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Integration of Endocrinology

INTRODUCTION

The title of this chapter might well have been "The Integrative Action of the Endocrine System," for an integration of endocrinology in itself will serve only to demonstrate more clearly the true homeostatic function of the humoral medium. The ability of man to respond and adapt successfully to his changing environment is made possible mainly by the successful coordinative activities of the two great integrating mechanisms, the nervous and endocrine systems.

The action of the nervous system in this respect has been the subject of intense investigation and research since the beginning of the twentieth century when Sherrington's magnum opus on this subject was published.¹ As a result, neuronal interrelationships and the function of various integrative portions of the central nervous system, such as the hypothalamus, cerebellum, basal ganglia and Area 4-S, have been clarified. A fundamental knowledge of hormonal interdependences, however, and correlative relationships with the "milieu intérieur" has been slower in evolving, most of the progress having been made only in the past two or three decades.

The purpose of this chapter is to demonstrate the homeostatic nature of physiologic, hormonal interactions and to discuss those factors which elicit and condition this endocrine equilibrium. The scope of this review precludes the possibility of entering

into a detailed discussion of the function or mechanism of action of all the hormones. Perhaps an appreciation of the intricate nature of humoral balance is best obtained by observing individual instances illustrating the modus operandi of the endocrine system. Numerous examples present themselves, and the problem is one of selection, for each has its merits. Arbitrarily, therefore, hormonal interactions in carbohydrate metabolism and in the menstrual cycle have been chosen for initial examination. A survey of the former will disclose the manifold agencies through which hormones may exert their influences; a review of the latter perhaps will help to reveal more clearly the nature, necessity and efficacy of the delicate system of checks and counterchecks which characterizes the endocrine regulation of metabolism. A third chapter will be devoted to the endocrine interrelations during stress, a subject which has been the central research problem of our group for many years.

HORMONAL INFLUENCES IN THE REGULATION OF CARBOHY- DRATE METABOLISM

The ultimate end of all endocrine activity, with regard to any aspect of metabolism, is to maintain the constancy of the "milieu intérieur," or more properly, to adjust the internal environment to the needs of the moment. Inasmuch as the level of blood sugar is one of the most important and most variable factors in the body's re-

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sponse to changing conditions, the humoral influences on carbohydrate metabolism will be examined first.

The endocrine system begins to exert its regulating effects on carbohydrate metabolism while foodstuffs are still in the digestive tract. Absorption of glucose from the intestine is retarded in cases of adrenal insufficiency, and the adrenal cortex is thought to be necessary for the phosphorylation which facilitates rapid absorption.² Similarly, hypothyroidism results in impairment of glucose uptake, while thyrotoxicosis is accompanied by increased absorption, thus indicating that the thyroid also influences the blood sugar level at this early stage.

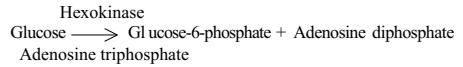
Once absorbed into the blood stream, glucose is carried to the liver and may, to a large extent, be converted and stored as glycogen. Also in the liver, glucose is formed from the deaminated residues of certain amino acids, and from glycerol and fatty acids. This gluconeogenesis is stimulated and, to a large extent, regulated by certain hormones of the adrenal cortex and of the anterior pituitary. In either event, glucose brought to or formed in the liver and deposited there in the form of glycogen represents the most important carbohydrate reserve of the body. Glycogen stores are reconverted to glucose as the requirements of the moment dictate. This transformation, glycogenolysis, is strongly influenced by the secretion of the adrenal medulla.

Injection of epinephrine results in an immediate rise in blood glucose because of an increase in hepatic glycogenolysis. However, secondarily, this causes a compensatory insulin secretion, due to resultant hyperglycemia, which ultimately tends to increase the amount of glycogen stored in the liver.

Epinephrine also causes glycolysis; it converts muscle glycogen into lactic acid. The latter returns, in part, to the liver where it is utilized in the formation of liver glycogen.

To be utilized in any manner, glucose

must first be converted to the compound glucose-6-phosphate. This phosphorylation reaction requires the enzyme hexokinase, the coenzyme adenosine triphosphate (ATP) and presumably proceeds in the following manner:



Once this compound, glucose-6-phosphate, is formed, the way is open for further glucose degradation or assimilation. Obviously, then, any factors modifying the catalytic activity of hexokinase in the original phosphorylation reaction will influence both the deposition of glycogen and the amount of glucose available for use as a source of energy. It is precisely at this stage of intermediary carbohydrate metabolism that several hormones appear to exert their effects.

Extracts of the anterior pituitary, corticoids and insulin have been shown to exert a pronounced influence on the activity of hexokinase, although there is considerable disagreement regarding the mechanism of these interactions.³ Another possible mode of action of insulin may be by the promotion of the rate of transfer of glucose across cell membranes, rather than solely through intermediary catalytic effects on enzyme systems.⁴ In addition to this participation in intermediate glucose breakdown, the endocrine glands also enter into many other aspects of carbohydrate metabolism. Several of these effects deserve at least passing mention.

The anterior pituitary secretes a diabetogenic principle.* The gonads may affect elimination of glucose by lowering the "renal threshold" in pregnancy. As many

* The exact nature of the diabetogenic factor or factors is not known. Growth hormone (STH) appears to have this property. On the other hand, the demonstration that splenic extracts and meningococcus endotoxin can be substituted for pituitary extracts in the Cori preparation with the same apparent inhibition of glucose phosphorylation suggests a certain degree of nonspecificity for the reaction. The exact nature of this mechanism and its relation to the hyperglycemic factor of the pancreas (glucagon) is an important avenue of current investigation.

as 35-40 per cent of women may exhibit glycosuria without hyperglycemia during the last months of pregnancy.⁵ Posterior lobe extracts have been shown to produce hyperglycemia,⁶ to prevent the hypoglycemic action of insulin⁷ and to antagonize the hyperglycemic effect of epinephrine.⁸ One authority points out that "there is not a single hormone which has not been shown to exert some influence on carbohydrate metabolism."⁹ This could be said with equal justification about protein metabolism, blood pressure and the sexual cycle, because they all exhibit some deviation from the norm under the influence of any hormone, at least when it is administered at toxic dose levels that are conducive to non-specific stress. It is remarkable that so many hormones exert highly specific effects on carbohydrate metabolism, presumably because nature has foreseen several alternative safety mechanisms capable of maintaining the homeostasis of the blood sugar, even when one or the other regulator is accidentally eliminated.

The details of the intricate mechanism through which carbohydrate metabolism is effected in health and disease will be discussed elsewhere in this book. The sole purpose of this chapter is to demonstrate the manifold media through which hormones may exert their metabolic effects, for example, by influencing intestinal absorption, acting biocatalytically on enzyme systems, modifying cellular permeability, altering the renal threshold and stimulating or inhibiting other endocrines. Of these, the last factor is one of the most important and characteristic aspects of hormonal activity, and is illustrated more vividly by the diagram showing hormonal interactions during the menstrual cycle.

HORMONAL INTERRELATIONS DURING THE MENSTRUAL CYCLE

This subject also will be discussed in a subsequent chapter of this book. Here it merely will serve as an interesting example

of hormonal correlations which affect a series of morphologic and functional changes in the body. To do this, it will suffice to examine and discuss the accompanying diagram (Fig. 1).

Follicle-stimulating hormone (FSH) acts on the ovary and causes follicle maturation. This is solely a morphogenetic effect, which in itself does not stimulate hormone production. However, FSH also initiates the production of luteinizing hormone (LH), which subsequently induces the follicle to produce folliculoid (or "estrogenic") hormone. After this, LH transforms the mature follicle into a corpus luteum and stimulates the latter to produce folliculoids, although it does not cause luteoid formation by itself. If follicle maturation has not proceeded far enough for luteinization, LH itself can elicit an FSH discharge to correct this.

The folliculoids cause "estrus" changes in the uterus, oviduct and vagina; they prepare these structures for the subsequent action of progesterone. It is questionable whether folliculoids exert important, direct effects on the mammary tissue, but they do act back on the pituitary, causing enlargement of the anterior lobe and an inhibition of both FSH and LH production. In addition, they stimulate luteotropin and, especially in combination with progesterone, the secretion of some "mammogenic hormone." Luteotropin (or "prolactin") maintains the structure and function of already existing corpora lutea, but does not form new ones. It also stimulates secretion in a previously developed mammary gland.

The luteoids formed under the influence of luteotropin cause "luteal phase" changes in the uterus, vagina and oviduct. They act back on the anterior lobe and inhibit FSH, but not LH, production. The growth of the breast is mainly dependent on direct stimulation by some mammogenic hormone (STH?), although this effect may be augmented by simultaneous treatment with steroids, particularly folliculoids and luteoids.

The regular recurrence of the female sex-

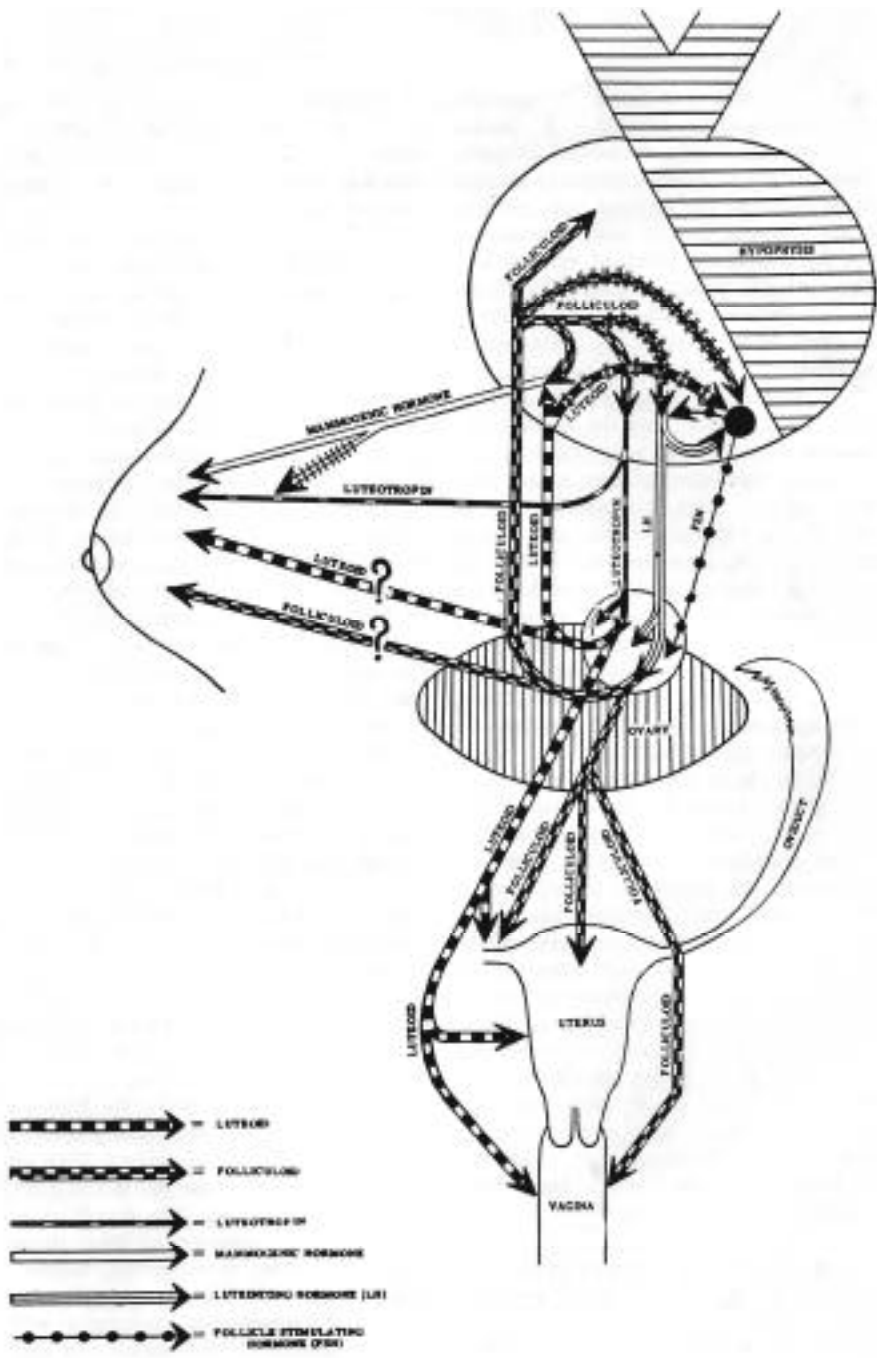


FIG. 1. Hormonal interrelations during the menstrual cycle (After Selye, H.: Textbook of Endocrinology, ed. 2, Montrea, Acta Inc., 1949). This schema should be read beginning at the large black dot in the anterior lobe. The arrows which end in a target organ without continuing into other arrows indicate purely morphigenetic actions. Simple arrows denote stimulation, crosshatched arrows inhibition.

ual cycle perhaps may be explained by the periodic production of FSH and LH with a resulting increased formation of folliculoids; the latter in turn inhibit FSH and LH formation to a point where the ovary fails to form sufficient folliculoids to maintain this inhibition so that FSH and LH production again rises, and the process is reinitiated.

HORMONAL INTERRELATIONS DURING THE GENERAL ADAP- TATION SYNDROME

As a third example of the important homeostatic role played by interactions between the endocrine glands, the general adaptation syndrome has been chosen for two reasons: first, because the entire concept of "biologic stress" has developed as a result of studies concerned with homeostatic hormonal interrelations; second, because some of the so-called adaptive hormones (for example, corticotropin, somatotropic hormone, cortisone, hydrocortisone and electrocortin) are just about to enter into the armamentarium of the practicing physician.

Some 17 years ago, animal experiments demonstrated that the organism responded in a rather stereotyped manner to widely different stimuli, such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue or x-ray irradiation. Each of these stressor agents had their own specific effects, in many cases diametrically opposed. Their common denominator was that they placed the body in a state of "biologic stress." The organism responded in the same stereotyped manner regardless of the nature of the provocative agent. Thus, the resultant effect was the summation and superimposition of the specific actions of the "stressor" on the general reactive pattern elicited by "nonspecific stress."

The initial nonspecific adaptive reaction, the "alarm reaction," which characterizes the body's response is in the nature of a call to arms of the organism's defenses. Further results indicated that this was merely

the first development of a more prolonged general adaptation syndrome which comprises three distinct phases: the "alarm reaction" in which adaptation has not yet been acquired, the "stage of resistance" in which adaptation is optimal and finally, the "stage of exhaustion" in which the acquired adaptation is lost. Thus, continued stress after adaptation has begun to develop leads to the "stage of resistance." At this time, inurement to the evocative stressor increases, but resistance to other damaging agents diminishes. When adaptation fails, the "stage of exhaustion" ensues with collapse of all defense and eventual death.¹⁰

The manner by which stress initiates the chain reaction of adaptation is unknown, but a dual course may be assumed. One response leads to damage or shock, possibly through nervous stimuli, deficiencies and/or toxic metabolites. The other involves a stimulation of the pituitary-adrenal axis.

In conditions of stress, the pituitary is stimulated to secrete corticotropin and, under certain circumstances, perhaps also somatotropin. The primary action of the former causes the secretion by the adrenals of cortisonelike gluco-corticoids, while somatotropin apparently sensitizes the tissues to the electrocortin and desoxycorticosteronelike mineralo-corticoids.

The mineralo-corticoids and the gluco-corticoids have many opposing effects. Deficiencies and imbalances in either the production or the activity of these corticoids result in derangements of the normal adaptive mechanism and can become the principal factors in the production of certain maladies considered to be essentially "diseases of adaptation."¹¹

The principal interrelationships between the hypophysis, the adrenal cortex and the peripheral target organs during the general adaptation syndrome are presented in the accompanying schematic diagram (Fig. 2).

The stressor, such as trauma, infection or burn, acting on the targets evokes a stimulus which induces the anterior pituitary to produce corticotropin; under certain cir-

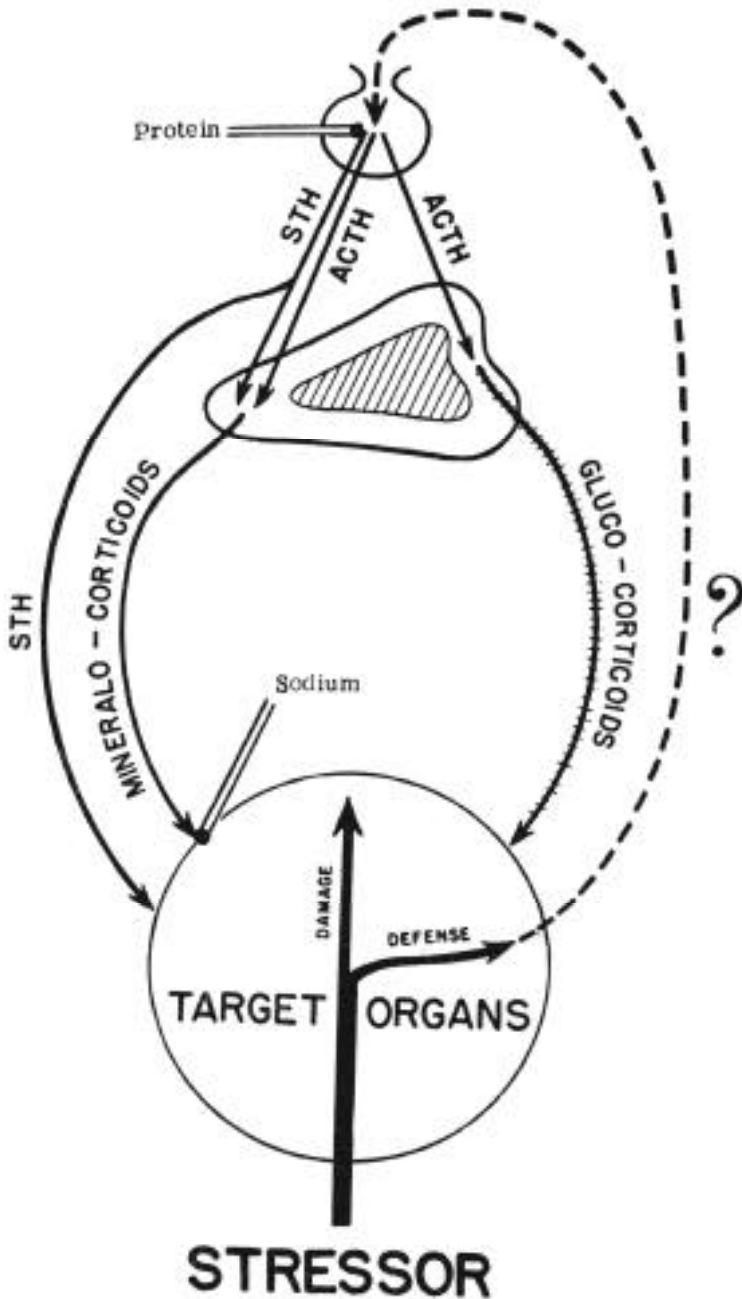


FIG. 2. Schematic diagram illustrating the principal interrelations between the hypophysis, the adrenal cortex and the peripheral target organs during the general adaptation syndrome (After Selye, H.: First Annual Report on Stress, Montreal, Acta Inc., 1951).

cumstances it may also cause a discharge of somatotropin. The nature of this first mediator between the directly injured organ and the anterior pituitary is not yet known; therefore, it is indicated in Fig. 2 merely by an interrupted line labeled with a question mark. Corticotropin induces the adrenal cortex to produce predominantly gluco-corticoid compounds, the effect of which upon the response of various target organs is generally inhibitory, for example, catabolism and diminution of granuloma formation and of allergic responses. Conversely, somatotropin enhances a variety of defensive reactions in the target organs, such as anabolism and augmentation of granuloma formation and of allergic responses, primarily by stimulating the connective tissue. Part of this action is undoubtedly not mediated through the adrenal cortex, but this direct effect sensitizes the connective tissue elements to the essentially similar actions of the mineralo-corticoids. Somatotropin perhaps also acts by increasing the production of mineralo-corticoids. However, in itself, it cannot maintain the cortical cells in a functional condition, hence its "corticotropic" effect is dependent on the simultaneous availability of corticotropin.*

In the final analysis, the physiologic and pathologic responses of the target organs to stressor agents largely depend on the balance between the mineralo-corticoids and somatotropin on the one hand, and corticotropin and the gluco-corticoids on the other. The entire reaction is highly subject to "extraneous conditioning factors" (individual variations of organ susceptibility, heredity, diet and previous exposure to

stress). Among these, particular attention has been given to dietary protein which appears to increase the production and/or activity of somatotropin and to sodium which augments the effects of mineralo-corticoids on certain target organs, especially the kidney,

Among the derangements of the general adaptation syndrome that may cause disease, the following are particularly important: (1) an absolute excess or deficiency in the amount of corticoids and somatotropin produced during stress; (2) a disproportion in the relative secretion, during stress, of corticotropin and gluco-corticoids on the one hand, and of somatotropin and mineralo-corticoids on the other; (3) production by stress of metabolic derangements which abnormally alter the target organ's response to somatotropin, corticotropin or corticoids to the phenomenon of "conditioning" and (4) although the hypophysis-adrenal system plays a prominent role in the general adaptation syndrome, other organs which participate in the latter, such as the nervous system, liver or kidney, may also respond abnormally and become the cause of disease during adaptation to stress.

GENERAL HORMONAL CORRELATIONS

In view of the complexity of the subject, a general discussion of the endocrine system as a whole will have to be superficial. However, a succinct outline of the field will serve as an introduction to the subsequent chapters of this book.

Figure 3 summarizes the most important hormonal interactions. It shows that the endocrine glands are governed both by hormonal and by nonhormonal stimuli; the former travel to them exclusively through the blood, the latter either through this medium or through nervous pathways.

As a regulator of endocrine activity, the anterior lobe of the pituitary occupies an

* F. G. Young presented a good deal of evidence suggesting that the so-called adrenal weight factor is associated with STH. This factor is presumed to be necessary for the maintenance of the adrenal cortex and may represent, in a sense, a "second corticotropin." However, the action of STH upon the adrenal can not yet be considered to be definitely established, while the peripheral synergism between STH and mineralo-corticoids has been demonstrated beyond the possibility of doubt.

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outstanding position. It stimulates the adrenal cortex (adrenocorticotrophic hormone, corticotropin, and perhaps the somatotrophic or growth hormone, somatotropin, "adrenal weight factor"), the pancreas (diabetogenic hormone), the thyroid (thyrotrophic hormone, thyrotropin) and the gonads (luteotropic hormone, LTH, luteinizing hormone, LH, and follicle-stimulating hormone, FSH). In this manner, it participates in almost all aspects of bodily function.

Thus, under the influence of corticotropin and perhaps somatotropin, the adrenal cortex is stimulated to produce gluco-corticoids, mineralo-corticoids and certain androgenic or testoid compounds. As can be seen in Figure 3 under the heading of target organs, these substances act on the accessory sex organs, carbohydrate metabolism, mineral metabolism, blood pressure, smooth muscle contraction, the thymus and other lymphatic structures. The diabetogenic hormone, which may be identical with somatotropin, influences carbohydrate metabolism, at least partly, through its effect on insulin secretion.¹²

The thyrotrophic hormone acts on the basal metabolic rate, growth, differentiation and metabolism via the thyroid hormone, thyroxin, whose production it stimulates. Similarly, the gonadotropins cause the ovary and testis to produce various sex hormones, which in turn control the development of secondary sex organs and also influence growth and general metabolism. Conversely, in addition to exerting their peripheral effects, the hormones produced by the endocrines under the control of the anterior pituitary act back upon the anterior lobe of the hypophysis to inhibit the formation of the corresponding tropic hormones. This self-regulating mechanism has been viewed, from the point of view of cybernetics, as a servo or "feed-back" system which is one in which "variations, or consequences of variations, in the quantitative output of an apparatus are fed back

for the control of the system."¹³ In this case, the regulation is achieved by the "compensatory atrophy and compensatory hypertrophy mechanisms." Outside of their influence on endocrine activity, the anterior lobe hormones also affect somatic growth in general (somatotropin), development of secondary sex organs (mammogenic hormone) and certain metabolic processes (anterior lobe hormones whose nature has not been fully elucidated).

The posterior lobe produces only directly acting hormones, namely, oxytocin, which influences uterine contractions, and vasopressin, which affects blood vessel contractions and diuresis. Its cells are not greatly influenced by hormonal stimuli, but are responsive to variations in water and salt metabolism, which probably affect its vasopressin production through the intermediacy of the nervous system.

The middle lobe of the pituitary produces intermedin, which acts directly on the chromatophores. Its cells are influenced mainly by light which affects them through the intermediacy of the nervous system.

The adrenal cortex is not significantly influenced through directly acting physiologic stimuli apart from those acting in conjunction with the corticotropins. Most of the numerous factors which affect its development and function reach it through the intermediacy of the anterior lobe, whose corticotrophic hormones are the most important regulators of adrenal cortical activity.

The adrenal medulla produces epinephrine and norepinephrine, which affect mainly the blood pressure, smooth muscle contractions and glycogenolysis. Unlike the cortex, the medulla does not respond to pituitary tropic stimuli and is almost entirely refractory to all types of stimuli, except those which reach it through its cholinergic, sympathetic (secretory) nerves. Increased amounts of epinephrine cause a stimulation of anterior pituitary corticotropins, and result in eventual adrenal cortical stimulation. Direct injection of acetylcholine, the hu-

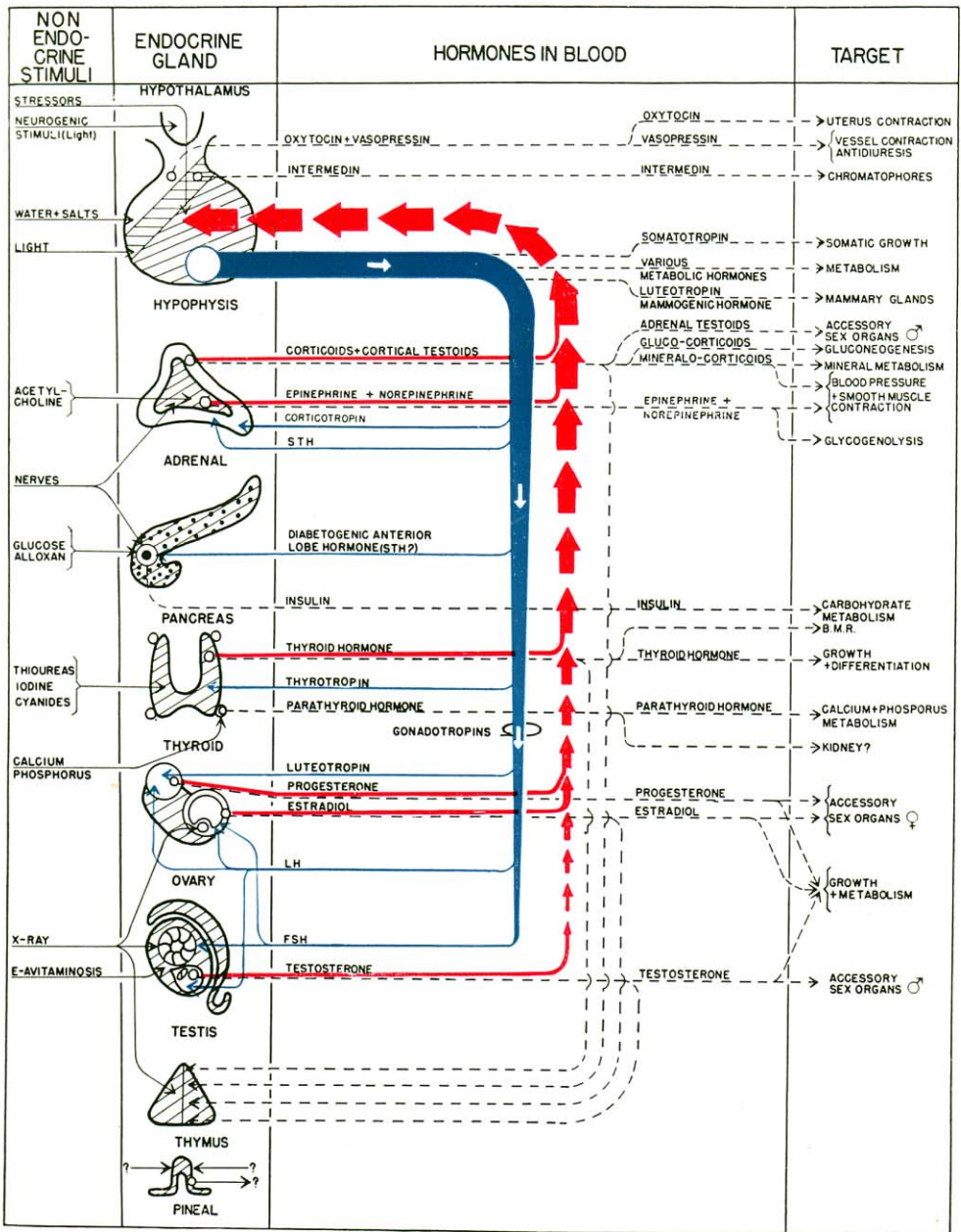


Fig. 3. General hormonal correlation. Dotted lines indicate hormones acting directly on peripheral target organs; solid lines correspond to anterior lobe hormones acting on other endocrine glands; interrupted arrows represent hormones acting on anterior lobe.

moral mediator of the splanchnics which synapse with medullary cells, also causes a discharge of epinephrine.

The pancreas produces insulin, which acts on carbohydrate metabolism as indicated in the first passages of this chapter. The function of the islets of Langerhans is dependent on stimulation by the "diabetogenic hormone," nervous impulses which reach it through the vagus, the glucose concentration of the blood and certain drugs, such as alloxan, which exert a specific toxic effect on islet tissue.

The thyroid appears to produce only one kind of hormone, which acts directly on its target organs. The elaboration of this thyroid hormone, probably a mixture of thyroxin and triiodothyronin, is stimulated by the thyrotropin of the anterior lobe, but certain drugs also exert a direct effect on the thyroid and its hormone production. The thioureas appear to inhibit the synthesis of thyroid hormone. Iodine is an essential constituent of this endocrine principle and hence is necessary for its synthesis; iodine also appears to inhibit the effect of thyrotropin on the thyroid cells. The role of the cyanides is less clearly understood. Perhaps they create an increased demand for thyroid hormone because of their toxic effects on those enzyme systems necessary for normal metabolism or perhaps they merely prevent the entrance of iodine into the thyroid.

The parathyroids do not appear to receive any important tropic stimuli from the anterior lobe or from the nervous system, their function being regulated largely by the calcium and phosphate content of the blood. They appear to produce only one type of hormone, which exerts its influence on calcium and phosphate metabolism through changes in the mineral stores of the skeleton and perhaps also through the renal elimination of calcium and phosphates.

The ovary responds to pituitary follicle-stimulating hormone by the formation of

mature follicles. The folliculoid hormone production of the latter and their transformation into corpora lutea is controlled by luteinizing hormone. The maintenance and progesterone formation of the corpora lutea, on the other hand, depend on luteotropin.

Most of the external stimuli affect the ovary through the intermediacy of the anterior lobe hormones, but x-rays exert a direct, destructive effect on the female gonad. It is relevant, though not specifically indicated in the chart, that folliculoids also appear to exert direct effects on the ovary, for example, formation of "pregnancy-type" corpora lutea in synergy with luteotropin.

In the testis, follicle-stimulating hormone stimulates spermatogenesis while luteinizing hormone increases the size, number and hormonal output of the Leydig cells. Testosterone is the only important testis hormone known. Like the ovary, the testis responds to external stimuli mainly through the intermediacy of the anterior lobe, although x-rays and vitamin E deficiency appear to exert a direct, destructive influence on it.

The thymus undergoes atrophy under the influence of corticoids, folliculoids and testoids; probably most steroid hormones exert a similar, though less pronounced, effect on thymocytes. It is doubtful whether the anterior lobe exerts any direct effects on the thymus other than that mediated by the glands mentioned, although somatotropin appears to be slightly thymotropic.

In spite of the extraordinary sensitivity of thymus tissue to any type of change in the external or internal environment, only radium and x-rays are known to affect it directly without the intermediacy of endocrine activity. The thymus is not known to produce any true hormonal principle.

On morphologic grounds, the pineal is often classified among the endocrines, but no definite data are available concerning the hormones which it might produce or the stimuli which influence its development and function.

It is hoped that this synopsis will act as introduction facilitating the study of the

material which is to be offered in the succeeding chapters.

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