# ENDOCRINE HORMONES

PATRICK A. DIASSI AND ZOLA P. HOROVITZ

*The Squibb Institute for Medical Research, New Brunswick, New Jersey*



This entire volume could easily be devoted to "Endocrine Hormones", and so we have decided to sacrifice the more popular areas of endocrine pharmacology, such as the adrenal and gonadal hormones, insulin, the catecholamines, etc., and devote this review to the pharmacology of some less popular and newer hormones. Arbitrarily we have chosen pineal hormone, thyroid hormones, hypothalamic hormones, gastrointestinal hormones, insect hormones, plant hormones, and the prostaglandins. We hope that this brief review of a seemingly strange conglomerate of pharmacologically active substances will be of benefit to update readers in this rapidly expanding area of scientific knowledge.

## PINEAL HORMONE

Although serotonin and other indole amines are found in many parts of the body, the pineal gland is the only mammalian organ known to convert serotonin to N-acetylserotonin and then by O-methylation to melatonin (1).

### ISOLATION

In 1917 McCord & Allen (2) observed that when bovine pineal extracts were fed to amphibians their skins changed in color. Lerner & Case (3) reported in 1959 that these pineal skin extracts could induce skin changes in amphibians by causing the melanin granules in the melanophores to congregate around the cell nucleus. Lerner et al. (4) reported on the isolation of melatonin as the one pineal gland factor that produced the changes seen with pineal extracts.

### ACTIONS OF MELATONIN

*Skin pigmentation.*—Melatonin, one of the most powerful skin lightening substances known, is about forty times as potent as epinephrine or norepinephrine. Serotonin, the precursor of melatonin, does not seem to have any skin lightening effects, even in doses as high as 4000 micrograms (5). Besides causing the aggregation of melanin granules, melatonin causes these granules to be reduced in perimeter and in volume (6) and, more slowly, a decrease in the formation and deposition of melanin in the skin (7). Melato-

nin also appears to antagonize the action of the melanocyte stimulating hormone (MSH) on the isolated frog's skin, probably by competing for its receptor site (6).

*Effects of melatonin on smooth muscle.*—Although the many biogenic amine indoles, such as serotonin, stimulate the contraction of certain types of mammalian smooth muscle, N-acetylation of serotonin seems to cause a total loss of its ability to do this (8). Rahamimoff in 1965 (9) studied the relationships between serotonin and melatonin in effecting several types of smooth muscle and found that, in general, melatonin inhibits the spontaneous contractions or bronchoconstriction caused by serotonin.

*Effect of melatonin on the gonads.*—Data are available to show that pinealectomy will cause an enlargement of the rats' gonads, both in males (10) and in females (11). The frequency of estrus is markedly increased when young females are pinealectomized, and pineal transplants later on will abolish this effect (12). When female rats are fed pineal extracts, the weight of the eventual litter is increased. When the male is fed the extract before mating, the weight of the litter is decreased. When both the male and the female are given the pineal extract, litter weight is also decreased, which suggests that the pineal effect is stronger in the male than in the female (13). Other investigators have found that the administration of melatonin to immature rats caused a marked decrease in ovarian weight (14). Kappers (15) has reported that the pineal hormone will reduce seminal vesicle weight in mature rats. Adams et al. (16) have shown that melatonin-treated rats have small ovaries, delayed vaginal opening and smaller pituitaries containing much more luteinizing hormone (LH) than normal.

Not only have there been some reports, however, which do not support the concept that melatonin exerts effects on the gonads (17, 18), but also the mechanism by which it might produce a gonadal effect is not at all clear. Martini and his collaborators (19) have recently presented evidence indicating that implants of melatonin in the median eminence or the midbrain reticular formation can influence the secretion of pituitary gonadotrophins. This finding indicates that the endocrine effects of the pineal gland and melatonin may work via an action on the endocrine centers of the brain. Melatonin has been shown to block the secretion of LH, but not that of follicle-stimulating hormone FSH (20).

There are some indications that the pineal-induced antigonadal may not be mediated by melatonin. Polypeptides have been isolated from pineal extracts, and these can inhibit the stimulation of mouse uteri and ovaries by pregnant mare serum gonadotrophin (21). Thieblot (22) has obtained a partly purified gonadotrophin inhibitor from pineal glands that appears to be distinct from melatonin. McIsaac and his co-workers (23) have reported that methoxytryptophol, another O-methylated derivative of serotonin, is also a potent inhibitor of rat gonadal function. It is also possible that this compound is naturally secreted by the pineal gland and produces biological effects. Thieblot (22) has been able to fractionate the pineal extract into both an antigonadotrophic factor and a progonadotrophic factor. Reiss et al.

(24) were able to separate, at least partially, the two factors by exposing crude suspensions of the gland to trichloroacetic acid. They found that the supernatant fraction has an inhibitory action on the gonads, while the precipitate showed a stimulatory effect.

*Effect of melatonin on the thyroid gland.*—It has been demonstrated (25) that melatonin will reduce thyroidal cell height and iodine$^{131}$-uptake in rats. Melatonin also has been shown to depress the rate at which the thyroid hormone is excreted in the rat (26). Pinealectomy increases the weight of the thyroid gland in mice, but this result is not obtained in animals treated with melatonin (27).

*Effects of melatonin and the pineal gland on biological rhythm.*—Wurtman & Axelrod (28) have suggested that the mammalian pineal gland functions as a biological clock that secretes more or less of its hormones in response to environmental lighting and the time of day. The data supporting this notion and the role of the pineal gland in the control of ovulation have been reviewed in detail by Wurtman, Axelrod & Kelly (29).

## THYROID HORMONES

Although several iodinated derivatives of L-tyrosine occur in the thyroid gland, the two active principles are the amino acids, L-thyroxin, and L-triiodothyronine. Thyroxin was first isolated in 1915 (30), and the structural formula was elucidated in 1926; the following year it was synthesized by Harington and his associates (31, 32). In 1953, Gross & Pitt-Rivers (33) described another naturally occurring aminoacid from the thyroid, triiodothyronine, and also described the synthesis of this compound, which had an activity qualitatively similar to that of thyroxin, but was much more potent on a molar basis. Evidence is also now available that the thyroid contains a separate endocrine system (the C-cells), which is responsible for secretion of a hormone called thyrocalcitonin that has a powerful effect on calcium metabolism (34); the effects of this hormone are also controlled by the parathyroid gland [for review see Talmage et al. (35)].

Since the literature is quite voluminous on the pharmacology of the thyroid hormones, we shall concentrate in this review on only a few of their pharmacological actions.

### Effects on the Heart and Catecholamines

Thyroid hormones will generally produce a tachycardia that is not a result of increasing metabolic rate. Thyroxin will generally cause quickening of the pulse (36) and in very high doses an increase of almost 50 per cent in the heart rate. Thyroid interactions with catecholamines are quite complex and thyroid hormones usually sensitize animals to various effects of epinephrine and norepinephrine, such as the cardiovascular, glycogenolytic, and lipolytic effects (37). There are a few reports which indicate that the heightened cardiovascular response of a hyperthyroid animal to endogenous catecholamines or the heightened response to exogenous catecholamines after the administration of thyroid hormone is attributable at least in a

large part to diminished myocardial binding of the catecholamines in the presence of thyroid hormones (38, 39).

Hill & Turner (40) have shown that a group of hyperthyroid patients had significantly higher intrinsic heart rates than normal subjects, while other subjects that were hypothyroid had significantly lower intrinsic heart rates than normals. They suggested that the increased intrinsic heart rates and exaggerated responses to sympathetic stimulation in the hyperthyroid condition or after thyroid hormone can be explained by an increase in tissue levels of cyclic adenosine 3′,5′-monophosphate (cyclic AMP). This substance, in normal subjects, can produce vascular changes identical to those found in hyperthyroidism and after $\beta$-adrenergic stimulation (41).

It has been shown in both guinea pigs and cats that the myocardium of thyroxin-treated animals demonstrates increased excitability even before the appearance of tachycardia. Thyroxin given to these animals caused significant mitochondrial ultrastructural changes in the heart, with an apparent increase in over-all activity of the electron transport chain (42). Triiodothyronine has been shown to potentiate the effects of catecholamines on the activity of phosphorylase in the heart; this potentiation does not seem to be a result of an interference with the uptake of catecholamines by the heart (43).

Tommaselli et al. (44) have demonstrated, using autoradiographic techniques, a preferential localization of L-thyroxin and triiodothyronine in the sinoventricular bundle (bundle of *His*) of the rat heart. These findings suggest the possibility of direct effects of the thyroid hormones on cardiac conductivity. Studies by Folkman et al. (45, 46), using dogs in which ligation of the bundle had been performed, support this theory. In these animals with complete heart block, autografts of thyroid tissue or implantation of thyroxin tablets in a local area of myocardium transformed this area into a new pacemaker, which became the dominant electrical focus of cardiac activity.

Thyroid activity also seems to affect the vascular activity of rats. Thus, Koehn et al. (47) have shown that aortic blood pressures were greater in hyperthyroid and lower in hypothyroid rats than in euthyroid rats, while angiotensin and norepinephrine were more active in hypothyroid than in euthyroid rats. Administration of thyroxin into otherwise hypothyroid rats did not alter the response to angiotensin and the animals were more responsive than hyperthyroid and euthyroid rats. Hypothyroid rats also appeared to be more sensitive to the vasodilator responses caused by either isoproterenol or papaverine than were their euthyroid counterparts.

### Effects of Thyroid Hormone on Blood Cholesterol Levels

Rosenman et al. (48) in 1951 showed that the hyperthyroid rat excretes more cholesterol into the bowel than does the hypothyroid rat. It has been known for some time that in hypothyroid states in rats the cholesterol level of the blood is elevated, and that the hypercholesterolemia can be corrected by the administration of thyroid.

Wren (49) has recently studied, in 74 patients with arteriosclerotic con-

ditions, especially involving the coronary vessels, the response to treatment with sodium L-thyroxin. The serum cholesterol levels were lowered in 51 of the patients and extensive clinical relief was experienced in 19 of the 22 patients with angina. When 48 thyroid-treated patients were compared with 48 patients undergoing conventional treatment, it was found that during the 2-year study period only two of the thyroid-treated patients died, whereas 12 of the control group died.

Gasper (50) did a post-mortem study on the thyroid glands of a group of 59 patients known to have arteriosclerotic disease. He found that only 17 of the 59 thyroid glands fell within the normal range, while 42 of the glands showed marked histological and pathological deviations from normal. He suggested from these studies that a definite correlation between thyroid deficiency and arteriosclerosis does exist.

Miettinen (51) has reported, however, that his studies in the myxedematous patient showed that the catabolism of cholesterol is accelerated during the thyroid-induced reduction in serum cholesterol values; the actual effect of thyroid on cholesterol synthesis is still unclear, even though the end-result, i.e., a reduction in serum cholesterol values, of thyroid therapy, seems evident.

Dextro-(D)-thyroxin is now commercially available for the treatment of hypercholesterolemic conditions. Searcy et al. (52) performed one study in which daily doses of 4 to 6 mg of D-thyroxin were given to hypercholesterolemic, but otherwise normal, patients. They reported changes in serum cholesterol content confined to the $\beta$-lipoprotein and also that the ratio of $\beta$- to $\alpha$-lipoprotein cholesterol was reduced. The compound had little effect on triglyceride levels and the patients did not show tachyphylaxis to the D-thyroxin as had been reported for the levothyroxin.

Although D-thyroxin has been reported previously to have little thyroid substituting effects, Schindler, in a recent clinical paper (53) has reported that in 20 hypothyroid patients he was able to control pathological elevation of serum lipid levels with D-thyroxin and also that the drug acted as substitute thyroid therapy.

Besides cholesterol, the thyroid hormones seem to effect serum uric acid and decrease the previously increased uric acid levels in the absence of thyroid hormone (54). Increasing levels of thyroid hormone also seemed markedly to increase serum ribonuclease activity (55). The activity of a number of thyroxin and triiodothyronine analogues on the uric acid serum ribonuclease and blood cholesterol levels are described in a structure-activity paper by Rawson (56).

Work on the mechanism of action of the thyroid hormones has been extensive, but the final answers concerning these mechanisms have not been obtained. The reader is referred to the following articles for discussions of possible biochemical bases for the actions of the thyroid hormones (57–59).

## HYPOTHALAMIC-RELEASING HORMONES

The development of the ideas of neurohumoral control of the pituitary gland began with the investigations of F. H. A. Marshall in the late 1930's.

These studies, as well as others pertinent to the history of the concept of hypothalamic-releasing factors or of hormones that influence the function of the gland, have been summarized by Harris (60). We shall attempt to bring the reader up-to-date concerning present knowledge of these various releasing hormones.

### Corticotrophin-Releasing Hormone (CRH)

The first direct evidence in support of the concept of a hypothalamic control of the release from the pituitary of an adrenocorticotrophic hormone (ACTH) came in 1955 (61). The first purification of the corticotrophin-releasing hormone (CRH) from hypothalamic tissue was reported by two groups of investigators in 1959 and 1960 (62, 63). More recent studies clearly demonstrate the presence of CRH in human hypothalamic tissue and also in neurohypophysial extracts (64). Highly purified CRH extracts have been made from beef posterior pituitary extracts by Schally and his group. These extracts, which were active at doses of less than 1 microgram (65), contain a basic peptide related to lysine-vasopressin, in which a disulfide ring system is present. Authoritative review on the subject of the physiological control of ACTH-release can be found in the following references (66–68).

### Thyroid-Releasing Hormone (TRH)

Although a hormone responsible for the release of thyroid hormones (TRH) was postulated as early as the middle 1950s, the first unequivocal demonstration of the presence of such a substance in hypothalamic tissue was performed in 1962 (69). TRH can be obtained when fragments of pig, beef, and sheep hypothalami containing the pituitary stalk in the median eminence region are lyophylized, pulverized on dry-ice, defatted with acetone and petroleum ether, and extracted with 2N acetic acid. TRH contains a high percentage of combined amino acids and Guillemin et al. have speculated that the TRH of sheep may be an octadecapeptide (70). The studies of Schally et al. have indicated a smaller molecular weight peptide for bovine and porcine TRH (71). Recent work by Bowers et al. has shown that administration of small amounts of bovine TRH to human cretins significantly increased the levels of thyrotropin in the plasma. This finding indicates that TRH is not species specific for man (72). A more complete discussion of TRH can be found in the review of Guillemin (73).

### Growth (Hormone)-Releasing Hormone (GRH)

The first demonstration *in vitro* of a growth hormone-releasing hormone (GRH) was made in 1964 (74). The first demonstration *in vivo* of GRH activity was made by Pecile et al. in 1965 (75). Work by Schally and his co-workers has demonstrated that GRH may be an acidic polypeptide with a molecular weight of about 2500 (76). The reader is referred to two reviews (77, 78), for further elaboration of the effects of GRH.

### Follicle-Stimulating Hormone-Releasing Hormone (FSH-RH)

FSH-releasing hormone was first demonstrated in rat hypothalamic extract in 1964 (79, 80). Present evidence suggests that FSH-RH has a molecular weight of about 300 and may be a polyamine derivative (81). Some amines that are known to be present in hypothalamic tissue, such as histamine, spermidine, and lysine, have been identified in highly purified FSH-RH preparations and are able, at very small doses, *in vitro,* to deplete pituitary FSH (82). Igarashi et al. (83) have demonstrated that beef FSH-RH, given to amenorrheic or anovulatory women, induced a significant increase in the release of FSH into the blood and also increased the secretion of estrogen into the urine and the amount of cervical mucus. A more complete review of the physiological evidence for hypothalamic control of FSH secretion can be found in (84, 85).

### Luteinizing Hormone (LH)-Releasing Hormone

The first evidence for the existence of a hypothalamic neurohumor regulating LH release was provided in 1960 and 1961 (86, 87). LH-releasing hormone probably has a molecular weight less than 1500; and, since it has a high amino acid content, it is most likely a polypeptide (88). There is some evidence that dopamine or other amines may play a role in LH-releasing hormone activity. The addition of dopamine to an *in vitro*-incubation system of median eminence tissue led to an increase in the release of LH, whereas serotonin, epinephrine, or norepinephrine in equivalent doses were ineffective (89). More complete reviews of this subject can be found in (90, 91).

## GASTROINTESTINAL HORMONES

The gastrointestinal hormones are produced by the mucosa of the distal portion of the stomach and the proximal small intestine. Unlike the hormones of the endocrine glands of mesodermal origin which are steroidal in nature, the hormones of the gastrointestinal mucosa are polypeptides. These hormones are involved in regulating the secretory and motor activities of the stomach, gallbladder, pancreas, small intestine, and biliary tract. The presently known intestinal hormones are gastrin, secretin, and cholecystokinin-pancreozymin, which have been the subject of an excellent review by Grossman (92).

The spectrum of activity of these hormones is surprisingly broad. Gastrin strongly stimulates the secretion of gastric acid, but only weakly that of pepsin and pancreatic bicarbonate. It also stimulates flow and enzyme secretion by both the stomach and pancreas (93). These activities can be considered to be physiological since they are observed at doses below those required for the maximal secretion of gastric acid. Secretin, which is released from the mucosa of the upper small intestine (94), stimulates the flow of pancreatic juice and bicarbonate output, stimulates biliary flow and bicarbonate output and inhibits gastrin-stimulated gastric acid secretion. Cholecystokinin-pancreozymin (CCK-PZ) is the term applied to a hormone iso-

lated from intestinal mucosa. Its spectrum of biological activity resembles that of gastrin; however, CCK-PZ is a very potent contractor of the gallbladder (95) and a weak stimulant of gastric acid secretion (96). Human gastrin II is a heptadecapeptide having the structure A. Gastrins obtained from other species, such as hog, dog, and sheep, are also heptadecapeptides, but each differs in respect to one or two of the amino acids.

Hog secretin is composed of 27 amino acids and has recently been synthesized (97). Unlike the other gastrointestinal hormones, significant activity is only observed if the molecule remains intact. Cholecystokinin-pancreozymin has the partial structure B (98). The C-terminal dodecapeptide, as well as intermediary peptide sequences, have been synthesized (99). The C-terminal of CCK-PZ resembles those of gastrin and the decapeptide, caerulin (100), isolated from the skin of the amphibian *Hyla caerulea*. The similarity to gastrin extends through the C-terminal pentapeptide.

Glu-Gly-Pro-Trp-Leu-Glu-Glu-Glu-Glu-Glu-Ala-Tyr-($SO_3H$)-Gly-Trp-Met-Asp-Phe-$NH_2$

*A*

Lys-($Ala_1$,$Gly_1$,$Pro_1$,$Ser_1$)-Arg-Val-($Ile_1$,$Met_1$,$Ser_1$)-Lys-Asn-($Asx_1$, $Glx_1$, $His_1$,$Leu_2$,$Pro_1$,$Ser_2$)-Arg-Ser-Asp-Arg-Asp-Tyr-($SO_3H$)-Met-Gly-Trp-Met-Asp-Phe-$NH_2$

*B*

[Glu-Gln-Asp-Tyr($SO_3H$)]-Thr-Gly-Trp-Met-Asp-Phe-$NH_2$

*CAERULEIN*

The C-terminal octa- and dodecapeptides of CCK-PZ elicit all the biological responses of the pure hormone (101), as does the C-terminal tetrapeptide of gastrin. However, whereas both the unsulfated as well as sulfated forms of gastrin have been isolated and show hormonal activity, only the sulfated CCK-PZ and partial structures are active. A number of synthetic variations of gastrin and C-terminal tetrapeptide amides have appeared (102, 103). Of five heptadecapeptides synthesized, none was found to inhibit gastric secretion in conscious dogs (104).

Synthetic secretin is identical with natural secretin with respect to all properties and physiological activities (105).

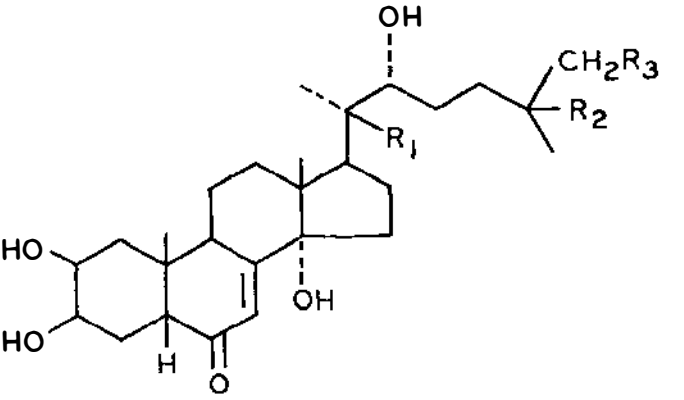
The response to continuous intravenous infusion of secretin into normal human subjects and into patients with duodenal ulcer, gallstones, acute pancreatitis, and chronic pancreatitis has shown that measurement of maximal bicarbonate response can be used to detect the impaired capacity of patients with chronic pancreatitis to secrete bicarbonate (106).

Other gastrointestinal hormones have been discovered and isolated; among the most recent are enterogastrone (107, 108) and gastrone (109, 110).

## INSECT HORMONES

### Moulting Hormones

The first crystalline insect moulting hormone, ecdysone, was isolated from dried pupae of the silkworm, *Bombyx mori*, by Butenandt & Karlson (111) in 1954. X-ray crystallographic studies by Huber & Hoppe (112) indicated its steroidal nature and led to publication of its complete structure A.




A $R_1 = H, R_2 = OH, R_3 = H$

B $R_1 = R_2 = OH, R_3 = H$

C $R_1 = R_2 = R_3 = OH$

D $R_1 = OH, R_2 = R_3 = H$

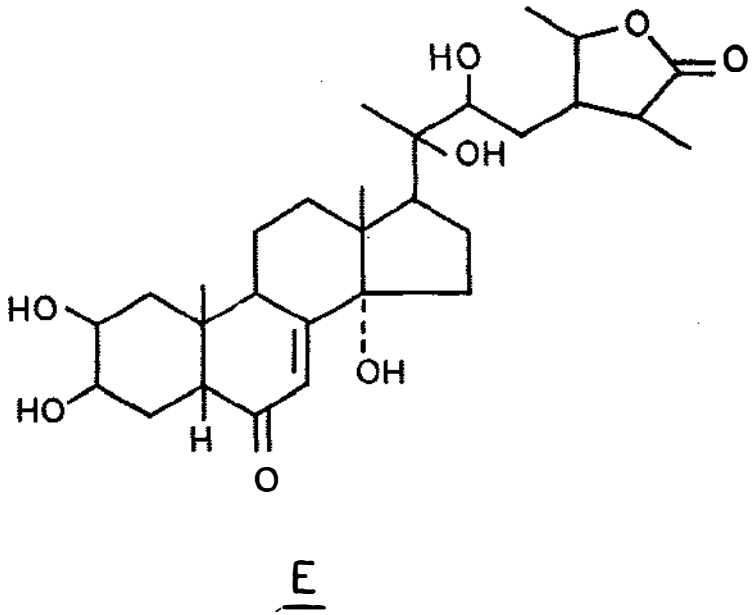
Fig. 1

Later another substance, ecdysterone, was isolated from the same insect (113, 114) and shown to have structure B. This compound also has been isolated from crayfish (as crustecdysone) (115), oak-silk moth (116), and tobacco hornworm (117); in addition, 20,26-dihydroxyecdysone (C) has been isolated from the tobacco hornworm (118).

Recently, a number of steroids possessing insect moulting hormone activity have been recognized to be distributed widely in plant sources. Ponasterone-A isolated from *Podocarpus nakaii* has been shown to be 25-desoxy-20-hydroxyecdysone (D) (119) and ecdysterone (C) has been isolated from the Australian timber tree, *Podocarpus elatus* (120). Four new $C_{29}$

and a $C_{28}$ insect moulting substances have been isolated; cysasterone (E), and amarasterones A and B (structures F and G), were isolated from *Cyathula capitata* (121–123), lemmasterone (H) from *Lemmaphyllum microphyllum* (124), and makisterone A (I) from *Podocarpus macrophyllus* (125). Other steroids possessing insect moulting hormone activity have been described (126–132).

That the compounds isolated from plants, as well as from insects, show strong insect moulting hormonal activity and are related chemically to sitos-



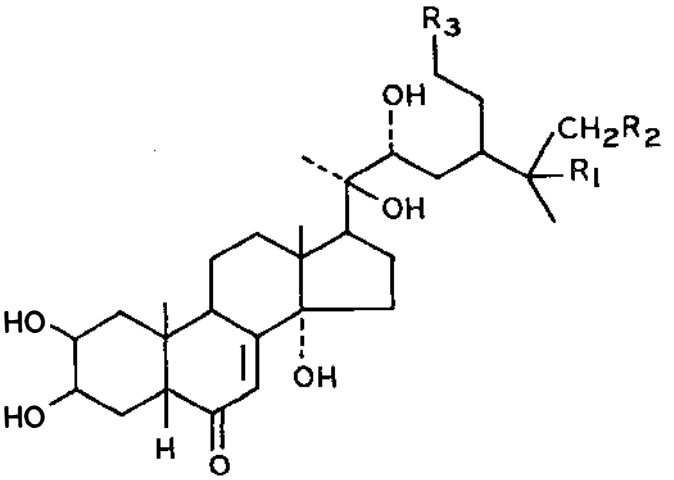

E

FIG. 2.

terol, makes it attractive to speculate that these substances may be exogenous factors, which an insect receives with its food (127). This assumption is substantiated by the isolation of compounds having insect moulting activity from adult insects in which the thoracic glands have degenerated.

These hormones regulate moulting and metamorphosis in insects. The standard test for insect moulting activity utilizes the ligated abdomen of the larva of blowfly, *Calliphora vicina*. A modification of this test which utilizes only one-third to one-fourth as much hormone as is required in the Calliphora test, makes use of the larvae of the house fly, *Musca domestica* (133).

An ultrastructural study of the origin and secretion of ecdysone in the moulting glands of the migratory locust, *Locusta migratoria*, has shown that this hormone may be emitted from small vesicles formed from agranular ergastoplasmic membranes (134). Little is known as to the biochemical activ-

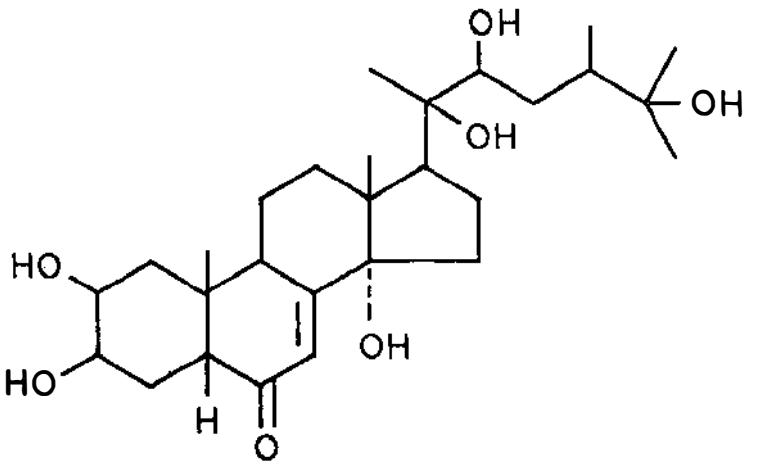



F $R_1 = R_3 = H,\ R_2 = OH$

G $R_1 = R_2 = H,\ R_3 = OH$

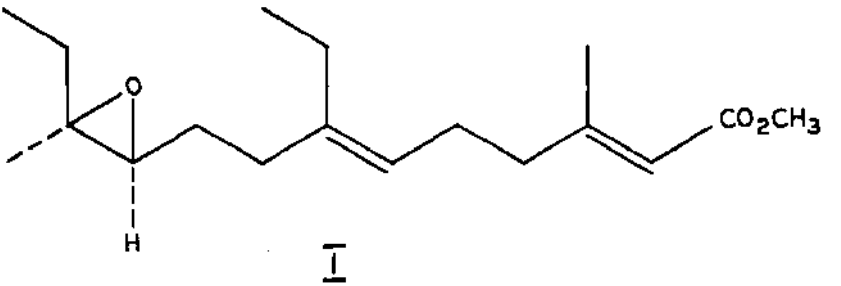
H $R_1 = OH,\ R_2 = R_3 = H$

FIG. 3.




I

FIG. 4.




I

FIG. 5.

ity of these hormones. One report states that ecdysterone activated dopadecarboxyläse four hours after injection into *Calliphora larvae* (135). Another study on the effects of ecdysone on inhibitors of RNA and protein synthesis indicates that induction of RNA synthesis at specific chromosomal loci by this hormone is independent of protein synthesis (136). Several moulting steroids, as well as anabolic steroids, have been shown to enhance the uptake of amino acids by the mouse liver, both *in vivo* and *in vitro* (137).

Rubrosterone, first isolated from *Achyranthes rubrofusca* and shown to be a $C_{19}$-steroid, is most likely a metabolic product of the insect moulting substances, ecdysterone and inokosterone, also isolated from the plant (138).

### JUVENILE HORMONE

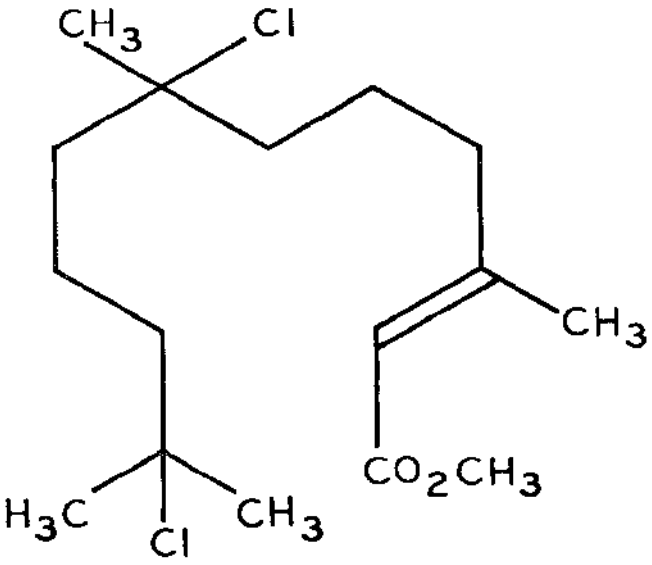
The "juvenile hormone," synthesized in the corpora allata of the Cecropia moth, has been shown to be methyl cis-10,11-oxido-3,11-dimethyl-7-ethyltrideca-trans,trans-2,6-dienoate (I) (139, 140). This substance, which controls the post-embryonic growth and development of insects, shows promise as an ideal insecticide (141). Three highly ingenious stereoselective syntheses of this hormone have recently been reported (142–144).

The morphogenic effect of juvenile hormone on higher Diptera such as the large blowfly *Sarcophaga bullata* has been studied (145). Injection of juvenile hormone into larvae prevents puparium development at about the third day of pupal-adult development. Topical application to the abdomen of young pupae results in the secretion of a second pupal cuticle.

Methylfarnesoate dihydrochloride (II), which shows potent juvenile hormonal activity (146), has been studied as an insecticide for pests of stored grain (147). Although it did not prevent production of viable eggs of *Tibolium castenum,* the first and third instar larvae failed to pupate or to become adult.

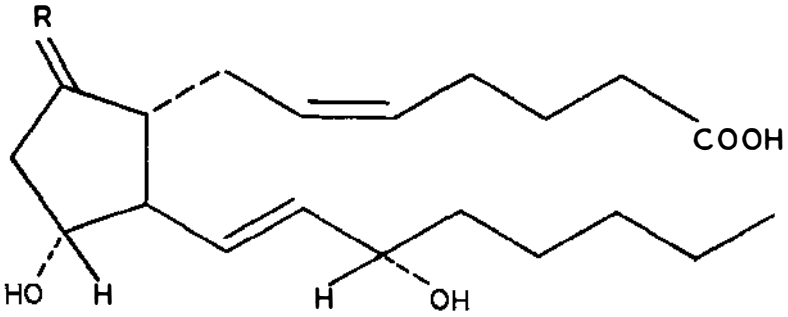
## PLANT HORMONES

Sexual reproduction in the aquatic fungus, *Achlya bisexualis,* is governed by specific substances (148, 149). Antheridiol is secreted by the fe-




II

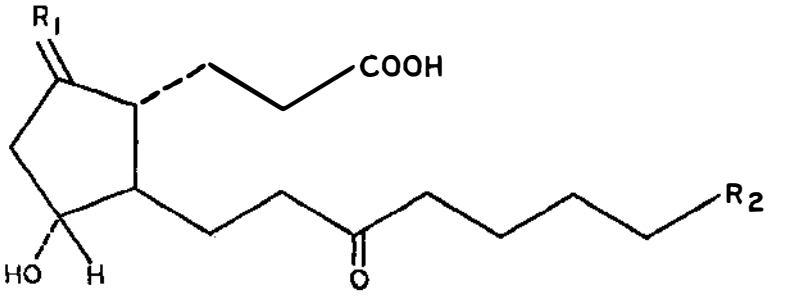
FIG. 6.




I R = HO···H

III R = O

FIG. 7.




II $R_1$ = HO⋰⋱H , $R_2$ = $CH_3$

IV $R_1$ = O , $R_2$ = COOH

V $R_1$ = HO⋰⋱H , $R_2$ = COOH

FIG. 8.

male plant and brings about formation of antheridiol hypae on the male plant (150, 151). A structure of this steroid was proposed recently (152) and the compound synthesized (153); the synthetic material exhibited an activity within the same range as that of the natural compound.

## PROSTAGLANDINS

The tissue prostaglandins are a group of unsaturated lipid-soluble acids derived from dihomo-γ-linolenic and arachidonic acids. Although originally found in human seminal fluid, they now have been identified in most, if not all, mammalian tissues. They are formed by cyclization and oxidation of these fatty acids, and enzyme systems that are particularly active in effecting these transformations are found in human and sheep seminal fluid. The prostaglandins have a wide spectrum of biological activities varying from lowering blood pressure, stimulating smooth muscle, affecting sperm transport, inhibiting lipolysis, aggregating platelets, to causing uterine movements and the secretion of gastric juice. Excellent reviews on the physiological role of the prostaglandins have been published recently (154–156). Although their precise physiological function is not yet known, their variety of effects, both qualitative and quantitative, may serve as biological regulators. Prostaglandins liberated by nerve stimulation, which then have actions opposite to the nerve stimulation, suggest a role as feed-back inhibitors.

The total synthesis of both natural and enantromeric forms of prostaglandin $E_1$ has been accomplished (157).

The main urinary metabolite of prostaglandin $F_{2\alpha}$ in the guinea pig is 5α,7α-dihydroxy-11-ketotetra-nor-prostanoic acid (II) (158). In man, prostaglandin $E_2$ (III) is metabolized to the dicarboxylic acid IV (159) and prostaglandin $F_{2\alpha}$ to the dicarboxylic acid V (160).

Recent work has described the synthesis of oxygen-containing analogues of prostaglandin that inhibit the activity of natural prostaglandins on smooth muscle (161). At certain concentrations these compounds can manifest agonistic activity on the gerbil colon (162).



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