins affect smooth muscles and blood pressure and often the activities of individual prostaglandins oppose one another. For example, prostaglandin E₂ (PGE₂) dilates blood vessels and bronchi, and prostaglandin F_{2α} (PGF_{2α}) constricts these smooth muscle tissues.

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The prostaglandins perform a wide variety of biologic activities :

1. As mentioned earlier, they bring about contraction or relaxation of the smooth muscles of the uterus, *esp.*, at the time of ovulation. This may be due to a chelation of calcium ions. As little as 1 ng/ml can cause contraction of the smooth muscles. They, thus, resemble oxytocin in this regard. They are modulators of hormone action.
2. They lower down blood pressure.
3. They inhibit lipolysis in adipose tissue, possibly by inhibiting the conversion of ATP to cyclic AMP and inhibition of platelet aggregation. The prostaglandins, thus, have the opposite effect of epinephrine, norepinephrine, glucagon and corticotropin on the release of fatty acids from adipose tissue.
4. They behave both as pressor and depressor agents under different conditions and thus affect the cardiovascular system.
5. They appear to control the secretion of gastric hydrochloric acid.

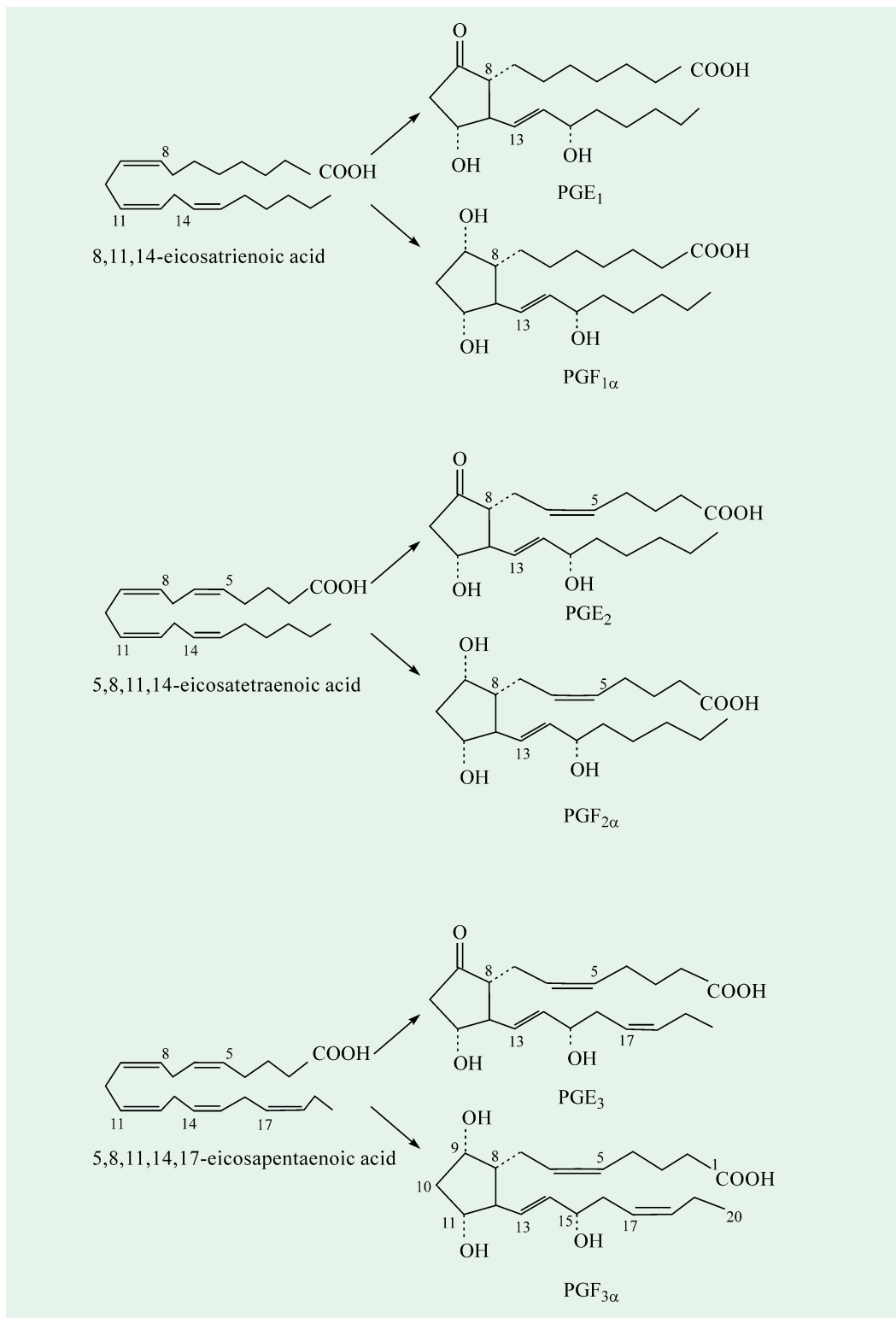


Fig. 31-60. The 6 primary prostaglandins and their biosynthetic origins

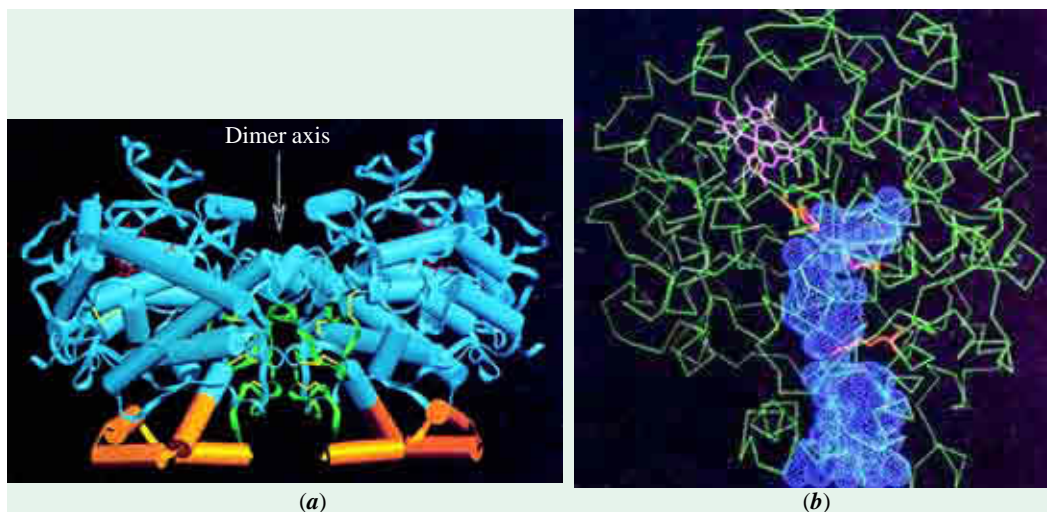


Fig. 31-61. The x-ray structure of PGH_2 synthase from sheep seminal vesicles

- (a) A diagram of the dimer as viewed along the dimer interface with its twofold axis of symmetry vertical. The EGF module, the membrane-binding motif, and the catalytic domain are colored *green*, *tan*, and *blue*, respectively, whereas the heme is *red* and the five disulfide bonds in each subunit are *yellow*.
- (b) A C_α diagram of a PGH_2 subunit (*green*), the left subunit in Part (a) as viewed from 30° to the left. The peroxidase active site is located above the heme (*pink*). The hydrophobic channel, which penetrates the subunit from the membrane-binding motif at the bottom of the figure to the cyclooxygenase active site below the heme, is represented by its van der Waals surface (*blue dots*). The three residues in the channel that are shown in *yellow* are, from top to bottom: Tyr 385, which forms a transient radical during the cyclooxygenase reaction; Ser 530, which is acetylated by aspirin; and Arg 120, which forms an ion pair with the NSAID flurbiprofen when it binds in the channel.

(Courtesy : Michael Garavito, University of Chicago)

6. They also have some beneficial effect in the control of the acid-induced gastric ulcers.
7. Prostaglandins are best known for their effects on reproductive system. There seems to be a strong link between male fertility and seminal prostaglandin content. Human semen is rich in prostaglandins, which when deposited in vagina through coitus, facilitate conception. Thus, low prostaglandin content in the human semen is related to infertility.
8. They are effective labour inducers in pregnant women also.
9. Recent work indicates that the prostaglandins are also involved in the inflammatory reaction and pain. Anti-inflammatory drugs such as aspirin, in part, act by inhibiting the synthesis of prostaglandins. However, paracetamol (an analgesic drug like aspirin) is not anti-inflammatory as it does not inhibit the synthesis of prostaglandins.

The widespread distribution of prostaglandins and their capacity to carry out varied metabolic effects have, however, led some to question the propriety of their being called hormones.

Thromboxanes and Prostacyclins

Thromboxanes (TXAs) and prostacyclins (PGIs) are structurally-related compounds that arise from a nascent prostaglandin. In compounds of both these categories, carbons 8 and 12 are joined and an oxygen atom is added to form the six-membered ring (*cf* prostaglandins, where a five-membered ring is formed). **Thromboxane A_2** (TXA_2) was first isolated, in 1975, by Samuelsson *et al* from blood platelets (also known as thrombocytes, hence the nomenclature). The following year, John Vane and colleagues at the Royal College of Surgeons, London identified yet another type of eicosanoid,

prostacyclin I₂ (PGI₂), which is produced primarily in vascular tissues, *i.e.*, blood vessels.

The striking similarity and diversity in the physiological roles of thromboxanes and prostacyclins displays a critical balance required for the normal functioning in the body. TXA₂ and PGI₂ are medically important examples of how such a balance operates *in vivo*. TXA₂ is a highly effective vasoconstrictor (blood vessel constrictor) and platelet aggregator; conversely, PGI₂ is a potent vasodilator and inhibitor of platelet aggregation. Platelets are the blood cells that first appear and aggregate at the site of injury to produce a temporary plug that serves as a base on which the strong fibrin clot ultimately forms. However, for maintenance of normal blood flow, TXA₂-induced aggregation of platelets would quickly prove fatal. Thus, a vital opposing role of PGI₂ is to prevent platelets from aggregating on blood vessel walls, a site of PGI₂ production.

Unlike other eicosanoids, PGI₂ is not metabolized during passage through the lungs. Thus, TXA₂ and PGI₂ are continuously engaged in a 'tug of war' with respect to platelet aggregation (Fig. 31–62).

In 1982, Nobel Prize in Physiology or Medicine was awarded to **Sune Bergström** (born, 1916) and **Bengt Ingemar Samuelsson** (born, 1934), both from Sweden, along with **John Robert Vane** (born, 1927) from England, for their work on eicosanoids (prostaglandins). Bergström and Samuelsson are both at the Karolinska Institute, while Vane is at the Wellcome Foundation in Beckenham, England.

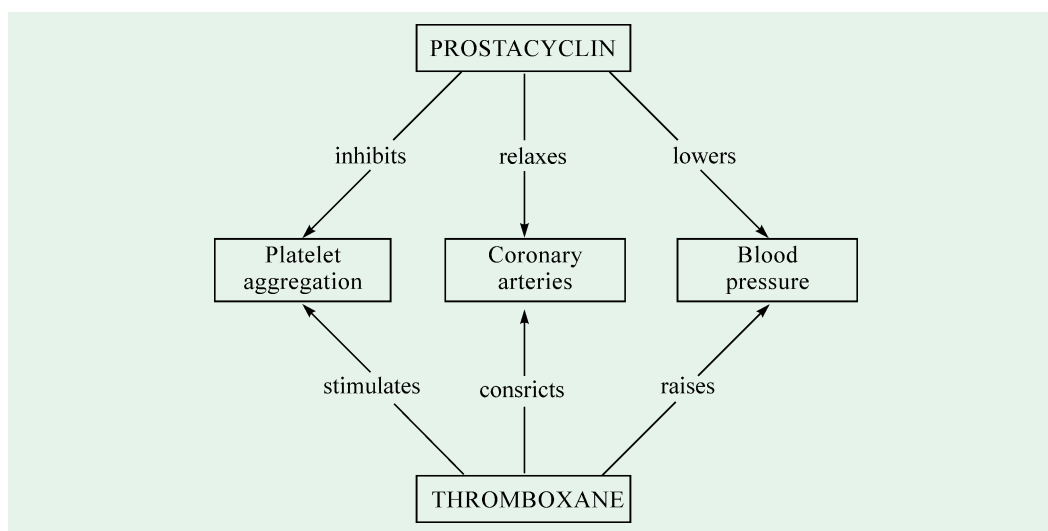


Fig. 31–62. Opposing effects of prostacyclin and thromoboxane on the cardiovascular system

Leukotrienes

Leukotrienes (LTs), first found in leukocytes, are cysteinyl-containing derivatives of arachidonic acid with a series of three conjugated double bonds in its molecule (Fig. 31–63), hence their nomenclature.

Leukotriene B₄ (LTB₄) has two hydroxyl groups at C-5 and C-12 and three conjugated double bonds at C-6, C-8 and C-10. An additional double bond is present between C-14 and C-15. **Leukotriene C₄** (LTC₄) contains the tripeptide glutathione (γ-Glu-Gly-Cys) covalently bonded to a derivative of arachidonic acid. **Leukotriene D₄** (LTD₄) possesses the dipeptide, Gly-Cys (Glu residue is eliminated) and **leukotriene E₄** (LTE₄), the amino acid Cys (Gly residue eliminated).

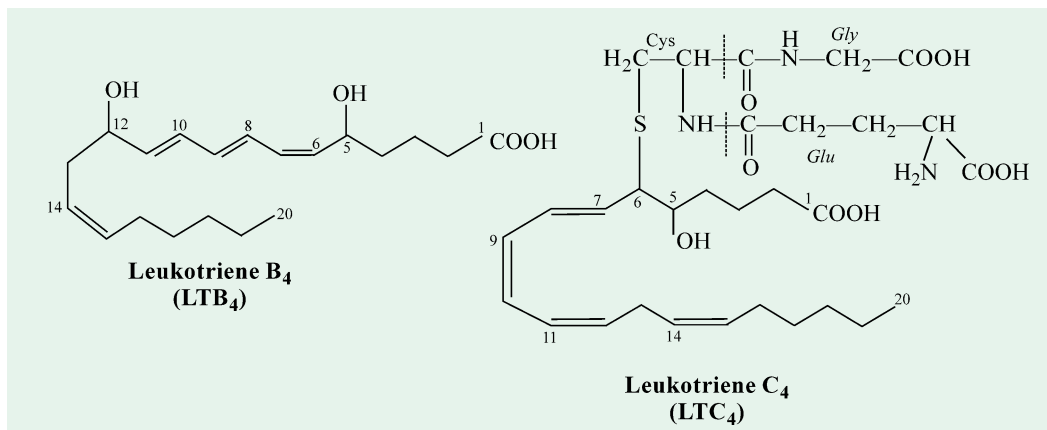


Fig. 31–63. Two common leukotrienes

Neutrophils make one class of leukotrienes to alter mobility and act as chemotactic agents. *Mast cells* make another class, formerly known as **slow-reacting substances**, which is responsible for bronchial constriction and other anaphylactic allergic reactions.

Leukocytes are powerful biological signals ; for example, they induce contraction of the muscle lining the airways to the lung. They also cause a slow and persistent contraction in the smooth muscle of blood vessels. Overproduction of leukotrienes causes asthmatic attacks and also stimulates mucus secretion.

B. Biosynthesis

Various eicosanoids are produced in different cell types by different synthetic pathways, and have different target cells and biological activities. While prostaglandins are made everywhere in the body, synthesis of thromboxanes and leukotrienes occurs in restricted locations. Both compounds are synthesized in platelets, neutrophils and the lung. Some amount of thromboxane production also takes place in the brain.

Fig. 31–64 depicts various reactions involved in the biosynthesis of 3 types of eicosanoids from arachidonic acid. Arachidonic acid is generated from phospholipids by the action of *phospholipase A₂* (PLA₂), or from diacylglycerol by the action of a *lipase*. The biosynthesis of most eicosanoids starts at arachidonate, which has 4 double bonds at C₅, C₈, C₁₁ and C₁₄. In the first key reaction, arachidonate gets converted to prostaglandin H₂ (PGH₂) by the enzyme *prostaglandin synthase*, which is made up of two components, cyclooxygenase and hydroperoxidase. This is a two-step reaction. In *first step*, cyclooxygenase component of prostaglandin synthase catalyzes the addition of one mole of oxygen to C-9 of arachidonate and of a second mole to C-15. The bond formation between C-8 and C-12 accompanying this oxygenation produces the 5-membered endoperoxide ring structure, characteristic of eicosanoids. The compound so formed is called as **prostaglandin G₂** (PGG₂). The 4 oxygen atoms introduced into PGG₂ come from 2 moles of oxygen. In the second step, the hydroperoxidase component of prostaglandin synthase, then, catalyzes a two-electron reduction of the 15-hydroperoxy group of PGG₂ to a 15-hydroxyl group, producing **prostaglandin H₂** (PGH₂). The highly unstable PGH₂ is rapidly transformed into other prostaglandins, prostacyclins and thromboxanes. In fact, the biochemical fate of the PGH₂ synthesized is determined by tissue-specific enzymes. For example, in a tissue producing prostaglandin E₂, the enzyme endoperoxide isomerase is present and converts PGH₂ into **prostaglandin E₂** (PGE₂). The synthesis of PGE₂ from arachidonate was the first-ever pathway elucidated for eicosanoid production and was discovered by Bengt Samuelsson and his associates in 1964.

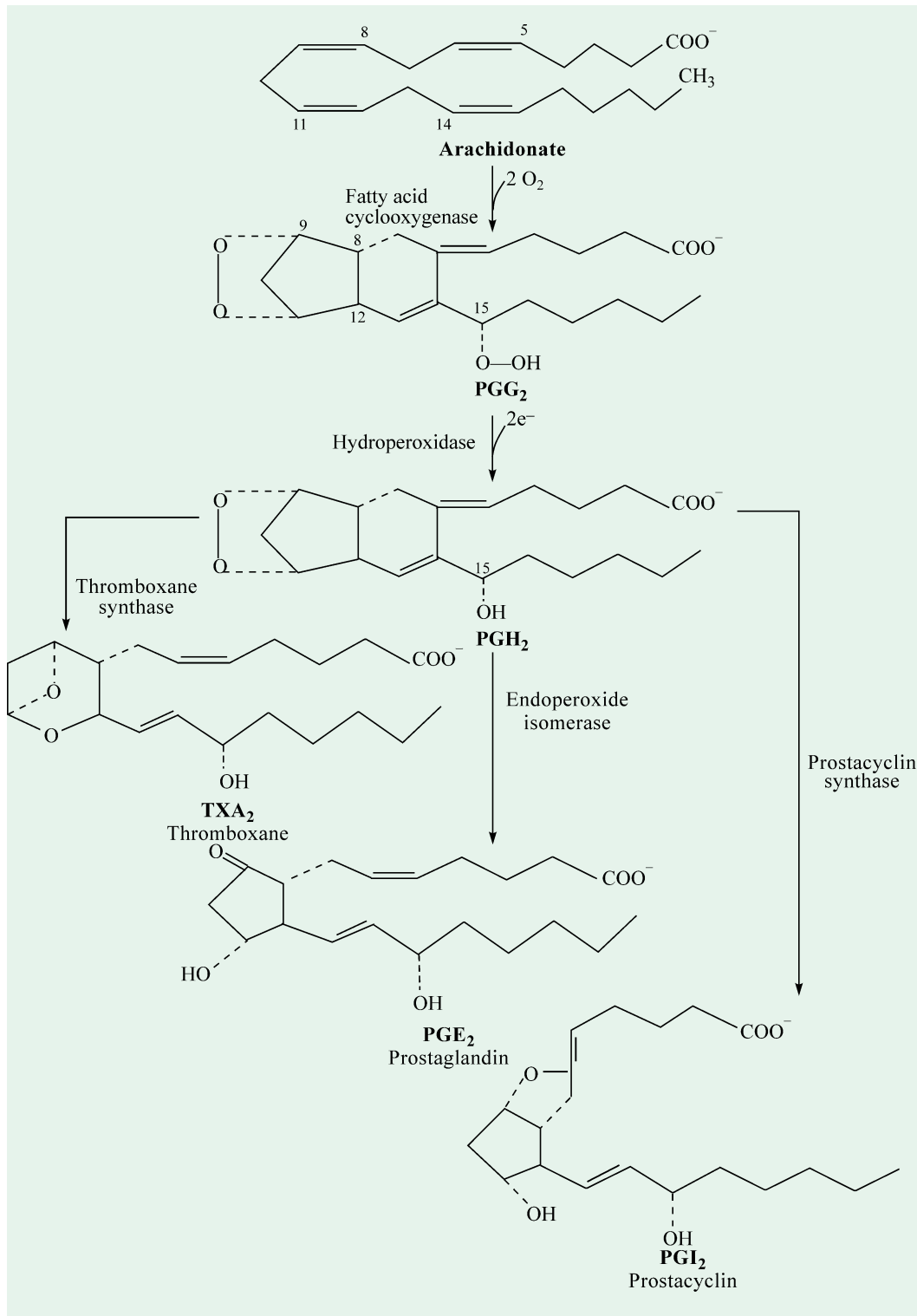


Fig. 31-64. Biosynthesis of 3 types of eicosanoids (PGE₂, PGI₂ and TXA₂) from arachidonic acid

The chemical name of **aspirin** is acetylsalicylic acid, $\text{CH}_3\text{CO}_2\text{C}_6\text{H}_4\text{COOH}$. The name 'aspirin' is derived from a plant genus *spirea* (from a Latin word which means spiral, which refers to the fact that most members of this genus are used for making wreaths and garlands, which are coiled or somewhat spiral in shape), whose members contain salicylic acid, and thus are its natural sources. However, salicylic acid also occurs in many other plants such as jasmine, patridge berry, legumes (pea, bean, clover), grasses (wheat, rye, sugarcane) and many trees (beech, birch, olive, poplar, willow). The chemical term salicylic acid itself comes from *Salix*, the Latin name for willow tree. The active ingredient in willow bark is a bitter glycoside called **salicin**. Salicin was first identified by the Italian chemists, Fontana and Brugnatelli in 1826, and isolated in pure form by the French pharmacist, Henri Leroux in 1829. On hydrolysis, salicin yields glucose and salicylic alcohol. The latter gets converted in the body to **salicylic acid**, which actually brings the fever down. Salicylic was first successfully extracted, in 1838, by an Italian chemist Rafelle Piria (the second name of this chemist, as one can probably note, has an earie similarity to the plant genus *Spirea*). Later in 1874, the same scientist Adolf Kolbe, who had earlier synthesized acetic acid, came out with an economical procedure for the laboratory synthesis of salicylic acid as well. In pure form, however, salicylic acid is too corrosive to the tissues that it peels off the upper horny layers of the skin and that is why it is an excellent agent for the removal of corns, callosities and warts. But taken orally, it produces severe vomiting and sometimes even comma. For internal administration, however, it had to be taken in the form of a salt. The most significant and potent salt, **acetylsalicylic acid** was, however, produced in 1899 by Felix Hoffmann (LT, 1868–1946) who also looked to its usefulness for a compelling reasons to try the same on his father suffering from rheumatoid arthritis and both remedies of pain (sodium, phenyl salicylate), available at that time, having had failed to give him relief. The drug fortunately worked on him. Heinrich Dreser, Director of the Friedrich Bayer & company, gave it the tradename '**aspirin**'. Aspirin is widely used to suppress platelet function in humans at risk of coronary heart disease, or deep vein thrombosis, and to treat patients that have suffered a heart attack or stroke.

The wondrous drug aspirin has been used for centuries to decrease inflammation, pain and fever. Its mode of action was an enigma until John Vane, in 1975, discovered that *aspirin inhibits the synthesis of prostaglandins by inactivating prostaglandin synthase*. Specifically, aspirin (acetylsalicylate) irreversibly inhibits the cyclooxygenase activity of this enzyme by acetylating a specific serine hydroxyl group (Fig. 31–65). Aspirin is a potent antiinflammatory agent because it blocks the first step in the synthesis of prostaglandins. This drug is also widely used to prevent excessive blood clotting, which can lead to heart attacks and strokes. Aspirin is antithrombotic also because it blocks the formation of thromboxane A_2 (TXA_2), a potent aggregator of blood platelets. Inhibition of the cyclooxygenase blocks the formation of prostaglandin H_2 , PGH_2 (Fig. 30–65). PGH_2 , which is

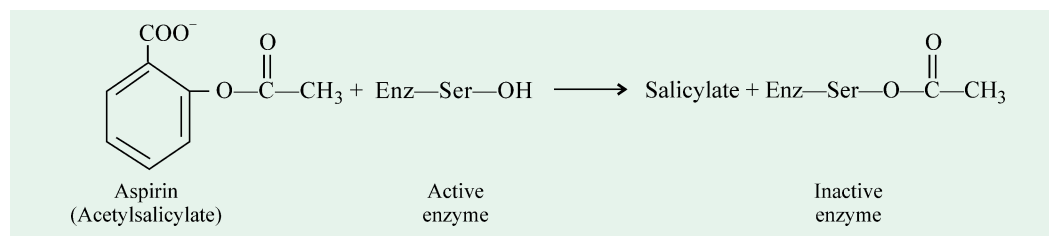


Fig. 31–65. Inactivation of prostaglandin synthase by aspirin

produced in the platelets, is also the precursor of thromboxane A_2 (TXA_2); the reaction being catalyzed by the enzyme *thromboxane synthase*. **Prostacyclin I_2** (PGI_2) is synthesized from PGH_2 and the reaction is mediated by *prostacyclin synthase*. Thus, we see that the tissues are differently endowed with enzymes that transform endoperoxides into specific types of eicosanoids.

Leukotrienes are made from arachidonate by another pathway, beginning with the addition of oxygen to C-5 of arachidonate; the reaction being catalyzed by *lipoxygenase*. This reaction is not affected by antiinflammatory drugs.

4. Opiate Peptides

Opiate peptides are compounds that bind to specific receptors and exhibit hormone-like actions. The various opiate peptides fall under 3 families, enkephalins, dynorphins and endorphins, which are generated in the body by the action of protease.

- Enkephalins.** These consist of 5 to 7 amino acids and are derived from a precursor, *proenkephalin*. These have been isolated from extracts of brain and pituitary and exhibit morphine-like properties.
- Dynorphins.** These consist of 10 to 17 amino acids and are derived from a precursor, *prodynorphin*. These are endogenous compounds made in several locations, but the major locations are brain, pituitary, adrenal medulla and peptidergic neurons.
- Endorphins.** These consist of 16 to 27 amino acids and are derived from a precursor, proopiomelanocortin (POMC). These have also been isolated from extracts of brain and pituitary and exhibit morphine-like properties.

It has been suggested that there are at least 3 types of receptors, δ , μ and k , through which these drugs mediate their physiological effects.

Though these opioids produce major effects on the central nervous system, they also function as neurotransmitters and neurohormones to modulate neurotransmission. Some of the effects that opiate peptides produce are analgesia, drowsiness, nausea, vomiting, respiratory depression, decreased gastrointestinal motility and modulations of endocrine and autonomic nervous systems.

VASOACTIVE PEPTIDES

There are three groups of well defined peptides that possess vasoactive properties. These are : *neurohypophyseal hormones* (ocytocin and vasopressin), *angiotensins* and *kinins*. Ocytocin and vasopressin have already been described on pages 715 and 716. The remaining two groups of vasoactive peptides are described below.

1. Angiotensins

Goldblatt (1947) demonstrated that the partial occlusion of the renal artery in a dog results in permanent hypertension. Obviously, slowing the circulation causes the formation of a substance that produces vasoconstriction. The presence of such a substance has been demonstrated in the blood from such ischemic kidneys. The mechanism behind this operates as follows (Fig. 31-66). An enzyme renin is formed in the kidney and is released into the blood. It is a proteinase and acts on *angiotensinogen*, a plasma protein synthesized in the liver, to split off a decapeptide called *angiotensin I*. This decapeptide, in turn, is acted upon by a peptidase called converting enzyme, present in serum, to form an octapeptide called

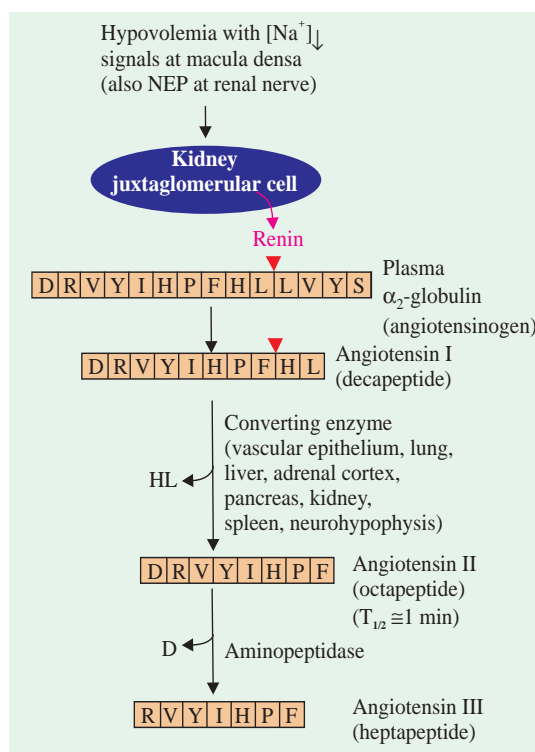
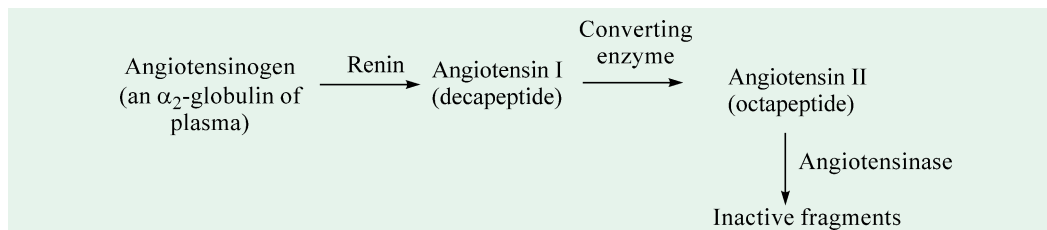


Fig. 31-66. Renin-angiotensin system

Amino acid abbreviations are found in Appendix VIII. NEP = norepinephrine

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angiotensin II. Another peptidase, termed angiotensinase, produced by kidney, hydrolyzes angiotensin II to produce *inactive fragments*. Angiotensinase, thus, serves as a balancing antipressor agent. The sequence of biochemical steps leading to its release is as follows :



Various synonyms exist in the literature for the above substances. Angiotensinogen has been variously called as hypertensinogen or renin activator. Likewise, angiotensin II is also known as hypertensin or angiotonin and angiotensinase as hypertensinase.

The two angiotensins, I and II are peptides and their amino acid sequence (refer Fig. 31–67) was determined by Page and coworkers in 1960.

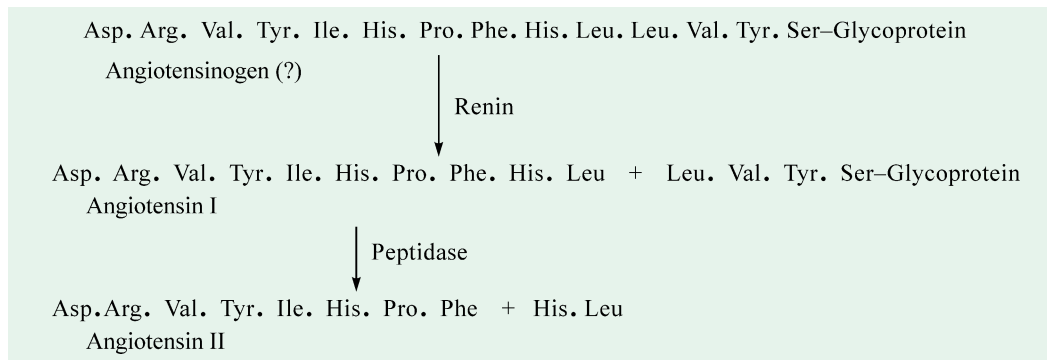


Fig. 31–67. Formation of angiotensin II

Angiotensin I has only a slight effect on blood pressure, whereas angiotensin II is the most powerful vasoconstrictor now known and produces hypertension. It is 200 times more active than norepinephrine in this respect.

2. Kinins

“Kinins is the generic name for a group of peptides with potent biologic activities in causing smooth muscle contraction, vasodilatation, lowering of blood pressure, increasing blood flow and microvascular permeability, and inducing the emigration of granulocytic leukocytes” (Orten and Neuhaus, 1970). They, thus, have some properties similar to and other properties different from the remaining vasoactive peptides. Kinins are liberated from plasma protein called *kininogen* exposed to snake venom or to the proteolytic enzyme. Kininogen is an α_2 -globulin containing about 18% carbohydrate. Chemically, the kinins are small peptides of 9 to 11 amino acid residues. Since they are derived from protein precursors, these peptides contain only protein amino acids. They are rapidly inactivated by the *kininases* of tissues. The biological significance of the kinins is not clear as yet. However, they appear to be the chemical mediators of inflammation. They are also powerful hypotensive agents. *Bradykinin* and *kallidin* are typical examples of kinins.

Bradykinin. It is formed from its precursor *bradykininogen*, an α_2 -globulin in serum, in the presence of an enzyme kallikrein. Bradykininogen has been found in a variety of tissues. Heart contains the most, followed by liver, kidney and brain. The amount of bradykininogen in the blood is 6 to 8 μg per ml. Bradykinin is a nonapeptide with the amino acid sequence shown in Fig. 31–68.

Arg. Pro. Pro. Gly. Phe. Ser. Pro. Phe. Arg

Fig. 31–68. Bradykinin

Bradykinin is released by active sweat and salivary glands. It is a powerful vasodilator that enormously increases the blood flow locally and thus promotes secretion of sweat and saliva. But its role as a vasodilator is mainly conjectural.

Kallidin. Kallidin (Fig. 31–69) is a decapeptide and contains lysine, in addition, on the N-terminal of the peptide chain of bradykinin. Hence, it is also called *lysylbradykinin*.

Lys. Arg. Pro. Pro. Gly. Phe. Ser. Pro. Phe. Arg

Fig. 31–69. Kallidin

HORMONE FROM THYMUS

The thymus is present in all jawed vertebrates. It is a flat, pinkish, bilobed structure, located in the chest behind the sternum. The gland arises as a proliferation of the gill pouch epithelium which becomes infiltrated with lymphocytes. It grows rapidly to acquire a large size in the young animals and atrophies in the adults. In man, the gland reaches its greatest development at the age of 14 to 16, after which it atrophies because of the activity of the sex cells. Thymus is, however, absent in the hagfishes and in the lamprey, it is represented by a group of cells beneath the gill epithelium. This is called as a *prothymus*.

Structure. Purification of thymus extracts have yielded an active glycopeptide.

Functions. Certain biochemical functions are attributed to this gland. These are as follows :

1. It is the primary source of lymphocytes in the mammals. The lymphocytes are responsible for the immunological functions of the body by producing antibodies.
2. It helps the body to distinguish between its own tissue proteins and the foreign proteins such as those present in tissues transplanted from another animal. This has been inferred from the fact that when the thymus is removed at birth, skin grafts in animals persist for a long period. However, when the thymus is left intact, the graft or the transplanted tissue is rejected.
3. It is concerned with accelerating growth and as such metamorphosis is postponed.

Antibodies are substances that help the animals to combat with the invading bacteria and viruses.

Thymectomy. Removal of the thymus gland has resulted in the following dysfunctions :

1. reduction in lymphocyte population (lymphopenia)
2. atrophy of the lymphoid tissue
3. loss of immunological competence.

The renal hormones, the prostaglandins, the angiotensins, the kinins and the thymus hormone are all sometimes collectively referred to as **parahormones** or **tissue hormones** as many of them act very locally. They are all produced endogenously by specialized groups of cells. These are different from hormones as they produce their effects without entering the blood stream. Moreover, their secretion is controlled by hormones, metabolic products, enzymes etc.

PHEROMONES OR 'SOCIAL' HORMONES

Definition. The pheromones or smell signals, as they are also called, are species-specific chemical substances or 'odours' which are released from animals (insects to mammals) into the environment and evoke behavioural, developmental or reproductive responses. The term '*pheromones*' was first used by Karlson and Luscher to designate active substances that mediate humoral correlations among individuals of a given species. *The pheromones work on other members of the same species (i.e., they*

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are species-specific) whereas the hormones proper confine their activities to the animal which produces them. Unlike the hormones, which are produced in glands to act on target tissues internally, the pheromones are produced in glands and discharged externally to influence other members of the same species. The pheromones, for the same reason, have also been christened as 'social hormones'. These include substances responsible for olfactory attraction between the sexes, alarm substances which warn other members of the species of danger and 'markers' which establish territories and trails or mark rich sources of food. They are well known sex-attractants also. These peculiar 'odours' or 'scents' are elaborated by different epithelial glands in the epidermis, the oro-anal and the urinogenital regions.

Structure. Chemically, they belong to a diverse category of compounds ranging from amino acids to lipids, alcohols and organic acids. Female silkworm moth (*Bombax mori*) secretes a sex-attractant which excites male moths (Fig 31-70). The sex-attractant of the silk moth (Fig. 31-71) is a long-chain alcohol (C₁₆H₃₀O) with two double bonds at C₁₀ and C₁₂ (Adolf Butenandt, Hecker and Stamm).

In fact, Adolf Butenandt and his colleagues obtained only 12 mg of the compound from half a million glands of the silkworm moth. Only as low as 10⁻¹⁸ g per millilitre of this substance placed in the vicinity of the male silk moth is enough to induce flutter, dancing movements and other symptoms of sexual excitation. The signals could be detected even 1.5 kilometres away by the male silk moth making it one of the most active biological substances known. The *trans*-12 isomer requires 10¹² times the quantity for equal effectiveness as an attractant.



Fig. 31-70. The male silkworm moth (*Bombax mori*)

The female moth releases sex attractants such as the pheromone bombykol into the air in minute quantities. The male is extremely sensitive to these pheromones, because his antennae are large and crammed with many specialist receptors. This male has about 17,000 receptors in each antenna that respond only to bombykol.

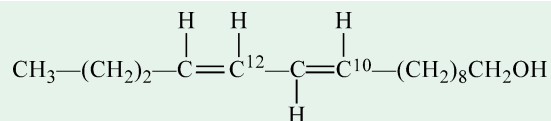


Fig. 31-71. Sex-attractant of the silk moth
(*trans*-10-*cis*-12-hexadecadien-1-ol)

The fall army worm utilizes *cis*-9-tetradecen-1-ol (Fig. 31-72) as the sex-attractant. This alcohol could be derived through biological reduction of myristoleic acid.

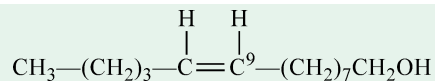


Fig. 31-72. Sex-attractant of the fall army worm, bombykol

Insects also produce alarm pheromones. Many of these are hydrocarbon, oxidized hydrocarbon, also hydrocarbon, or terpenoid in nature. The chemical structure of 4 such pheromones is given in Fig. 31-73, along with the name of the insect which produces them.

Types. Based on their functional aspect, the pheromones have been grouped under two categories.

1. *Releaser pheromones*—They initiate specific patterns of behaviour. They serve as powerful sex-attractants, mark territories or trails, initiate alarm reactions or bring about aggregation of individuals.
2. *Primer pheromones*—They trigger physiological changes in endocrine activity, esp., related to sexual maturation, growth or metamorphosis.

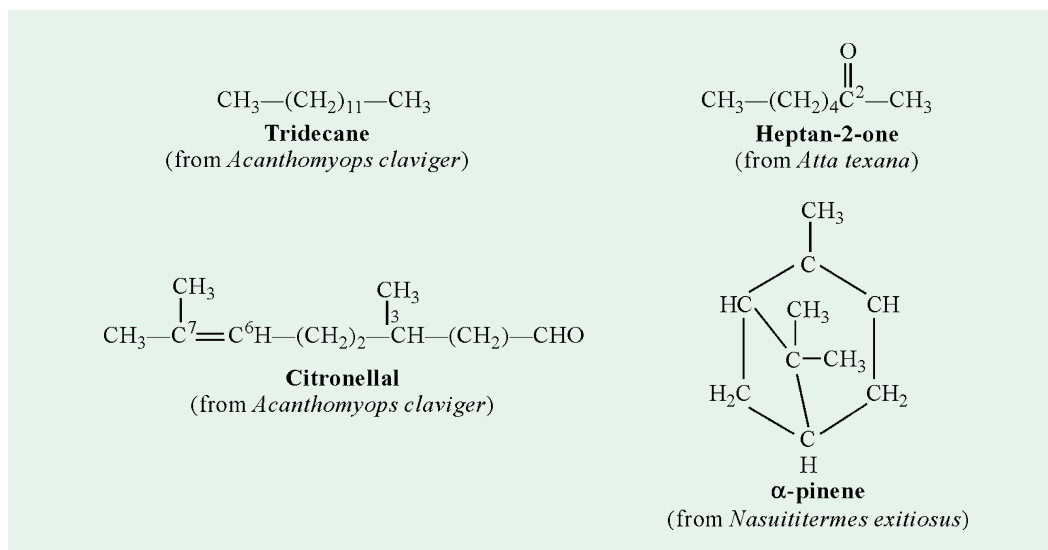


Fig. 31-73. Four alarm pheromones from insects

Examples. Many of the insects live in a world dominated by odours which greatly affect their social life. Two such interesting examples are given below.

In the honeybee colony, the queen bee secretes from its mandibular glands a pheromone called ‘queen substance’ which inhibits the growth of the ovaries in the worker bees. The latter obtain this substance by occasionally licking queen’s body. If, however, an accident occurs to the queen or else she is removed from the hive, the ovaries of the worker bees start developing. The ‘queen substance’ has been isolated and synthesized by Englemann in 1970. Chemically, it is 9-oxododecenoic acid.

The female gypsy moths, *Porthetria dispar* cannot fly and have to depend, for luring the winged males for copulation, on sex-attractants which they secrete. Only very little amount of this substance (*i.e.*, 1×10^{-12} μg) is sufficient to attract males from some distance.

Many social insects produce alarm substances which excite other members of the species to attack intruders. The honeybee, for instance, injects a pheromone called 2-heptanone in the body of the victim it stings. This marks the invader so that its chances of getting more stings increase (Free and Simpson, 1968).

Pigs have been known to detect truffles buried as deep as 3 feet below the ground by scent alone. It has been discovered that truffles contain a pig sex pheromone called *5 α -androst-16-en-3 α -ol*. This might also explain why we like the fungus which is said to taste like a cross between musk, nuts and ozone. The above steroid is synthesized by human males in the testes and secreted by axillary sweat glands !

A human baby even when 2-days old has already learnt to recognize the adour of the breast of the mother, given off probably by the areola of the breast. Thus, if two wads of cloth—one infiltrated with the odour of the mother’s breast and the other with the odour of the breast of another woman—are placed on either side of an infant’s head, the child instinctively turns towards the wad with the odour of its mother’s breast.

A survey, held in 1982, at a ‘Taste and Smell’ clinic, Georgetown (U.S.A.) has shown that there is a strong link between sex and smell. According to this survey, sexual desire is conveyed by a hormonal substance secreted by the body. Synthetically-produced rostenol can give the right fragrance to make love.

In an attempt to find whether a link between sex and smell in humans exists, studies have been conducted on two possible pheromones, androstenone and copulins. **Androstenone**, a hormone found in perspiration from the armpit and genitals is found more prevalent in men than in women. **Copulins** are estrogen-dependent fatty acids found in vaginal secretions of some women. Earlier French romantic

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literature reports that a man can become irresistible to women if he wears a handkerchief with which he has previously rubbed his armpits while fully aroused. This belief may account for a rather odd feature of male attire– the exposed breast pocket handkerchief– and it now seems it may have some physiological basis. The testes form a particular steroid, 5 α -androst-16-en-3 α -ol, for which the trivial name **priapol** (Fig. 31–74) is suggested. Priapol is transported through the blood, and is secreted by the axillary glands along with the corresponding ketone. The alcohol has a musky odour whereas the ketone is said to smell like urine. Only sketchy trials have tested humans for positive reaction to exposure to the scents ; the best evidence for the potency of the alcohol comes from the behaviour of the swine. The concupiscent (or lusty) boar generates a salivary foam rich in priapol, and the odour induces the sow to stand for him. Curiously, truffles are rich in the compound, which explains why sows are dedicated truffle hunters.

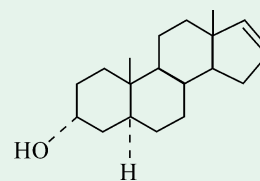


Fig. 31–74. Priapol
(5 α -androst-16-en-3 α -ol)

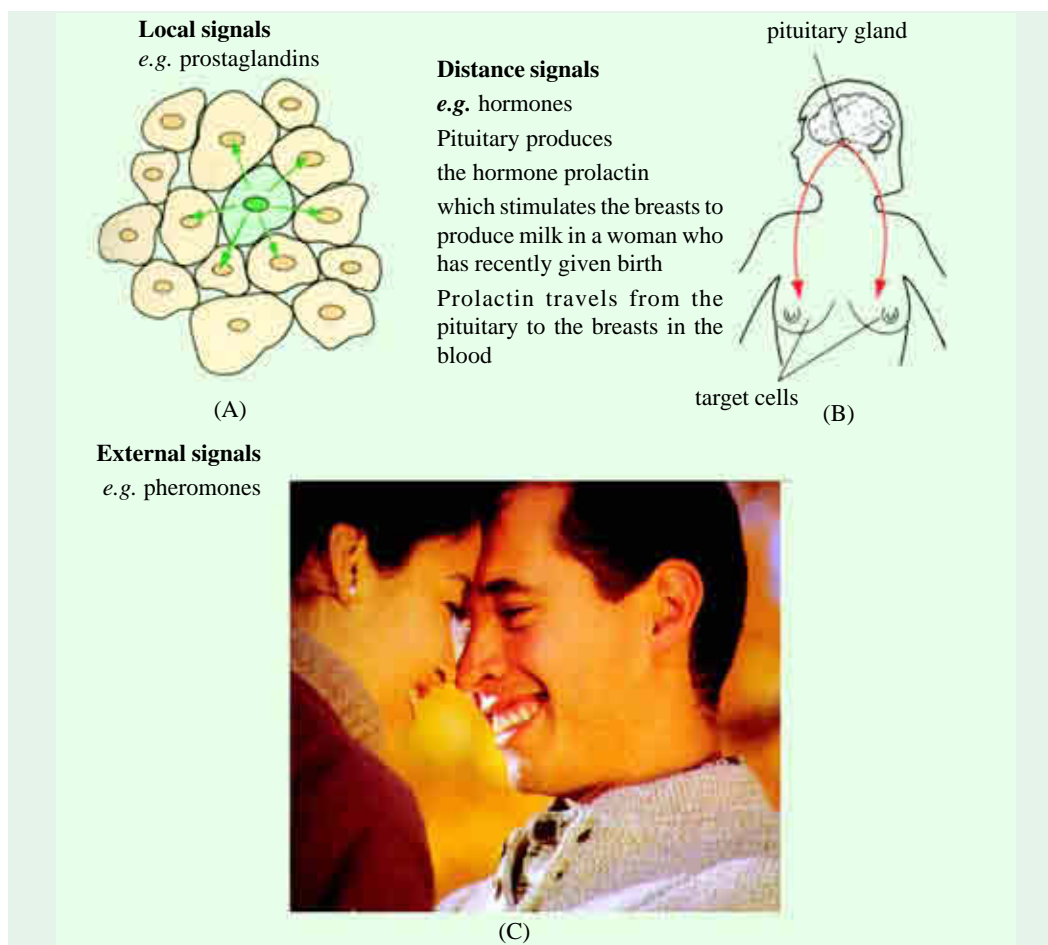


Fig. 31–75. A summary of the different types of chemical signalling that exist within and between organisms

(A) Local signals include neurotransmitters such as acetylcholine and local messengers such as prostaglandins, endorphins and histamines. (B) Distant diagonals such as hormones allow communication between different organs, via and blood. (C) Externally produced messengers allow communication between organisms.

Dr. George Dodd, the father of the psychology of perfumery, has the world's only laboratory for sensitivity to smell. He has chemically identified and synthesized all the human pheromones. Dr. Dodd (1996) has also developed a synthetic human pheromone booster, the *Pheromone Factor*. He has discovered that the 7 families of human pheromones correspond to the aroma of the foods traditionally considered aphrodisiac : truffles, caviar, shellfish, champagne, beer, ripe cheese and vintage wine. Currently, an attempt is being made to synthesize pheromones to alleviate problems related to stress, sleep, diet and smoking.

A general emerging trend is now to classify the various chemical signals, that exist within and between organisms, into 3 discrete categories : local signals, distant signals and external signals (Fig 31–75).

MECHANISMS OF HORMONE ACTION

The function of different hormones is to *control* the activity of levels of target tissues. To achieve this, the hormones may alter either the permeability of the cells or they may activate some other specific cellular mechanism. Although the exact site of action of any hormone is not established, five *general sites* have been proposed.

A. Hormonal Action at Cyclic Nucleotides Level.

Many hormones exert their effect on cells by first causing the formation of a substance, cyclic 3', 5'-adenosine monophosphate (Fig. 31–76) in the cell. Once formed, the cyclic AMP causes the hormonal effects inside the cell. Thus, *cyclic AMP acts as an intracellular hormonal mediator*. It is also frequently referred to as the *second messenger* for hormone mediation ; the *first messenger* being the original hormone itself.

The effects of cyclic AMP on the action of a hormone was first described by Earl W. Sutherland and T.W. Rall in 1960. They found that the effect of epinephrine on hepatic glycogenolysis (breakdown of glycogen) is a result of the conversion of inactive phosphorylase b into an active form by cyclic AMP. Epinephrine was found to activate the enzyme, adenylyl cyclase which, in turn, converts ATP to cAMP. Besides epinephrine, other hormones like glucagon, parathormone, ACTH, TSH, ICSH, LH, α -MSH and vasopressin are now known to have a stimulatory effect on cAMP levels. Several hormones, on the contrary, decrease cAMP levels and thus produce an opposite effect. These include insulin, melatonin and the prostaglandins. From the many names of hormones given above, it appears that hormone action not mediated by cAMP may be an exception rather than the rule.

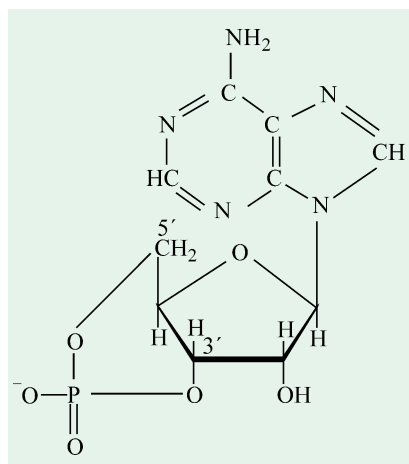


Fig. 31–76. Cyclic 3', 5'-adenosine monophosphate, cAMP

EARL WILBUR SUTHERLAND JR.

(LT, 1915-1974)

Sutherland was an American pharmacologist and physiologist. He was awarded the coveted **Nobel Prize in Physiology or Medicine in 1971** for his discoveries in cellular signal transduction. He showed that hormones such as adrenalin goad phosphorylase into action, indirectly, by increasing the production of another biochemical called cyclic AMP (cAMP). The latter is known as the 'second messenger,' the first messenger being the hormone itself.



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Fig. 31-77 depicts, in a schematic way, the effect of cAMP on hormone action. The cell contains receptor for hormones in the plasma membrane. The stimulating hormone acts at the plasma membrane of the target cell and combines with a specific receptor for that particular type of hormone. The specificity of the receptor determines which hormone will affect the target cell. The combination of the hormone with its receptor leads to the activation of the enzyme, adenylyl cyclase, which is also bound to the plasma membrane. The portion of the adenylyl cyclase that is exposed to the cytoplasm causes immediate conversion of cytoplasmic ATP into cAMP. The reaction representing cAMP synthesis may, thus, be written as :

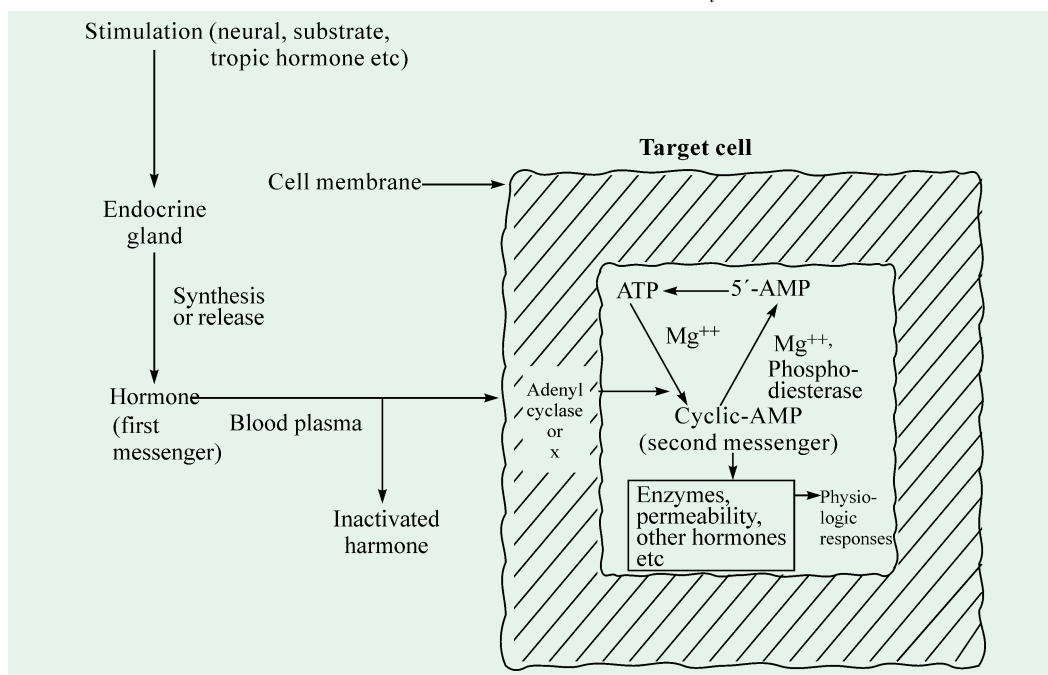


Fig. 31-77. Role of cyclic AMP in hormone actions

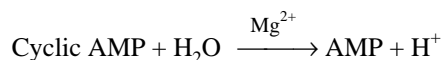
(Modified from R.W. Butcher, 1968)

The reaction is slightly endergonic and has a $\Delta G^{\circ'}$ value of about 1.6 kcal/mol. The cAMP then acts inside the cell to initiate a number of cellular functions before it itself is destroyed. The various functions initiated include :

- activating the enzymes
- altering the cell permeability
- synthesizing the intracellular proteins
- contracting or relaxing the muscles
- releasing other hormones (*third messengers*).

It should, however, be emphasized that *what cAMP does in a particular effector cell is determined by the cell itself, rather than by cAMP.*

Cyclic AMP is, however, destroyed (or inactivated) by a specific enzyme called *phosphodiesterase*, which hydrolyzes it to AMP. Like adenylyl cyclase, the phosphodiesterase is present in practically all tissues.



This reaction is highly exergonic, having a $\Delta G^{\circ'}$ value of about -12 kcal/mol. Cyclic AMP is a very stable compound unless hydrolyzed by a specific phosphodiesterase.

An important feature of the second messenger model is that *the hormone need not enter the cell and its impact is made at the cell membrane*. The biological effects of the hormone are mediated inside the cell by cAMP rather than by the hormone itself.

cAMP and the Protein Kinases — Cyclic AMP elicits many of its effects by activating protein kinases. Protein kinases are ubiquitous in nature and are activated by cAMP at extremely low concentrations of 10^{-8} M. These kinases molecule the activities of different proteins in different cells by phosphorylating them. The enzyme *protein kinase* (Fig. 31–78) consists of two subunits : a catalytic subunit and a regulatory subunit which can bind cAMP. In the absence of cAMP, the catalytic and regulatory subunits form a complex that is enzymatically inactive. In the presence of cAMP, however, the complex disintegrates, freeing the catalytic subunit which now becomes catalytically active. The regulatory subunit binds cAMP to form a complex. Thus, the binding of cAMP to the regulatory subunit relieves its inhibition of the catalytic subunit. The cAMP acts as an allosteric effector.

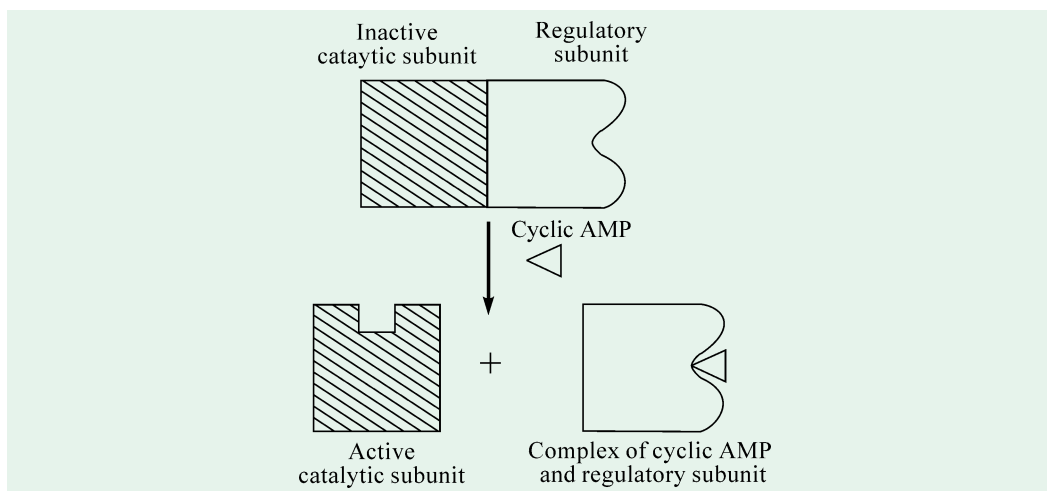


Fig. 31–78. Activation of protein kinase by cAMP

[Cyclic AMP activates protein kinases by dissociating the complex of the catalytic and regulatory subunits.]

(Adapted from Lubert Stryer, 1975)

cAMP as an Ancient Hunger Signal — It is interesting to note that cAMP has a long evolutionary history as a regulatory molecule. In bacteria, it stimulates the transcription of certain genes. Thus, in these microorganisms, it acts as ‘hunger signal’. The word signifies an absence of glucose and leads to the synthesis of enzymes that can exploit other energy sources. In mammalian liver and muscle cells, cAMP has retained its ancient role as a hunger signal. But here cAMP acts by stimulating a protein kinase, rather than by enhancing the transcription of certain genes as is the case in bacteria. Moreover, cAMP has become a second messenger in higher organisms.

The query emerging apparently from this discussion is that why was cyclic AMP chosen during evolution to be a second messenger? This is because of the following three important reasons :

1. cAMP is derived from ATP which is an omnipresent molecule.
2. cAMP is very stable except for the presence of phosphodiesterase.
3. cAMP has a number of active groups that can bind it tightly to the receptor proteins such as the regulatory subunit of the protein kinase in muscles.

Other Intracellular Hormonal Mediators — It has been postulated that, besides cAMP, other types of intracellular hormonal mediators also exist.

1. One almost-certain mediator is **cyclic guanosine monophosphate** (= cyclic GMP). Cyclic GMP is a nucleoside similar to cAMP and is found in most tissues. It can probably catalyze some intracellular functions in a manner similar to that of cAMP.
2. Another type of intracellular hormonal mediator is a group of compounds referred to as

prostaglandins (refer page 730). These substances frequently cause intracellular inhibition, in contrast to the activation usually caused by cAMP.

B. Induction of Enzyme Synthesis at the Nuclear Level. A second major mechanism by which the hormones, *esp.*, the steroidal and thyroidal ones, act is to cause synthesis of proteins in the target cell. These proteins are presumably the enzymes which, in turn, activate other functions of the cells. The mechanism behind the **steroidal hormones** is depicted in Fig. 31–79. The sequence of events is as follows :

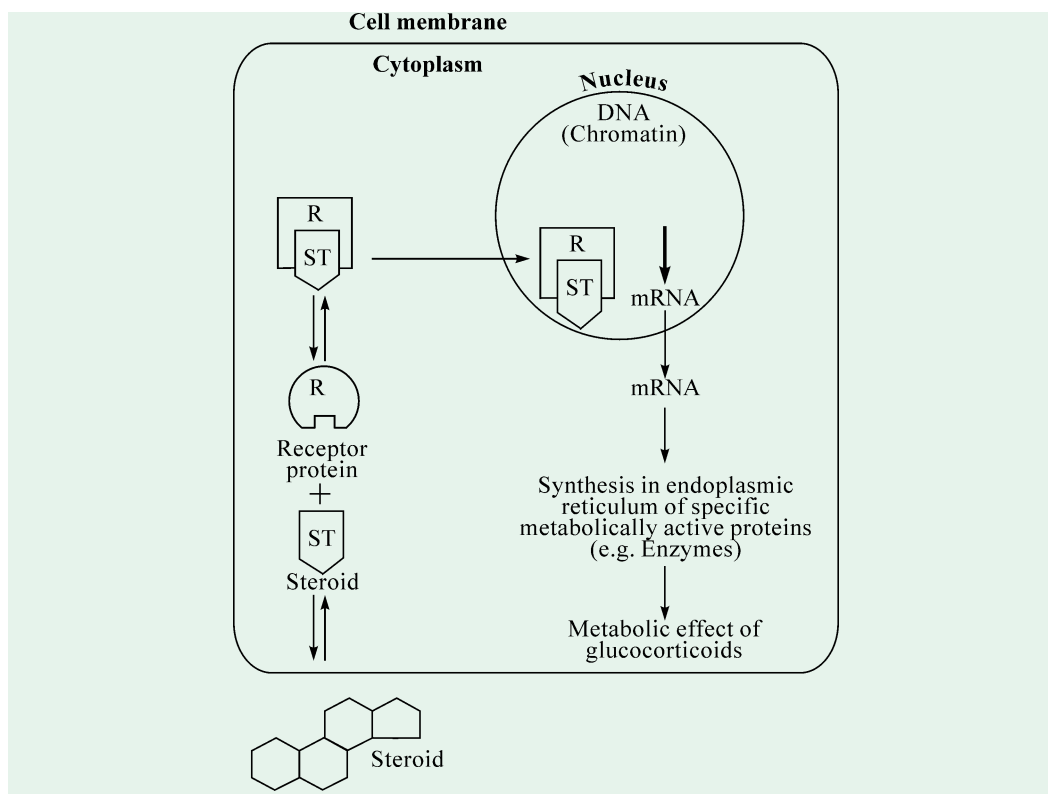


Fig. 31–79. Mechanism of action of steroidal hormones

ST = Steroid ; R = specific receptor protein

[The dissimilar shapes of R are intended to represent different conformations acquired by this protein.]

(Adapted from Baxter and Forsham, 1972)

1. The steroidal hormone enters the cytoplasm of the target cell where it binds with a specific, high-affinity receptor protein.
2. The receptor protein-hormone complex, so formed, then diffuses into (or is transported into) the nucleus, where it reacts with the nuclear chromatin.
3. Somewhere along this route, the receptor protein is structurally altered to form a smaller protein with low molecular weight. Or else the steroid hormone is transferred to a second smaller protein.
4. The combination of the small protein and hormone is now the active factor that stimulates the specific genes to form messenger RNA (mRNA) in the nucleus.
5. The mRNA diffuses into the cytoplasm where it accelerates the translation process at the ribosomes to synthesize new proteins.

It is, however, noteworthy that a direct chemical reaction of the hormone with DNA or RNA polynucleotide is not likely. Instead, the hormone must first combine with a specific receptor protein and it is this combination that acts on DNA chromatin. It is possible that the chromatin proteins may influence hormonal activity by modifying the ability of the receptor complex to bind with DNA.

To cite an example, the aldosterone, one of the mineralocorticoids secreted by adrenal cortex, enters the cytoplasm of the renal tubular cells. These tubular cells contain its specific receptor protein and hence above sequence of events follows. After about 45 minutes, the proteins begin to appear in the renal tubular cells that promote sodium reabsorption from the tubules and potassium secretion into the tubules. This characteristic delay, of about 45 minutes, in the final action of this steroid hormone is in marked contrast to the almost instantaneous action of some of the peptide hormones.

The **thyroidal hormones** act similarly to enhance RNA and enzyme synthesis but may do so by directly binding with the specific receptor proteins present in the nuclear chromatin. The receptors present in the cytoplasm are less effective in this regard.

C. Stimulation of Enzyme Synthesis at Ribosomal Level. In the case of some hormones, the activity is at the level of translation of information carried by the mRNA on the ribosomes to the production of enzyme protein. For example, the ribosomes taken from animals, which have been given growth hormone, have a capacity for protein synthesis in the presence of normal mRNA.

D. Direct Activation at the Enzyme Level. It has been experimentally observed that treatment of the intact animal (or of isolated tissue) with some hormones results in a change in enzyme behaviour which is not related to *de novo* synthesis. The cell membrane is usually required for such activity. Henceforth, it is possible that activation of a membrane receptor might be an initial step in hormone action.

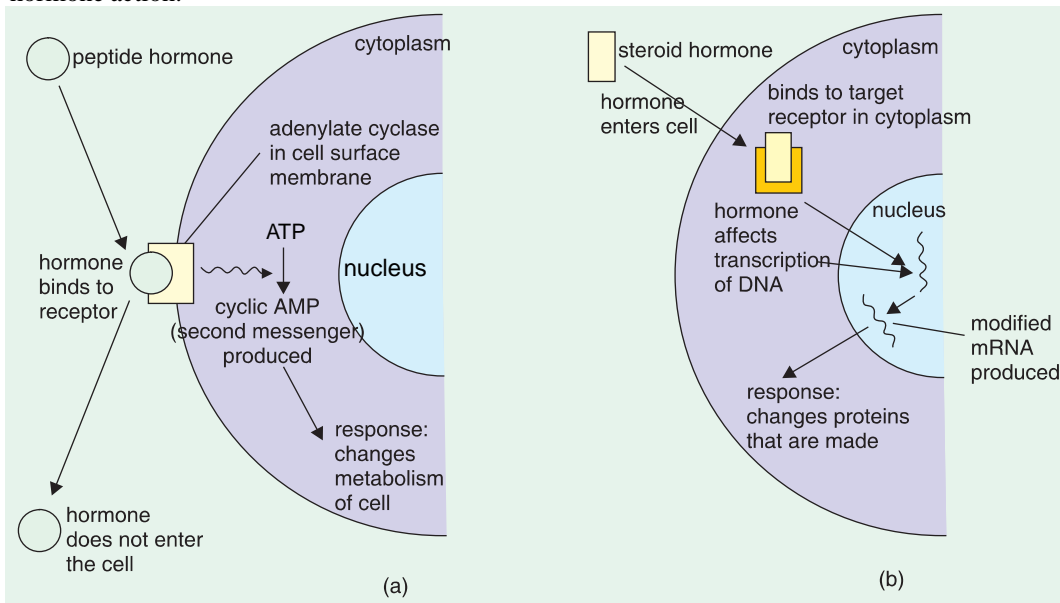


Fig. 31-80. Two principal mechanisms of hormone action

- (a) Water-soluble hormones work *via* a second messenger which is formed inside the cell when they bind to receptors on the cell surface.
- (b) When steroid hormones bind to a receptor inside the cytoplasm, they form a complex similar to an enzyme–substrate complex. This enters the nucleus of the cell and binds directly to the DNA, interfering with the cell's ability to read some of its genes. A steroid hormone can either switch on or switch off protein synthesis of particular genes. The overall effect of hormone action is different for each steroid hormone.

E. Hormone Action at the Membrane Level. Many hormones appear to transport a variety of substances, including carbohydrates, amino acids and nucleotides, across cell membranes. These hormones, in fact, bind to cell membranes and cause rapid metabolic changes in the tissues. Catecholamines (epinephrine and norepinephrine) and many protein hormones stimulate different membrane enzyme systems by direct binding to specific receptors on cell membrane rather than in the cytoplasm.

A schematic representation of the two principal mechanisms of action involving water soluble hormones and steroid hormones is presented in Fig. 31-80.

Table 31–10. Vertebrate Hormones

S.No.	Secretory Organ	Hormone	Chemical Nature	Physiological Role	Hypofunction	Hyperfunction	Effect of Removal of Secretory Organ
1.	GONADS Ovary	Estrogens β-estradiol Estrinol Estrone	C ₁₈ sterioids (Derivative of estrane)	Proliferation of endometrium Deepening of uterine glands; Increase in vasculature; Development of secondary sex characters	—	—	Suspension of menstrual and reproductive cycles; Atrophy of uterus & vagina; Involted mammary glands
	Testes	Androgens Testosterone Androsterone DHEA	C ₁₉ sterioids (Derivative of androstane)	Development of secondary sex characters	—	—	Ossification of long-bone epiphyses; Increased adiposity; Extrusion of chest; Suppressed penis
		Androstenedione* Androstenetrione					
2.	ADRENALS Cortex	Corticosteroids Aldosterone DOC Cortisone Cortisol Corticosterone	C ₂₁ sterioids	Water-salt balance of the body; Regulate NaCl contents of blood; Control carbohydrate metabolism; Inhibit protein synthesis; Regulate lipogenesis	Decreased metabolism; Excessive pigmentation; Anorexia; Anemia; Hypoglycemia	Cushing's syndrome	Addison's disease
	Medulla	Epinephrine Norepinephrine	Amino acid derivatives	Regulate carbohydrate metabolism; Regulate blood pressure	—	—	Pheochromocytoma
3.	CORPUS LEUTEUM	Progesterone Relaxin	C ₂₁ steriod (Derivative of pregnane) Polypeptide	Proliferation of uterine mucosa; Growth of mammary glands; Inhibition of uterine contraction Relaxation of pelvic ligaments during childbirth	—	—	—

Table 31-10. (Continued)

S.N.	Secretory Organ	Hormone	Chemical Nature	Physiological Role	Hypofunction	Hyperfunction	Effect of Removal of Secretory Organ
4.	ISLETS OF LANGERHANS β-cells	Insulin	Polypeptide -51 AARs [†]	Lowers sugar level in blood; Promotes protein synthesis; Promotes lipid synthesis	Diabetes mellitus	—	—
		Glucagon	Polypeptide -29 AARs	Increases sugar level in blood Catabolic action on proteins; Accelerates ketogenesis	Hypoglycemia	—	—
5.	HYPOPHYSIS Pars distalis	Thyrotropin	Polypeptide	Stimulates thyroid activity	Dwarfism	Gigantism (in children)	Atrophy of gonads, thyroid and adrenal cortex;
		Corticotropin	Polypeptide	Stimulates adrenal cortex	Panhypopituitarism	Acromegaly (in adults)	Loss of body tissue
		Gonadotropins	Polypeptide	Induces growth of graafian follicles	Pituitary myxedema		
		FSH	Polypeptide	Induces ripening of ovarian follicles			
		LH	Polypeptide	Lactation during parturition			
		LTH	Polypeptide	Controls skeletal growth			
		Somatotropin	Polypeptide	Darkening of the skin			
Pars intermedia	Pars nervosa	Intermedins	Polypeptide	Stimulates contraction of smooth muscles <i>esp.</i> of uterus			
		Oxytocin	Polypeptide -9 AARs	Causes a rise in blood pressure; Antidiuretic action			
		Vasopressin	Polypeptide -9 AARs				

Table 31-10. (Continued)

S.N.	Secretory Organ	Hormone	Chemical Nature	Physiological Role	Hypofunction	Hyperfunction	Effect of Removal of Secretory Organ
6.	GASTROINTESTINAL TRACT	Secretin Pancreozymin Gastrin	Polypeptide Polypeptide Polypeptide	Stimulates flow of pancreatic juice Stimulates flow of pancreatic juice Stimulates flow of gastric	—	—	—
7.	PARATHYROID	Parathormone	Polypeptide -84 AARs	Bone resorption; Renal reabsorption of calcium	Tetany	Osteitis fibrosa	—
8.	THYROID	TIT or T ₃ Thyroxine, T ₄	Amino acid derivative Amino acid derivative	Deamination reactions in the liver; Deiodination in extrahepatic tissues	Cretinism (in children) Myxedema (in adults)	Exophthalmia; Goiter	—

* Secreted from adrenal gland

† AARs = Amino acid residues

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PROBLEMS

1. The hormone progesterone contains two ketone groups. At pH 7, which side chains of the receptor might form hydrogen bonds with progesterone ?
2. Ingesting large amounts of glucose before a marathon might seem to be a good way of increasing the fuel stores. However, experienced runners do not ingest glucose before a race. What is the biochemical reason for their avoidance of this potential fuel ? (**Hint** : Consider the effect of glucose ingestion on the level of insulin.)
3. Insulin-dependent diabetes is often accompanied by hypertriglyceridemia, which is an excess blood level of triacylglycerides in the form of very low density lipoproteins. Suggest a biochemical explanation.
4. The hormone glucagon signifies the starved state, yet it inhibits glycolysis in the liver. How does this inhibition of an energy-production pathway benefit the organism ?
5. Sildenafil (Viagra) is a drug widely used to treat male impotence. Sildenafil exerts its effect by inhibiting a cGMP phosphodiesterase isozyme (PDE5) that is especially prevalent in smooth muscle. Interestingly, certain airlines restrict pilots from flying for 24 hours after using sildenafil. Suggest a reason for this restriction.
6. How would you determine whether an inability to produce cortisol in response to stress was caused by a problem in the hypothalamus, the anterior pituitary, or the adrenal cortex ?
7. Steroidal anti-inflammatory drugs inhibit prostaglandin synthesis in at least two ways— inhibition of phospholipase A₂ and inhibition of cyclooxygenase. Why are the new generation of antiinflammatory drugs called COX2 inhibitors (Celebrex, Vioxx) better tolerated than the older drugs ?
8. What is the relationship between 7-dehydrocholesterol and 1 α , 25-dihydroxycholecalciferol ?
9. Marathon runners preparing for a race engage in “carbo loading” to maximize their carbohydrate reserves. This involves eating large quantities of starchy foods. Why is starch preferable to candy of sugar-rich foods ?
10. Ketone bodies are exported from liver for use by other tissues. Because many tissues can synthesize ketone bodies, what enzymatic property of liver might contribute to its special ability to export these compounds ?
11. During a “fight or flight” situation, the release of epinephrine promotes glycogen breakdown in the liver, heart, and skeletal muscle. The end product of glycogen breakdown in the liver is glucose. In contrast, the end product in skeletal muscle is pyruvate.
 - (a) Why are different products of glycogen breakdown observed in the two tissues ?
 - (b) What is the advantage to the organism during a “fight or flight” condition of having these specific glycogen breakdown routes ?
12. Certain malignant tumours of the pancreas cause excessive production of insulin by the β cells. Affected individuals exhibit shaking and trembling, weakness and fatigue, sweating, and hunger. If this condition is prolonged, brain damage occurs.
 - (a) What is the effect of hyperinsulinism on the metabolism of carbohydrate, amino acids, and lipids by the liver ?
 - (b) What are the causes of the observed symptoms ? Suggest why this condition, if prolonged, leads to brain damage.
13. Thyroid hormones are intimately involved in regulating the basal metabolic rate. Liver tissue of animals given excess thyroxine shows an increased rate of O₂ consumption and increased heat output (thermogenesis), but the ATP concentration in the tissue is normal. Different explanations have been offered for the thermogenic effect of thyroxine. One is that excess thyroid hormone causes uncoupling of oxidative phosphorylation in mitochondria.

How could such an effect account for the observations ? Another explanation suggests that the thermogenesis is due to an increased rate of ATP utilization by the thyroid-stimulated tissue. Is this a reasonable explanation ? Why ?

14. What are the possible advantages in the synthesis of hormones as prohormones or preprohormones ?
15. Which of these hormones inhibits FSH production in a female mammal ?
 - (a) estrogen
 - (b) adrenalin
 - (c) thyroxine
 - (d) testosterone
 - (e) luteinizing hormone
16. Does it make any difference when you take a thyroid hormone ?
17. During pregnancy, the chief source of progesterone is the :
 - (a) ovary
 - (b) placenta
 - (c) pituitary gland
 - (d) mammary gland
 - (e) uterus
18. Name two animal hormones that are peptides (or proteins) and steroids.
19. Name two animal hormones that are antagonistic in their effects.
20. Why are diabetes patients more sensitive to skin diseases ?
21. On the basis of their physical properties, hormones fall into one of two categories: those that are very soluble in water but relatively insoluble in lipids (*e.g.*, epinephrine) and those that are relatively insoluble in water but highly soluble in lipids (*e.g.*, steroid hormones). In their role as regulators of cellular activity, most water-soluble hormones do not penetrate into the interior of their target cells. The lipid-soluble hormones, by contrast, do penetrate into their target cells and ultimately act in the nucleus. What is the correlation between solubility, the location of receptors, and the mode of action of the two classes of hormones ?
22. Which is the most widely-used drug in the world ?
 - (a) Aspirin (b) Morphine (c) Paracetamol (d) Progesterone
23. Acetylcholine is a :
 - (a) Neurotransmitter (b) B-vitamin (c) Enzyme (d) Protein
24. Name the gland which acts both as an 'endocrine' as well as an 'exocrine' gland.
 - (a) Pancreas (b) Pituitary (c) Thyroid (d) Adrenal
25. Can obesity affect life expectancy in humans ?
26. Why is edible salt iodized ?
27. The gland that degenerates during adolescence is :
 - (a) Thymus (b) Liver (c) Pituitary (d) Pineal
28. Excess production of thyroxine leads to :
 - (a) Diabetes (b) Cretinism (c) Gigantism (d) Exophthalmic goitre
29. Which is the hormone that lowers the concentration of calcium in the blood ?
 - (a) Somatostatin (b) Oxytocin (c) Calcitonin (d) Androgens
30. Which of the following contains iodine ?
 - (a) Insulin (b) Thyroxine (c) Oxytocin (d) Adrenalin