

Prospects for Research for Disorders of the Endocrine System

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ENDOCRINOLOGY, THE BRANCH OF medicine that deals with the chemical communication between cells and organs via hormone messengers (as distinct from neurogenic and immune communication), is concerned largely with the hormones themselves and the principal organ systems that synthesize the hormones, namely the pituitary, the thyroid, the parathyroids, the adrenal glands, the gonads, and the pancreas. As a cause for hospital admissions, diabetes mellitus (discussed by Olefsky¹ in this issue of THE JOURNAL) is more common than all other endocrine disorders combined,² but worldwide, and probably in the United States as well, disease of the thyroid is more frequent. In many countries, largely areas covered at one time by glaciers, enlargement of the thyroid gland with or without hypothyroidism occurs in more than 20% of the population (endemic goiter).^{3(pp368-389)} This disorder is due to iodine deficiency, compounded by dietary goitrogens and possibly by other factors,^{3(pp368-389)} and despite marked improvements in public health, iodine deficiency and its sequelae are major components of the health burden in many countries.⁴

In the remainder of the world estimates of prevalence depend on the means of ascertainment, but enlargement of the thyroid gland is present in 8% or more of most populations,^{3(pp578-587)} always more frequent in women. Hyperthyroidism is the most common thyroid cause for hospitalization,² and as many as 14% of women older than 60 years have chemical hypothyroidism.⁵ Diseases of

Endocrine disorders, primarily diseases of the thyroid, parathyroids, pituitary, gonad, and adrenal glands, constitute a major health problem in all societies. As a result of improved insight into the diagnosis, pathophysiology, and molecular bases, it is now possible to diagnose the disorders earlier in their development, and the treatment of the deficiency states for most hormones is successful. Furthermore, with recognition that many of these disorders are either the consequence of single-gene mutations or have a major genetic component, it is now possible to diagnose affected fetuses and family members at risk. Therapies for the syndromes of hormone overproduction are less successful and frequently result in destruction of the endocrine organ involved, and the treatment of hormone resistance states is similarly unsatisfactory. These disorders are candidates for the development of superagonists/antagonists and gene therapies.

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all other endocrine organs combined are about half as common as thyroid disease, although estimates of prevalence of these disorders also depend on the means of ascertainment. For instance, parathyroid disease and pituitary tumors are now being diagnosed more frequently because of improved diagnostic tests.

Developments in the Field

Endocrinology is a discipline of the 20th century. The initial focus was on the identification and purification of hormones, characterization of the regulatory processes that control their secretion, definition of the effects of hormone deficit and excess, and delineation of the syndromes that result from such disorders. The achievements in this field constitute some of the most dramatic applications of organic chemistry to medicine. By 1950 the chemical isolation and characterization of pituitary, parathyroid, pancreatic, adrenal, gonadal, and thyroid hormones made it possible in almost every instance to re-

place these hormones successfully in deficiency states.

A crowning achievement of the collaboration between chemistry and physiology was the development of oral contraceptives.⁶ This line of investigation was followed in the 1960s and 1970s by the development of assay techniques, largely based on the immunoassay, that made it possible to define the regulatory feedback control processes that control the synthesis and secretion of hormones and to identify additional classes of hormones that operate at very low plasma levels (ie, dihydrotestosterone, catechol estrogens, enteroglucagon, activin and inhibin, follistatin, somatostatin, pituitary releasing hormones). These assays and improved imaging

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techniques make possible the early diagnosis of even the most subtle derangements of hormone physiology.

During the past 25 years, the emphasis has shifted to hormone action, specifically to the transport mechanisms, cellular receptors, and messenger systems that mediate the effects of hormones within cells and the role of these processes in the pathogenesis of disease. The concept that disorders can result from abnormalities of hormone action as well as from hormone excess or deficit began with the report by Albright and colleagues⁷ that pseudohypoparathyroidism is a disease not of hormones per se but of resistance to the action of parathyroid hormone, and resistance to virtually every known hormone is now recognized to cause disease in humans.⁸ Indeed, if obesity and type 2 diabetes mellitus are due to hormone resistance, then disordered hormone action is one of the most important causes of endocrine disease.

The 1990s witnessed a remarkably productive interdigitation between genetics and endocrinology and between immunology and endocrinology. Genetic tools provided improved diagnostic techniques. The characterization of the mutations that cause many of the single-gene endocrine diseases made it possible to investigate the origin, transmission, and expression of the mutations responsible and, at the same time, made possible identification of family members at risk, diagnosis in utero, and in a few instances successful therapy of the affected fetus. Indeed, the prevention of the disfiguring anatomical abnormalities in female fetuses with congenital adrenal hyperplasia due to steroid 21 hydroxylase (CYP21) deficiency by administration of the missing adrenal hormone across the placenta constitutes the most successful example to date of prevention of the consequences of a common, serious congenital disorder.⁹

Equally dramatic, at a time when germ line DNA testing for cancer has been enveloped in controversy, the syndrome of multiple endocrine neoplasia type 2 has provided a clear example of the effi-

cacy of molecular diagnosis in cancer prevention because of 3 features of this endocrine disorder: (1) the high incidence of a life-threatening cancer (medullary thyroid cancer); (2) the ease and accuracy of DNA diagnosis; and (3) the availability of a lifesaving intervention (thyroidectomy).¹⁰

The techniques of molecular genetics have been particularly informative in expanding insight into the complex pathophysiology of disorders of hormone receptors. In regard to loss of function mutations, such as the receptor defects that impair the action of androgens¹¹ and thyroid hormones,¹² the availability of genetic tools has expanded the field enormously, but it was unexpected that these same tools would also provide insight into some disorders of endocrine excess, namely the recognition that gain of function mutations can activate receptor systems in the absence of ligand.

By way of example, the most common cause of premature puberty in boys is the result of germ line mutations that cause constitutive activation of the luteinizing hormone receptor (and production of testosterone by the testes) in the absence of luteinizing hormone,^{13,14} and germ line mutations can cause constitutive activation of the thyrotropin receptor and the syndrome of autosomal dominant hyperthyroidism.¹⁵ Similarly, mutations that cause activation of the parathyroid hormone receptor cause Jansen disease, a lethal disorder in children that is associated with biological effects mimicking those of parathyroid hormone excess.¹⁶

Even more interesting, perhaps, is the recognition that somatic mutations in cell lines can cause overproduction of hormones. For example, overproduction of thyroid hormone by thyroid adenomas can result from constitutive activation of the thyrotropin receptor^{17,18} or of the Gs gene that mediates the production of cyclic adenosine monophosphate,¹⁷ and the McCune-Albright syndrome is due to activating heterozygous somatic mutations that cause activation of the Gs protein in a mosaic pattern in tissues and hence causes over-

production of one or more hormones by affected endocrine organs.¹⁹

The role of immune mechanisms in the pathogenesis of endocrine disease has been inferred for decades. For example, the most common serious disorder of the thyroid, Graves disease, is due to the formation of an antibody to the thyrotropin receptor that mimics the capacity of thyrotropin and stimulates the thyroid gland in a fashion that is not subject to feedback control,²⁰ and immune destruction causes failure of a variety of endocrine organs in sporadic disorders such as impairment of adrenal (Addison disease),²¹ thyroid,²² and parathyroid²³ function. Some of these disorders are believed to have a hereditary component—a relationship that has been clearly established for polyglandular autoimmune failure, type 2.²⁴ The mechanisms involved in the pathogenesis of autoimmunity are now being defined in detail,²⁵ leading to the widespread expectation that such insights will lead to improved prevention and therapy for these disorders.

Current Scientific Foundation

Clinical endocrinology is at the same time one of the most quantitative of clinical disciplines and one of the most therapeutically successful. The combination of specific and sensitive hormone assays, dynamic tests of endocrine function, and newer imaging techniques makes possible the recognition of even minor derangements in the endocrine system, including subtle hormone resistance states. Likewise, replacement therapy for hormone deficiencies of the pituitary, parathyroids, thyroid, gonads, and adrenal glands constitutes a triumph of pharmacology.

However, in regard to some categories of endocrine disease—disorders of hormone excess and abnormalities of hormone action—therapy is generally unsuccessful. In regard to the common disorders of hormone excess—Graves disease, Cushing disease, acromegaly, hyperparathyroidism—it is particularly striking that medical therapies are imperfect and rarely directed to the underlying pathology and that

surgery and radiation often cause destruction of the tissues responsible resulting, in the conversion of a disease of excess into a state of deficiency. The relative lack of progress in this arena of pharmacology is due to a variety of causes: the paucity of animal models for most of these disorders so that many issues of pathophysiology are poorly understood, the toxic effects and ineffectiveness of immunomodulatory drugs, the fact that some consequences of hormone excess (ie, cortisol excess in both sexes and androgen excess in women) are not reversible, and the fact that some of the disorders have space-occupying effects independent of hormone secretion, as a consequence of which treatment of the tumor mass is of primary concern.

Current Research Endeavors and Needs

One of the most innovative and successful advances in endocrinology in the past 25 years was the introduction by Besser and colleagues²⁶ of the dopamine agonist bromocriptine for treatment of hyperprolactinemic states, a therapy subsequently shown to cause shrinkage of prolactin-secreting tumors themselves and to control tumor growth for the long-term. The concept that superagonists could overcome metabolic blocks, together with the development of pure hormone antagonists and recognition that constant administration of agonists may cause antagonistic effects, has had a widespread impact. For example, the antagonistic effects of gonadotropin-releasing hormone analogs are useful in the treatment of diverse conditions such as precocious puberty, prostate carcinoma, and endometriosis.

Agonistic effects have been beneficial in treating hypogonadotropic hypogonadism, cryptorchidism, and hypothalamic amenorrhea and beneficial in diagnostic testing.²⁷ Likewise, antiandrogens and (both selective and general) antiestrogens are effective in the management of inappropriate or unwanted androgen and estrogen effects. Antiprogestational agents have

been used successfully for several purposes, including termination of pregnancy. Similarly, inhibitors of the synthesis of thyroid and steroid hormones are useful both for diagnostic and therapeutic purposes.

Abundant clinical and experimental evidence indicates that the availability of more potent agonists and antagonists of hormone action would have a revolutionary impact on the management of endocrine diseases. This evidence stems from 2 types of research: First, the single-gene mutations that cause resistance to hormone action (including resistance to androgen, thyroid hormone, luteinizing hormone, and vitamin D) are most frequently the consequence of missense mutations that impair the interaction between the hormone and the receptor protein and can sometimes be overcome by supraphysiological levels of hormone. The availability of superagonists for these disorders would have a major impact on management. Second, many of the tumors that cause hormone overproduction (thyroid adenomas, corticotropinomas of the pituitary) are, similar to prolactinomas, the consequence of somatic missense mutations that impair the regulatory feedback control of hormone formation and are prime candidates for such agents. In the past, the development of receptor agonists and antagonists was largely a matter of trial and error, so many of the approved agents are of limited effectiveness and not free of adverse effects. The availability of the crystal structure of hormone receptors and of the enzymes that mediate hormone synthesis should make it possible to devise more effective and more specific inhibitors and agonists for therapy.

Prospects for the Future

In endocrinology, as in other medical disciplines, the focus will shift to prevention. Genetic predispositions underlie many or most endocrine diseases, and, as a byproduct of the Human Genome Project, it will be easier, indeed routine, to identify such predispositions in family members at risk and probably those at risk in the population at large. As a

consequence, it will be necessary to educate people at risk to the advantages of maintaining healthful lifestyles, avoiding risk, and seeking out preventive therapies. Although the educational challenge is formidable, success in the prevention of 3 disorders—obesity, diabetes mellitus, and autoimmune thyroid disease—would have an enormous impact on public health.

It is premature to predict the role that gene therapy will have in endocrinology (except for type 1 diabetes mellitus). Another arena in which gene therapy would be extraordinarily useful would be for treatment of hormone resistance states associated with mutations of hormone receptors. These disorders are lifelong and are candidates for such attempts.

The poor understanding of the pathophysiology of disorders of hormone excess (contrasted to hormone deficiency) will almost certainly be corrected in the foreseeable future. The use of gene knockout and knockin technologies will make available animal models for a whole variety of endocrine diseases, such as hyperthyroidism, multiple endocrine neoplasia, Cushing disease, and acromegaly, that at present are poorly understood. One consequence will be the identification of drug targets for improved therapy of these conditions.

The clinical and scientific discipline built on the concept of chemical control of physiological processes will become blurred. Recognition that the endocrine, immune, and neurogenic systems are not separate but in fact constitute components of an interlocking control process will accelerate with the increasing body of evidence that many chemical mediators do not circulate as classic hormones but in fact act in a paracrine/autocrine fashion or circulate in limited compartments. In this sense, that branch of endocrinology concerned with hormone action and cellular control mechanisms will lose its original identity and be incorporated into the larger field of cellular biology. This development is probably an inevitable and desirable consequence of the many ad-

vances in molecular genetics and biology that have served to breach the disciplinary barriers that previously separated the branches of biology.

Nevertheless, endocrinology will persist as a clinical and scientific discipline. It is now apparent that many physiological processes are under the control of complex control mecha-

nisms that cannot be explained by the effects of single hormones. Such processes include growth, temperature regulation, gender identity/role behavior, sexual drive, potentia, and the drive for reproduction, biological rhythms, metabolic rates, food assimilation, and the integration of chemical and neuro-genic control mechanisms within the

central nervous system. Endocrinology is poised to lead a renaissance in whole animal-organ system physiology that has been eclipsed by the revolutionary developments in genetics and molecular biology.

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