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ENDOCRINOLOGY: Survival as a Discipline in the 21st Century?

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Endocrinology, the branch of physiology that deals with the communication between cells and/or organs via chemical messengers, (as distinct from neurogenic and immune communication), is for all practical purposes a discipline of the 20th century. Most physiological disciplines evolved slowly as the result of the accumulation of knowledge, but historians are in agreement that endocrinology began on June 1, 1889. On that date the neurophysiologist Charles-Edouard Brown-Sequard (then 72 years of age) reported at a meeting in Paris of the Societe de Biology that following the self-injection of aqueous extracts of guinea pig and dog testes he had experienced enhancement of physical strength, improvement in mental capacity, and increased sexual potency (1). In the words of Herbert Evans, endocrinology had "suffered obstetric deformation in its very birth" (2). Brown-Sequard's sensational presentation was reported widely in the press both within and beyond France. At the clinical level, this fiasco gave impetus to a bevy of rejuvenation quacks who continue to the present day to prey on the incredulous and the desperate (3), and it required many years and many appropriately controlled studies to prove the rejuvenation concept wrong. According to Dale, clinical endocrinology achieved respectability only with the discovery of insulin (4). On the other hand, in disproving the Brown-Sequard claims, the fundamental principles of endocrine physiology were established, and evidence was accumulated for many types of chemical messengers.

Some of the early milestones of endocrinology are listed in Table 1. From its inception endocrine science was a mixture of clinical and basic endeavors, and by 1922 the discipline was in the forefront of biomedical science since it was possible to treat three human endocrine disorders successfully–hypothyroidism, diabetes insipidus, and diabetes mellitus (3). The initial focus in the field was on the identification and purification of hormones, characterization of the regulatory processes that control their secretion, and definition of the effects of hormone deficits and excess. The fact that the synthesis and/or secretion of all hormones is controlled by complex regulatory feedback control processes was recognized to be a distinguishing feature of endocrine physiology. The chemical isolation and characterization of hormones, including epinephrine and norepinephrine, the thyroid hormones, testosterone, aldosterone, ecdysone, estradiol, glucagon, and cortisol, and the pituitary hormones, represent some of the most dramatic accom-

TABLE 1 Some early endocrine milestones

1889	Brown-Sequard injects himself with testicular extracts
1891	Murray treats myxedema with thyroid extracts
1894	Oliver and Schaefer demonstrate a pressor substance in the adrenal
1897	Abel crystallizes epinephrine
1903	Bayliss and Starling discover secretin
1904	Starling delivers Croonian Lectures and coins the word hormone
1909	MacCallum and Voegtlin establish role of parathyroids in calcium metabolism
1912	Antidiuretic hormone characterized in posterior pituitary extracts
1914	Kendall crystallizes thyroxine
1916	Endocrine society founded as the Society for the Study of Internal Secretions
1917	Volume 1 of *Endocrinology* published
1921	Evans and Long describe growth hormone
	Posterior pituitary extract made available for treating patients with diabetes insipidus
1922	Banting and Best provide insulin for treatment of diabetes mellitus

plishments of organic chemistry in this century. By the 1950s the major hormones had been identified, and the pathophysiology of most hormone deficiency states had been characterized. (Elucidation of the pathophysiology of hormone excess states has lagged somewhat behind because of the paucity of appropriate animal models for such studies prior to the development of transgenic technology.)

Since 1950 the field has been altered profoundly by advances of several types. First, development of the radioimmunoassay and of other immunometric techniques made it possible to quantify rapidly and accurately even small changes in hormone levels. As a consequence the discipline has become one of the most quantitative not only in medicine but in all of biology, making it possible to recognize minor perturbations in the physiology of the standard hormones and to identify an additional class of chemical messengers that operate at very low plasma concentrations (dihydrotestosterone, catechol estrogens, enteroglucagon, activin and inhibin, follistatin, somatostatin, pituitary releasing hormones, etc). An unanticipated consequence of these advances in quantification is that cellular regulation by chemical messengers is now recognized to be more complicated than originally formulated. Indeed, hormones that circulate in the plasma are only one class of chemical mediators, some of which work in limited circulatory compartments such as the hypothalamic-pituitary portal circulation, others exert effects on cells adjacent to the sites of synthesis (paracrine or juxtacrine actions), and still others work on the same cells in which they are synthesized. The net consequence is that the borders between endocrinology and cellular biology are no longer distinct.

Second, separation of the endocrine system (chemical control) from the neurogenic and immune control systems has also become blurred with the recognition that many hormones (norepinephrine, epinephrine, vasoactive intestinal peptide, etc) act under some circumstances as neuromediators. Likewise, hormones interdigitate with immune mediators in many circumstances so that all homeostatic control mechanisms must now be viewed as a complex interacting system.

Third, beginning with the recognition by Fuller Albright and his colleagues that pseudohypoparthyroidism is a disorder not of hormones per se but of hormone action (5), the focus in the field has shifted from hormones themselves to the receptors, second messengers, and enzymatic processes that mediate hormone effects in cells. Resistance states to the action of almost every hormone are now recognized to cause human disease, and if diabetes mellitus type II proves to be a primary disorder of insulin resistance, disorders of hormone action will be more common causes of endocrinopathy than states of hormone deficiency and excess combined. At the basic level, the focus on hormone action has served to blur even further the distinction between endocrinology and cellular physiology and biochemistry. By way of example, investigation of the mechanism of action of insulin has provided major insight into intracellular control processes.

These various developments have so eroded the concept of endocrinology as a distinct field as to make it uncertain whether the discipline will survive in its present form during the next decades, much less the next century. This uncertainty is not unique to endocrinology and may be an inevitable and desirable consequence of the many advances in molecular genetics and cellular biology that have served to breach the disciplinary barriers that have separated the branches of biology and physiology. Such branches were erected when the methodologies of science were so limited that the divisions were useful formulations. If endocrinology does survive as a distinct field, it may do so only because of recognition of the fact that many of the unresolved issues in the field involve whole animal physiology. Such issues include the interactions of multiple hormones in the control of complex physiological processes (growth, temperature regulation, metabolic rates, etc), the interaction of biological rhythms with the endocrine system, the integration at the level of the central nervous system of chemical and neurogenic control mechanisms, and the complex behavioral and physiological processes involved in sexual differentiation, gender role behavior, and reproduction. Indeed, endocrinology is poised to lead the renaissance in the physiology of organ systems and whole animals, an arena that is now eclipsed by the revolutionary developments in genetics and molecular biology.

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