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With 41 Figures

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Preface

Endocrinology and Metabolism: Progress in Research and Clinical Practice is a new series that has been designed to present timely, critical reviews of constantly evolving fields; to provide practical and up-to-date guidance in the solution of pertinent clinical problems; to offer an alternative to the laborious search of the literature (and the often frustrating reading of highly technical articles); and to translate the language of the laboratory into that of the practice of medicine.

We think that this volume and those to come will prove useful to physicians (and to physicians in training), as well as to investigators in a wide variety of specialties; in short, to anyone who seeks answers to questions in endocrinology and metabolism.

The first chapter of this volume could well serve as a general introduction to the entire series. It points out how our growing understanding of the molecular basis of biologic communication has led to the discovery of a growing number of clinical syndromes, as well as to the realization that phenotypically similar diseases may have radically different pathogenetic mechanisms and thus may require radically different therapeutic stratagems.

Endocrinology and metabolism deal with complex systems comprising innumerable components responsible for signal transmission, rapid adjustment and fine-tuned responses, and many layers of "fail-safe" protection. Sometimes one component of the system misfires, masquerading as a teleologically counterproductive or "paradoxical" event. Our hope is that this volume and those that follow will provide at least some explanation for such events, teaching us that paradoxes do not exist in nature, but only in the minds of the uninformed.

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Introduction: The Journey of the Endocrine Signal: *A Paradigm of Murphy's Law*

PIERO P. FOÀ

"The harmony of life," wrote Claude Bernard in 1866 (1), depends on the integrity of two types of "organic elements," one type represented by muscle and nerve fibers, which functions through direct anatomical connections, and one type represented by the "organs of internal secretion," which influences distant structures through "peculiar substances" introduced into the blood. After more than a century, this concept continues to serve us well, even as we know that "peculiar substances" can be produced by neurons and that, as in paracrine and autocrine relationships, they need not be released into the circulation. Indeed, intercellular communication through chemical signals starts during the earliest stages of embryologic development, when cells begin to segregate toward the formation of specific tissues and well before the appearance of a cardiovascular system. From this beginning and from the embryogenesis of the endocrine system, the journey of the signal molecules takes them through many steps including biosynthesis, release and transport, recognition by the target cell, transduction of the message, and, finally, extinction of the signal through counterregulation, metabolism, and excretion.

The purposes of this chapter are to review selected experiments, biologic models, and clinical syndromes that illustrate these steps and their malfunction and to speculate about future developments, thus introducing the other chapters of this volume, in which some of these clinical syndromes are discussed in detail.

I. Chemical Control of Morphogenesis

Normal morphogenesis requires the orderly succession of cell division, movement, adhesion, differentiation, and death (2). The crucial role of chemical messengers in this process was recognized many years ago by the French physiologist Gley (3), who, perhaps inspired by Claude Bernard's "harmony of life," suggested that some endocrine products be called "harmozones" (from the Greek, meaning "I create an orderly

union''), citing among others the hormones of the thyroid, for their role in amphibian metamorphosis. To Gley's list, we could add the Müllerian inhibiting substance, the testis-determining factor, and the gonadal steroids for their role in sexual development and the many peptides that stimulate differentiation and growth of specific tissues (4–13). Among these peptides are fibronectin, ubiquitin, the cell adhesion molecules (CAM), and other widely distributed substances that promote mutual attraction between cells of similar ancestry and thus the formation of different organs and tissues (2,14,15).

Once contact between cells has been established through these or other mechanisms, portions of adjacent cell membranes fuse to form ''tight junctions,'' or structures capable of creating separate compartments by sealing off intercellular spaces, whereas other portions form transmembrane channels or ''gap junctions,'' providing the structural means for paracrine functions, such as the traffic of ions, nutrients, metabolic regulators, and electrical charges between cells (16–21). Although the degree of opening or ''gating'' of the gap junctions is regulated by membrane potential and by the concentration of hydrogen and other ions and can thus be modified by pharmacologic agents (22; see Section VIII), specific abnormalities of CAM, ubiquitin, or gap junctions have not been described. Nevertheless, the changes in the level of intercellular communication following exposure to prostaglandins (23), tumor promoters, or viruses that cause unregulated growth (24), or following the phosphorylation of gap junction proteins (25) and, finally, the functional deficiencies caused by the experimental disruption of intercellular connections (26–28), suggest that a pathology of these molecules may indeed exist.

By contrast, the developmental defects that lead to hypo- or hyperplasia of specific endocrine tissues are well known (4) and need not be discussed here, except for two recently described animal models. The first is a mutant mouse in which the absence of preoptic nuclei leads to a deficiency of gonadotropin releasing hormone (GnRH) and consequent gonadal failure, a syndrome that can be corrected by transplants of normal fetal hypothalamic tissue (29) and that in some ways resembles idiopathic hypothalamic hypogonadism in humans (30). The second is another mutant mouse with an inherited form of thyroid hypoplasia, in which the presence of low or undetectable levels of thyroxine (T4) and increased secretion of thyroid-stimulating hormone (TSH) resembles human congenital primary hypothyroidism (31).

II. Hormone Biosynthesis

The biosynthesis of the signal molecules by normally developed endocrine tissues depends on the structure and expression of genes encoding peptide hormone precursors (prohormones) and enzymes that either

regulate the posttranslational conversion of prohormones into active hormones or the synthesis of hormones from other molecules, such as amino acids, fatty acids, and cholesterol (Fig. 1.1). Missing prohormone genes or defective gene transcription may result in endocrinopathies such as growth hormone (GH)- or growth hormone–releasing hormone (GHRH)-deficient dwarfism (32–35), isolated corticotropin (ACTH) deficiency with hypoglycemia (36,37), or GnRH-deficient hypogonadism (30). Alternatively, endocrinopathies may arise from defects in gene structure. Such may be the case of dwarfism due to the secretion of a growth hormone variant with normal immunologic properties but decreased biologic activity, a syndrome which, as may be expected, responds to treatment with "normal" recombinant human GH (38).

Other structural abnormalities may lead to the synthesis of inactive TSH (39), of proinsulin molecules that cannot be converted to insulin, and of abnormal insulin variants with decreased biologic activity (40). Theoretically, it should be possible to correct these deficiencies by introducing the missing gene, a feat that so far has been attempted with some success only for the gene of growth hormone, using a viral vector (41,42), for that of insulin using liposomes (43), and by the above-mentioned transplant of normal hypothalamic tissue into GnRH-deficient mice.

In cases where the missing or abnormal gene may be one that normally encodes a prohormone-processing enzyme, the result is either a defective production of the active hormone or a change in the relative amounts of different peptides that derive from the same precursor. Although since the discovery of proinsulin (44), many prohormones have been identified (45–54), and although it is known that different tissues process them in different ways, producing specific peptides in characteristic amounts,

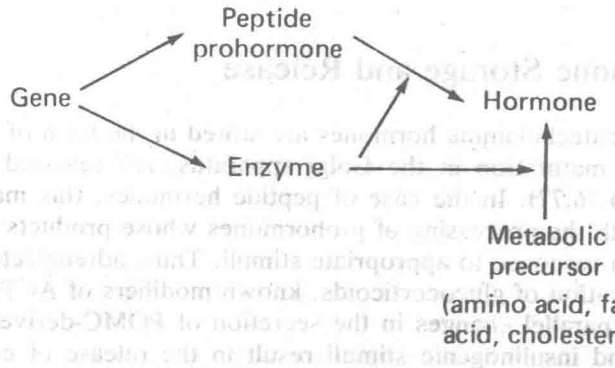

FIGURE 1.1. Schematic representation of hormone biosynthesis through posttranslational processing of peptide prohormones or through enzymatic conversion of metabolic precursors.

only relatively few examples of conversion defects are known to exist. Among them are familial hyperproinsulinemia (55), the abnormal production of glucagonlike peptides in animals and patients with glucagon-producing tumors and other disorders (56–59), a form of pituitary dwarfism due to posttranslational polymerization of growth hormone (60), and the production of a high-molecular-weight TSH with impaired biologic activity in a euthyroid man (61).

Still other enzymatic deficiencies may block the conversion of metabolic precursors into hormones. Such is the case of defective steroidogenesis from cholesterol leading to adrenal hyperplasia and to male pseudohermaphoditism (4,62–64) and of the impaired neurotransmitter biosynthesis associated with autonomic disorders (65) and loss of memory (66). Finally, the structure and the processing of genes may be normal, but their expression may occur in "nonendocrine" tissues, such as the central nervous system (67,68), or it may occur "ectopically," contributing to the clinical syndromes due to hormone-producing tumors (69,70) and, possibly, to the growth of the tumor itself (71).

Finally, the synthesis of a hormone may be modified by environmental factors. Thus, iodine availability limits the synthesis of thyroid hormones (Fig. 1.2), the diurnal and seasonal cycles of light and darkness regulate the synthesis of pineal melatonin (72), and the abundance of polyunsaturated fatty acids (fish oil) in the diet may direct the synthesis of relatively inactive thromboxane A3 (TXA3) at the expense of the more active TXA2, decreasing the risk of thromboembolic disease (73). Endocrinopathies due to ectopic hormone secretion are well known (70) and need not be described here except to mention the additional diagnostic difficulties created by prohormones and by abnornormal posttranslational products when they react in presumably "specific" radioimmunoassay systems (38,56,74,75).

III. Hormone Storage and Release

Peptide and catecholamine hormones are stored in the form of granules which, after maturation in the Golgi apparatus, are released through exocytosis (4,76,77). In the case of peptide hormones, this maturation coincides with the processing of prohormones whose products are then coreleased in response to appropriate stimuli. Thus, adrenalectomy and the administration of glucocorticoids, known modifiers of ACTH secretion, induce parallel changes in the secretion of POMC-derived endorphin (45), and insulinogenic stimuli result in the release of equimolar amounts of insulin and C peptide, providing a convenient tool for measuring B cell function in patients with circulating insulin antibodies (78).

FIGURE 1.2. Congenital goiter in a 2-day-old offspring of a cretin suffering from chronic dietary iodine insufficiency. Failure to synthesize thyroid hormones caused the uninhibited secretion of TSH and thyroid growth. Courmayeur, Italy, ca. 1910. (Photograph by U. Cerletti.)

The release of hormones, whether in the form of granules or not, is under the control of neural, metabolic, and endocrine factors that regulate available energy, membrane polarization, and the concentration of calcium ions in the secretory cell. Although most of these factors are exhaustively discussed in many textbooks of endocrinology (4) and in other chapters of this volume (79,80), a few will be cited here either because they have been the object of renewed interest or because they have hypothetical or proven pathogenetic and therapeutic implications (see Section VIII).

One example is the inhibition of insulin secretion by islet cell surface antibodies (81). Another is the role of biogenic amines in the secretion of numerous hormones, including prolactin and luteinizing hormone (LH),

GnRH, GH, insulin, glucagon, renin, aldosterone, and melatonin, and hence in the regulation of gonadal activity (4,82–90). Still another example is the pulsatile, rather than the continuous, release of many hormones (91–95), a phenomenon that apparently increases such diverse biologic effects as those of glucagon and of insulin on hepatic glucose production (96,97) and of GnRH when used in the treatment of hypothalamic amenorrhea (98) or delayed puberty (99). Finally, one should mention the "enteroinsular axis" whereby "incretins" (100) and other B cell–regulating hormones, such as the glucose-dependent insulinotropic peptide (GIP), are released following a meal.

The pathophysiologic role of these insulin-modulating intestinal peptides is not fully understood, but it is believed that they are the reason why food or an oral glucose load elicits a greater insulinogenic response than does an intravenous glucose load that results in a comparable degree of hyperglycemia (101–104). Although the mechanisms of action of these neural, metabolic, and endocrine factors may differ, the common final pathway in stimulus-secretion coupling appears to be the uptake of calcium ions by the secretory cell and subsequent binding to a specific protein such as calmodulin (calm), leading to the activation of Ca-calm-dependent and/or cAMP-dependent protein kinases and to the phosphorylation of the cytoplasmic proteins required for exocytosis (76,105–108).

IV. Hormone Transport

Hormones are transported from the site of production to their target tissues either free or bound to blood cells, to serum albumin, or to specific binding proteins (4,109). These different hormone compartments are in a state of dynamic equilibrium that determines the amount of free hormone available for biologic activity and for metabolic clearance. Thus, an increase in progesterone-binding protein may lead to hypogonadism and a decrease in androgen-binding protein to hirsutism (110,111), whereas estrogen-binding α-fetoprotein protects the fetus from the high maternal levels of estrogen and plays an essential role in the development of the sexual phenotype.

Carrier proteins for cortisol (4), for insulinlike growth factors (IGF) I and II (112), and for thyroxine (T4; 113) have also been described. Indeed, several inherited variants of thyroxine-binding protein, some with increased and some with decreased binding capacity, have been found in a number of individuals with otherwise normal thyroid function and may be a source of diagnostic difficulties (114,115) complicating the evaluation of thyroid function in malnourished rats (116) and in patients with severe nonthyroid illness (117). Finally, one of the functions of the binding proteins may be to aid in the transport of hormones through the target cell membrane (118) or through the vascular endothelium and the blood-brain

barrier (119–121), toward their sites of action and metabolic disposal (see Section VII).

V. Hormone Binding and Recognition

The recognition of a hormone by its target cell is a function of the receptors and depends on their number and their affinity and specificity for the hormone (122–127). The number of available receptors, in turn, depends on the equilibrium between synthesis, translocation to the site of action, degradation, and, in the case of membrane receptors, internalization and recycling (128,129). Thus, the absence of a gene or a gene defect may lead to a receptor deficiency syndrome, such as vasopressin-resistant diabetes insipidus, PTH-resistant pseudohypoparathyroidism, insulin-resistant acanthosis nigricans (n.) and leprechaunism, GH- and GHRH-resistant dwarfism, androgen-resistant infertility, male pseudohermaphoditism and testicular feminization, vitamin D–resistant rickets (5,30,130–136), and a form of cortisol resistance characterized by sodium retention, hypokalemic alkalosis, and hypertension (137).

In this syndrome, the anterior pituitary, lacking cortisol receptors, escapes the inhibitory feedback and secretes increased amounts of ACTH. The adrenal cortices are stimulated, the high levels of corticosterone and deoxycorticosterone result in the characteristic electrolyte imbalance, and the absence of cortisol receptors in the peripheral tissues prevents the development of signs and symptoms usually associated with Cushing's syndrome. In other circumstances, the genes for the receptors are normal, but their expression is modified by endocrine, dietary, or other factors. For example, the number of insulin receptors may be decreased by glucagon (138), the number of glucagon receptors may be increased by insulin (139), LH-releasing hormone (LHRH) increases estrogen binding (140), and GH induces the synthesis of its own receptors (141).

The list of examples may continue. The number of oxytocin receptors in the uterus and the mammary gland increases sharply at the end of gestation, triggering labor and lactation (142); estrogens control progesterone binding in human breast cancer (143); the angiotensin receptors in the adrenal cortex respond to changes in water and electrolyte balance (144,145); and those of triiodothyronine and insulin respond to obesity and to changes in the nutritional state (146–149). In still other circumstances, the number of receptors may be decreased for unknown reasons, as in the case of the muscarinic receptors in patients with Alzheimer's disease (150) or because of improper translocation to their site of action, as when the insertion of the insulin receptors into the cell membrane is defective, causing insulin resistance in patients with Rabson-Mendenhall syndrome (151).

Another control mechanism is "down-regulation," the decrease in the number of receptors with increasing concentrations of the hormone (122,123,152,153). Although down-regulation is a mechanism for the physiologic control of the endocrine signal, when exaggerated by the presence of excessive amounts of hormone, it may lead to clinically significant resistance. Such is the case of insulin-resistant obesity, acromegaly, type 2 diabetes, and other hyperinsulinemic states (130,152) and the refractoriness to adrenergic agonists that develops in rats with pheochromocytoma (154) or in patients treated with β-adrenergic drugs.

The opposite phenomenon, receptor "up-regulation," may also occur when the concentration of a hormone is low or its binding is prevented, a phenomenon that may explain the hypersensitivity to endogenous catecholamines and the occurrence of cardiovascular reactions upon sudden withdrawal of β-adrenergic blockers (126,127,155,156). Finally, the number of available receptors may be normal, but their effectiveness may be decreased by inhibitors of binding such as those found in the plasma of patients with ataxia telangiectasia (157) or by receptor antibodies such as those against the acetylcholine receptor in patients with myasthenia gravis (158,159), against the insulin receptor in type B acanthosis n. (160), or against TSH in women with primary myxedema (161).

Paradoxically, though receptor antibodies may block the binding of a hormone, they may also mimic its action, as in the case of antibodies against TSH (4,162,163) or against the insulin receptor (164). Perhaps this phenomenon occurs because the receptors contain different immunogenic determinants. Thus, antibodies against the binding site may promote receptor internalization or activation and have a hormonelike effect, whereas antibodies against the catalytic moiety may block its activity (164–166).

Affinity, the second essential property of the receptor, is a function of the molecular structure of the hormone (167–171), of the receptor itself (172), and of the degree of "occupancy" by the hormone. Thus, increasing concentrations of a hormone decrease not only the number of available receptors (down-regulation) but also their affinity, a phenomenon called negative cooperativity (122,123).

The third essential property of the receptor is specificity, and it is not always absolute. Indeed, when sufficient amino acid homologies exist either between the receptors or between the hormones, the hormones may "cross over" and bind to each other's receptors. Similarly, if one of the hormones is present in high concentration or if binding to its receptors is blocked, "spillover" to the other receptor may occur. Thus IGF1, acting through the insulin receptor, may stimulate glucose uptake and lipogenesis, whereas insulin, acting through the IGF receptors, may stimulate growth, explaining, for example, the increased growth of the placenta in insulin-treated rabbits (173), the development of organo-