Prospects for Research for Disorders of the Endocrine System

Jean D. Wilson, MD

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 (pp368-390) 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,5 (pp578-587) always more frequent in women. Hyperthyroidism is the most common thyroid cause for hospitalization,6 and as many as 14% of women older than 60 years have chemical hypothyroidism.7 Diseases of 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 replace 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...
techniques make possible the early di-
agnosis of even the most subtle derange-
ments of hormone physiology.

During the past 25 years, the empha-
sis has shifted to hormone action, spe-
cifically to the transport mechanisms, cellular receptors, and messenger sys-
tems that mediate the effects of hor-
mones within cells and the role of these
processes in the pathogenesis of dis-
ease. The concept that disorders can re-
sult from abnormalities of hormone ac-
tion as well as from hormone excess or
deficit began with the report by Al-
bright and colleagues7 that pseudohy-
parathyroidism is a disease not of hor-
mones per se but of resistance to the
action of parathyroid hormone, and re-
sistance to virtually every known hor-
mone is now recognized to cause dis-
ease in humans.8 Indeed, if obesity and
type 2 diabetes mellitus are due to hor-
mone resistance, then disordered hor-
mone action is one of the most impor-
tant causes of endocrine disease.

The 1990s witnessed a remarkably pro-
ductive interdigitation between gen-
etics and endocrinology and be-
tween immunology and endocrinol-
ogy. Genetic tools provided improved
diagnostic techniques. The character-
ization of the mutations that cause
many of the single-gene endocrine dis-
esases made it possible to investigate the
origin, transmission, and expression of
the mutations responsible and, at the
same time, made possible identifica-
tion of family members at risk, diag-
nosis in utero, and in a few instances
successful therapy of the affected fe-
tus. Indeed, the prevention of the dis-
figuring anatomical abnormalities in fe-
male fetuses with congenital adrenal
hyperplasia due to steroid 21 hydroxyl-
ase (CYP21) deficiency by adminis-
tration of the missing adrenal hor-
mine was the most successful example to date of pre-
vention of the consequences of a com-
mon, serious congenital disorder.9

Equally dramatic, at a time when germ
line DNA testing for cancer has been en-
volved 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 inci-
dence of a life-threatening cancer (med-
ullary thyroid cancer); (2) the ease and
accuracy of DNA diagnosis; and (3) the
availability of a lifesaving intervention
(thyroidectomy).10

The techniques of molecular genet-
ics have been particularly informative
in expanding insight into the complex pathophysiology of disorders of hor-
mone receptors. In regard to loss of
function mutations, such as the recep-
tor defects that impair the action of an-
drogens11 and thyroid hormones,12 the
availability of genetic tools has ex-
thandled the field enormously, but it was
unexpected that these same tools would
also provide insight into some disor-
ders of endocrine excess, namely the
recognition that gain of function mu-
tations can activate receptor systems in
the absence of ligand.

By way of example, the most com-
mon cause of premature puberty in boys
is the result of germ line mutations that
cause constitutive activation of the lu-
teinizing hormone receptor (and pro-
tuction of testosterone by the testes) in
the absence of luteinizing hormone.13,14
and germ line mutations can cause con-
stitutive activation of the thyrotropin re-
ceptor and the syndrome of autosomal
dominant hyperthyroidism.15 Simi-
larly, mutations that cause activation of
the parathyroid hormone receptor cause
Jansen disease, a lethal disorder in chil-
dren that is associated with biological ef-
fects mimicking those of parathyroid hor-
mone excess.10

Even more interesting, perhaps, is the
recognition that somatic mutations in
cell lines can cause overproduction of
hormones. For example, overproduc-
tion of thyroid hormone by thyroid ad-
renals can result from constitutive ac-
tivation of the thyrotropin receptor17,18
or of the Gs gene that mediates the pro-
duction of cyclic adenosine monophos-
phate,17 and the McCune-Albright syn-
drome is due to activating heterozygous
somatic mutations that cause activa-
tion of the Gs protein in a mosaic pat-
tern 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 ex-
ample, the most common serious dis-
order 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 im-
mune destruction causes failure of a va-
riety of endocrine organs in sporadic
orders such as impairment of adre-
nal (Addison disease),21 thyroid,22 and
parathyroid23 function. Some of these
disorders are believed to have a heredi-
tary component—a relationship that has
been clearly established for poly-
glandular autoimmune failure, type 2.24
The mechanisms involved in the patho-
genesis of autoimmunity are now be-
ing defined in detail,25 leading to the
widespread expectation that such ins-
sights will lead to improved preven-
tion and therapy for these disorders.

Current Scientific Foundation

Clinical endocrinology is at the same
time one of the most quantitative of clini-
cal disciplines and one of the most thera-
apeutically successful. The combination
of specific and sensitive hormone as-
says, dynamic tests of endocrine func-
tion, and newer imaging techniques
makes possible the recognition of even
minor derangements in the endocrine
system, including subtle hormone re-
sistance states. Likewise, replacement
therapy for hormone deficiencies of the
pituitary, parathyroids, thyroid, go-
ads, and adrenal glands constitutes a
triumph of pharmacology.

However, in regard to some catego-
ries of endocrine disease—disorders of
hormone excess and abnormalities of
hormone action—therapy is generally
unsuccessful. In regard to the com-
mon disorders of hormone excess—
Graves disease, Cushing disease, acro-
megaly, hyperparathyroidism—it is
particularly striking that medical thera-
pies 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 (i.e., 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 colleagues20 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 disciplin-
ary barriers that previously separated the branches of biology.

Nevertheless, endocrinology will per-
sist as a clinical and scientific disci-
pline. It is now apparent that many physiologica processes are under the
control of complex control mecha-
nisms that cannot be explained by the
effects of single hormones. Such pro-
cesses include growth, temperature
regulation, gender identity/role behav-
ior, sexual drive, potenta, 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. Endocrinol-
ogy is poised to lead a renaissance in
whole animal–organ system physiolog-
that has been eclipsed by the revo-
lutionary developments in genetics and
molecular biology.

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