Systematic Endocrinology

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Preface

Almost 200 years ago, Peter Mere Latham, a distinguished English physician and teacher, said, "A good book, though it be not necessarily a hard one, contains important facts, duly arranged and reasoned upon with care." The authors of SYSTEMATIC ENDOCRINOLOGY set out to write such a book. From 1966 to 1971, members of the Faculty of Medicine at the University of Toronto devised a new system-based curriculum. The material gathered to meet the demands of systems teaching was refined and elaborated to give an integrated view of endocrinology. To achieve comprehensiveness and cohesiveness, the authors of chapters on organs with overlapping or closely related functions were paired and their presentations integrated during serial revisions. Each chapter was assigned to a young authority—a well-qualified endocrinologist with considerable experience in research and practice, yet one still intimately involved in the day-to-day teaching of medical students.

The authors assume that the reader has recently completed studies of anatomy, physiology, and biochemistry, upon which any sound understanding of endocrinology depends. Therefore, only the structural, functional, biochemical, and other relationships essential to understanding endocrine function are presented. Important data and concepts not wholly essential to this understanding are summarized briefly or subordinated to the rest of the text. A great amount of supporting data is not provided except in the chapter on the adrenal.

We weighed the impact of the technical language on the learner, attempting to ascertain what ideas, terms, and definitions are common to senior medical students. Throughout we attempted to follow the principle that new learning must start with what the student already knows.

The field of endocrinology is rapidly changing, and we have made every effort to keep this book up to date. Addenda have been made where thorough understanding of the field called for additional information on current developments. These are assembled at the end of the book in an appendix. Also, to create a platform for further learning, we periodically introduced unsolved endocrinologic problems which may stimulate exceptional students to deeper thought and exploration.

In writing these chapters, we paused repeatedly to make sure that we had explained to the reader the purpose of the communication and that we had stated our objectives clearly at the outset so that the reader could adapt to them. In this, we succeeded only in part; nevertheless, the effort to do so helped us meet what we conceive to be the reader's needs.

References have been kept to a minimum to avoid distracting the student. However, each author is deeply conscious of an unacknowledged debt to his many colleagues, past and present, and the general references at the end of each chapter will direct the reader to some of the more important sources.

Most illustrations were prepared by Miss Elizabeth Blackstock and her colleagues in the Department of Art as Applied to Medicine, on the basis of material supplied by each author. I believe the illustrations testify to the success of this collaboration.

In short, SYSTEMATIC ENDOCRINOLOGY is not a compendium but a synthesis that emphasizes the alliance and interdependence of laboratory and clinic in the developments of modern endocrinology.

J. O. G.

A Special Acknowledgment

Authorship is a serious responsibility. Participation in a scientific textbook, if it is to represent a worthwhile contribution to medical education, commits the physician to a significant additional workload. Because they do not recognize this, or recognize but ignore it, many physicians fail. For this reason, the rate of "fetal wastage" in medical textbook publishing is high.

Soon after the inception of SYSTEMATIC ENDOCRINOLOGY, we recognized that we needed a manager to keep the book moving, particularly because the contributors, experienced teacher-practitioner-researchers, were already deeply committed when they accepted responsibility for their chapters. Thus, we invited Dr. John O. Godden, an internist and experienced editor, to join us. This managerial-editorial function is time consuming: The author's work is intermittent; the editor's work nearly continuous. If a chapter has been misconceived, or although properly conceived, has miscarried, the editor must persuade and assist the author, who is sometimes understandably reluctant, to begin again. In all of this, the editor, because he too is a physician, takes an active role, representing the reader and, where necessary, asking for clarification or elaboration.

In SYSTEMATIC ENDOCRINOLOGY, individual authors had from one to four chapters to worry about; John Godden had seventeen. His objective with each of us was to help the writer get his best on paper, in a form most useful to the medical students and practitioners for whom this book was written. If SYSTEMATIC ENDOCRINOLOGY is successful, it will be so because its authors contributed their best to it and because another physician saw it through.

C. E.

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Introduction to Endocrinology

Calvin Ezrin

The endocrine system is an important component of the automatic regulatory mechanisms by which the organism keeps in tune with its environment.[3] It is profitable to compare and contrast it with a similar regulating mechanism, the nervous system—a finite group of structural connections analogous to a telephone system. The endocrine glands communicate by "water travel" at a much slower rate than the nervous system. The neural and endocrine control of lactation and suckling illustrates clearly some important differences in these systems (Fig. 1-1). When an infant is put to the lactating breast, the stimulus of suckling travels by neural pathways up the spinal cord and brain to reach, in milliseconds, the secretory cells of the hypothalamic paraventricular nuclei and their neurohypophyseal connections. The release of stored oxytocin from the neurohypophysis into the circulation follows immediately. The oxytocin travels through the systemic circulation to reach, in a few seconds, the myoepithelial cells of the collecting ducts of the breast, which are filled with milk. The contraction of these cells occurs swiftly and causes the "milk let-down reaction," which expresses a small stream of milk into the infant's mouth. Often the sight of a hungry infant is enough to start milk dripping from the mother's breasts. The visual stimulus travels with the speed of light, but its effect is governed by the rate of impulse transmission from the retina to the hypothalamus and by the slower transport of oxytocin to the breast.

Prolactin, from the adenohypophysis, is the main hormone controlling the manufacture of milk in the breast that has been prepared by previous exposure to prolactin and other hormones. The factors governing the release of prolactin are manufactured in the hypothalamus. There seem to be two mechanisms operating here: (1) a tonic inhibition of prolactin secretion by a normal hypothalamic influence, prolactin inhibitory factor (PIF); and probably (2) an additional prolactin-stimulating factor (PSF), which is produced in response to suckling.

Whatever the substances concerned, they are delivered to the adenohypophysis by a two-stage neurovascular system from the hypothalamus. The first stage is a short neural pathway to the primary capillary network of the hypophyseal portal vessels in the neurohypophysis. The second stage is via the portal venous trunks to the secondary capillary network of this circulation within the adenohypophysis, which leads directly to the cell that manufactures prolactin. However, prolactin, which converts intermediary metabolites into the complex food called milk, takes much longer than oxytocin to act, as is shown by the interval required for the breast to fill up between feedings—usually a matter of 3–4 hours.

Endocrine secretion can be broken down into a

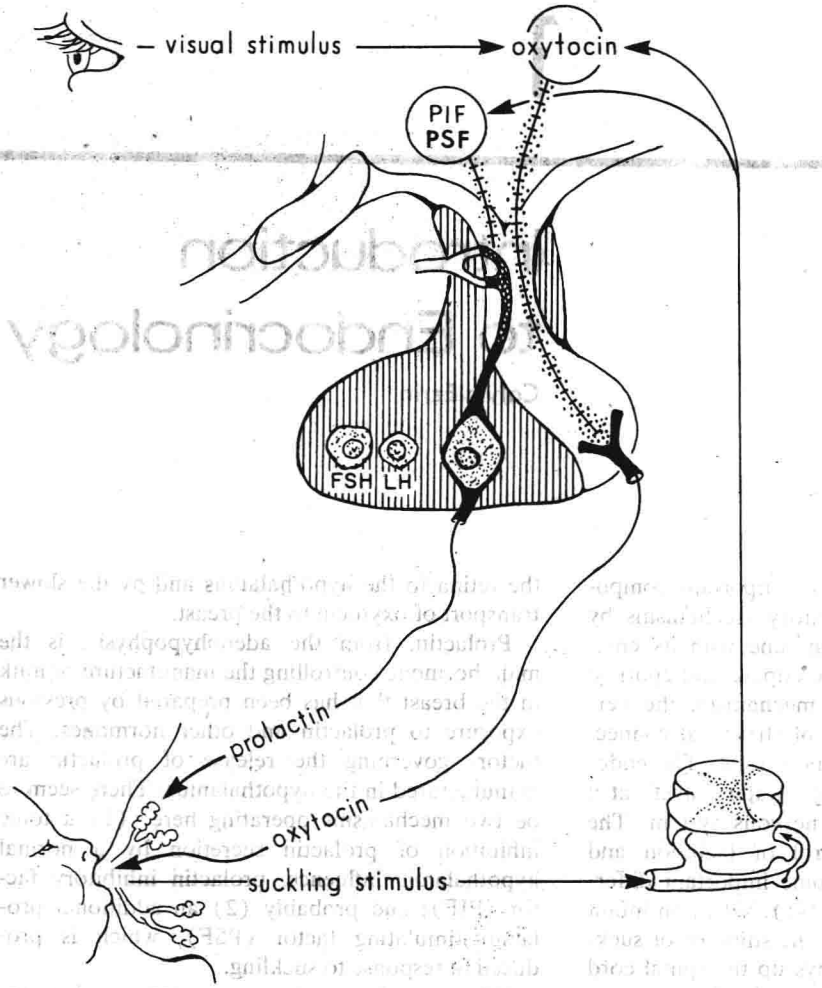

Fig. 1-1. Neuroendocrine control of suckling and lactation. Neurovascular pathways involved in milk production and secretion—hypothalamic neurohypophyseal (oxytocin) and hypothalamic adenohypophyseal (PIF-PSF prolactin)—differ from each other.

The oxytocin path, which begins with nipple stimulation (*lower left*) or visual stimulus (*upper left*), is entirely neural until hormone is delivered from neurohypophysis into veins of systemic circulation (*midright*). The prolactin path depends on secretion of hypothalamic releasing factors (hormones)—prolactin-inhibiting factor (PIF), sometimes called prolactin-inhibiting hormone (PIH), and prolactin-stimulating factor (PSF)—into primary capillary network of hypophyseal portal circulation.

The adenohypophysis contains several different cell types: possibly one for each hormone it secretes. Only three are shown here: one for follicle-stimulating hormone (FSH), one for luteinizing hormone (LH), and one for prolactin (lactogenic hormone). Only in lactation and in the last two trimesters of pregnancy does the prolactin cell contain an abundance of stored stainable granulation. The prolactin cell hyperplasia and hypersecretion in pregnancy may be due to stimulation by high estrogen levels. However, the resultant high levels of circulating prolactin are not enough to induce lactation in pregnancy in the presence of other peripheral interfering factors, e.g. excessive estrogens, which disappear at the time of delivery. Nonpuerperal lactation (galactorrhea) may result if, through the effect of disease or drugs, PIF is blocked, because the prolactin cell is normally held in check by a sustained secretion of this factor.

series of steps similar to those that occur in exocrine cells. The synthesis, storage, release, and transport of hormones are related events that can best be understood if considered separately. Synthesis of the hormones is under the control of nuclear DNA, which regulates the nucleotide sequences of RNA messengers. The amino acid sequences of the polypeptide or protein hormones are transcribed at the ribosomes; the steroid hormones are probably synthesized at the smooth endoplasmic reticulum. In most glands, the product is sufficiently electron-dense to be easily visible by electron microscopy only after it has passed from the ribosomes and their associated rough endoplasmic reticulum to the Golgi apparatus where membrane-bound granules are formed. In most endocrine glands these granules are stored within the neighboring cytoplasm. In the specialized hypothalamic neurosecretory cells of vertebrates, granules containing oxytocin or vasopressin, in association with a stainable carrier substance, pass inside the axons into terminals in the neurohypophysis, where they are temporarily stored until special stimuli induce their release into the circulation. The significance of this mode of transport may be appreciated by recalling that, from the time of its manufacture until its release into the circulation, the hypothalamic hormone is held within a controlled system analogous to sealed railway cars traveling to a storage depot.

Intact secretory granules do not escape as such from the cell. Instead, the membrane coating them partly fuses with the cell membrane and the contents are then extruded in a soluble form. Some of the hormones, such as thyroxine and cortisol, are transported in the bloodstream bound to specific carrier proteins, which limit their free entry into the tissues. Insulin and other protein and peptide hormones appear to travel to their cellular sites of action without being bound to any carrier substance.

The cell responds to a given hormone only after it is bound to a specific receptor site on the cell membrane. With the receptor the hormone may form a new entity, which is capable of generating a signal. The action of a hormone may be regarded as a specific chemical signal producing a specific adaptive response by the cell. However, a relatively nonspecific mechanism involving the ultimate production of one of the adenine nucleotides—3′,5′-adenosine monophosphate (cyclic AMP)—has been implicated in a large number of metabolic responses involving hormones.[1] Many of the hormones appear to act on their target cells by activating an enzyme system, adenyl cyclase, which is associated with binding sites on the cell membrane that can accept only the specific hormone. Adenyl cyclase converts adenosine triphosphate (ATP) to cyclic AMP.[11] Cells respond to increased levels of cyclic AMP with reactions that are characteristic of the particular tissue involved. Thus specificity of the cellular response to hormones is insured mainly by the particular binding sites that initially accept the hormone.[2] Several hormones may evoke a similar response in a tissue (e.g., lipolysis in fat cells may be induced by ACTH, glucagon and epinephrine), but the selective sites for binding of different hormones are different in each case.* There is also considerable evidence that before steroid hormones (e.g., aldosterone) act on target cells, they are bound to specific sites within the nucleus. There the hormone probably liberates or de-represses certain genetic information in the chromosomes, where the messenger RNA is synthesized.

Further details of the cellular action of the hormones will be considered in appropriate sections of the book. In general, it appears that hormones, like enzymes, do not initiate new reactions but act as powerful catalysts in a wide range of physicochemical situations. Life usually continues when a hormone is deficient, although its quality may be considerably altered. Sometimes failure of specific endocrine function, as in severe adrenal cortical insufficiency, is incompatible with life.[7] It is obvious that continuation of life to the succeeding generation depends on normal gondal function.[6]

Since this book concerns clinical endocrinology there will be little mention made of hormones of gastrointestinal origin, such as gastrin and secretin. Some attention will be paid to those hormones derived from tissues not usually considered to be glandular—e.g., the placenta and a variety of nonendocrine neoplasms. The remaining endo-

* See Appendix A: Addendum to Chapter 1.

crine tissues and their hormones may be subdivided according to their physiology, as follows.

Pituitary-Target Gland Model (thyroid, adrenal cortex, and gonads)

Morphologic studies have shown that the adenohypophysis probably produces each of its seven hormones from a specific cell type. Thus the anterior pituitary may be regarded as a confederation of seven relatively independent endocrine glands over which the hypothalamus exerts higher control.[4] Under this type of control, a small change in the central regulator may produce very large peripheral effects. The hypothalamus produces, in picogram quantities, a number of releasing or governing factors that affect the anterior pituitary gland. In turn, the pituitary glands produce, in nanogram quantities, hormones that stimulate target cells, such as thyroid, to produce, in microgram quantities, hormones that have widespread effects on peripheral tissues. Another principle operating to regulate this group of endocrine glands is "negative feedback," which is easiest to observe in the control of thyroid activity[8] (Fig. 1-2). An increase above the normal level of either of the two thyroid hormones (thyroxine or triiodothyronine) reaching the hypothalamic-pituitary region will inhibit the release of thyrotropin from the adenohypophysis, either by affecting the pituitary directly or by suppressing the hypothalamic thyrotropin-releasing factor, which stimulates the cells of the anterior lobe that manufacture this hormone (Fig. 1-2**A**). Conversely, if the level of the thyroid hormones falls below normal, more thyrotropin is secreted. This drives the thyroid gland to produce and release more hormone—if it can (Fig. 1-2**B**). An enzyme defect may severely impair the synthesis of thyroid hormones in a gland that is still capable of further growth. In this case, lack of thyroid hormone is associated with continued overproduction of thyrotropin, which leads to enlargement of the thyroid gland or goiter (Fig. 1-2**C**). Such a goiter may be reduced greatly if the patient is treated early with a daily ration of thyroid hormone sufficient to inhibit the secretion of thyrotropin (Fig. 1-2**D**).

Pituitary-Peripheral Tissue Model (growth hormone, prolactin, and melanocyte-stimulating hormone)

This model is similar to the foregoing in that the effect of each of the hormones is amplified as one moves from the center to the periphery, but it differs in that a target endocrine gland does not take part in this amplification. The control is vested in the hypothalamus, which causes the pituitary to act on some or all of the peripheral tissues. This regulation is complex and depends in large measure on "tonic inhibition"—the sustained suppression of secretion that would otherwise occur, especially with regard to the production and release of prolactin. Growth hormone or somatotropin has been linked with body growth because, in its absence, growth is deficient and when it is present in excessive quantities, as in pituitary gigantism, growth is stimulated. Thus there appears to be a basal secretion of growth hormone related to growth. Also growth hormone seems to respond to other poorly understood influences that cause its secretion to fluctuate rapidly. These factors presumably operate through hypothalamic regulation and vary with age, sex, sleep, and nutritional status.[5]

Hormones Regulating Glucose

In addition to its powerful anabolic effects that are brought about in conjunction with growth hormone, insulin is the hypoglycemic hormone.[10] All the other hormone regulators of blood glucose (growth hormone, epinephrine, glucagon, cortisol and thyroxine) *raise* the glucose level by acting in homeostatic competition with insulin and thus provide an elaborate defense against hypoglycemia. Such a defense is essential because the central nervous system must have a continuous supply of glucose if the organism is to survive.

Hormones Regulating Calcium

The hormones that regulate calcium metabolism are parathyroid hormone—from the parathyroid gland, and calcitonin—from the ultimobranchial body, which is represented in part by the

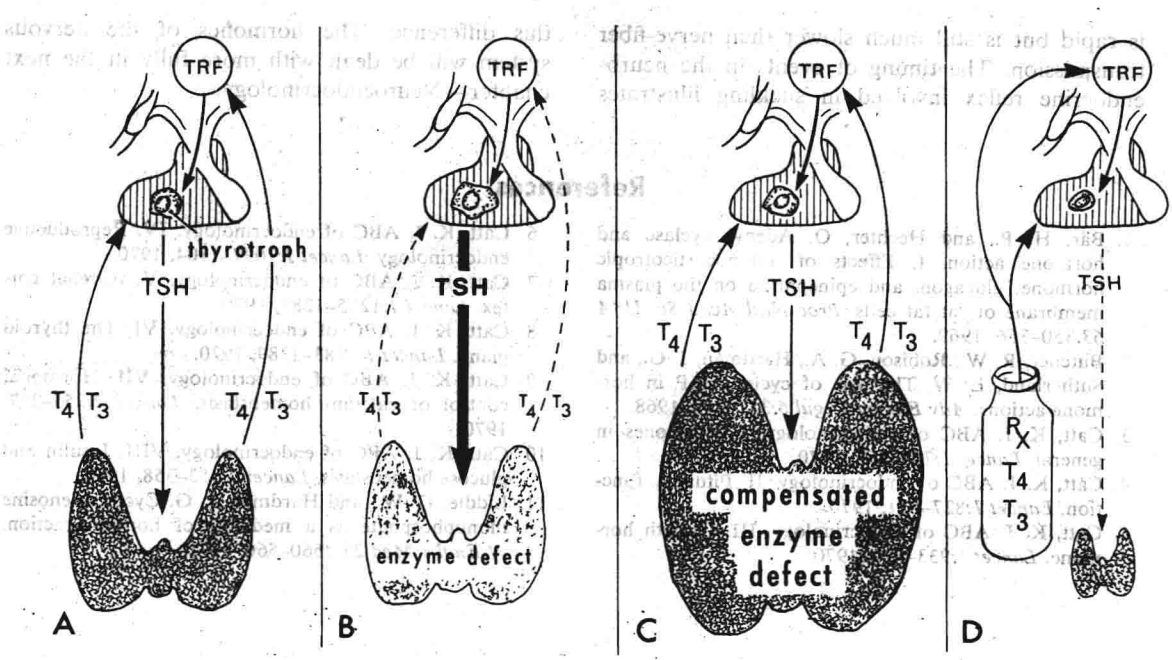

Fig. 1-2. Hypothalamic-pituitary-thyroid relationships in diffuse goiter due to enzyme defect. These figures illustrate activity of the "thyrotroph"—the cell which produces thyroid-stimulating hormone (TSH) or thyrotropin.

A. In normal individual, hypothalamic hormone—thyrotropin-releasing factor (TRF)—has stimulated release and production of TSH, which in turn acts on thyroid to increase output of two thyroid hormones: tetraiodothyronine or thyroxine (T_4) and triiodothyronine (T_3). These hormones, carried in circulation to hypothalamus and adenohypophysis, inhibit further TRF production and TSH release. (Note in **B, C,** and **D** that size of thyrotroph changes commensurate with its activity in these several situations. Variations in TSH output are indicated by arrows of various width. Broken line indicates deficiency or absence of T_4, T_3, and TSH.

B. In individual with enzyme defect, production of thyroid hormones is reduced below level needed to inhibit TSH output. (See also Chapter 4, Physiology of Hormones Produced in the Adenohypophysis.)

C. Thyroid hypertrophy will sometimes overcome effects of enzyme deficiency and raise thyroid hormone production to a level sufficient to again control TSH output. (See also Chapter 5, Goiters Due to Enzymatic Defects.)

D. Treatment of hypertrophied gland with T_4 and T_3 inhibits thyrotroph.

parafollicular cells in the human thyroid gland. The secretion of both of these hormones is regulated directly by the level of calcium ions in the blood. There is no evidence of significant pituitary control. The calcium level of the blood and tissues is also influenced by many other factors: the calcium content of the diet, the vitamin D available in the diet and from sunshine acting on the skin, intestinal absorption, renal function, and contributions from calcium stored in the bones. Because calcium is the key to many hormone-membrane interactions, its regulation is vital to all glandular functions.[9]

Hormones Made by Nervous Tissue (hypothalamic releasing factors, oxytocin and vasopressin, epinephrine and norepinephrine)

Hormones in this group are characterized by low molecular weight and rapidity of action. Compared with the other hormones, their action

is rapid but is still much slower than nerve-fiber transmission. The timing of events in the neuroendocrine reflex involved in suckling illustrates this difference. The hormones of the nervous system will be dealt with more fully in the next chapter—Neuroendocrinology.

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