Advancing in Tandem: Clinical Endocrinology and Clinical Chemistry

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Here I review some of the recent accomplishments in clinical endocrinology and clinical chemistry, point out the direction of future work, and try to predict some of the advances of the next decade. Endocrinology, perhaps more than any other branch of clinical medicine, is rooted in biochemistry and physiology. Endocrinologists have been leaders in the development of methods, which have been adapted by clinical chemists for wider applications than those conceived originally. For the sake of brevity, I shall not recount the early history of endocrinology in this century—or the enormous progress since Starling coined the term “hormone” and stated the physiological role of these chemical messengers in 1905. Progress in endocrinology in recent years has been astounding.

Immunoassay

Fuller Albright, who defined the clinical features of hyperparathyroidism in the 1930s, enunciated one of the maxims of clinical investigation when he advised: “Measure something!” (1). In the early days of endocrinology this meant measure the effect of a hormone in the organism. Such effects were based on measurements in patients, for example, the above-normal serum calcium concentration in hyperparathyroidism. Direct measurements of hormones depended on bioassays, which were usually too insensitive to measure hormone concentrations in blood. The modern era of clinical endocrinology began with the marriage of immunology and endocrinology.

Solomon Berson, more than any other person, in my judgment, was responsible for the great leap forward. Berson and his colleague, Rosalyn Yalow, developed the radioimmunoassay for insulin in serum in 1960 (2). Berson was a chemist, a thyroid endocrinologist, a nuclear medicine specialist, an excellent internist, a fine musician, and an unusually inspiring person. He not only developed the technique of hormone measurement with antibodies, but also developed a sound theoretical analysis of the data and clearly set forth the principles of radioimmunoassay (3). Unfortunately, he died before he could be recognized by sharing the Nobel prize with his eminent colleague, Yalow. Berson and his coworkers developed workable radioimmunoassays for human somatotropin, parathyroid, corticotropin, and gastrin.

The assay of human somatotropin caused an explosion of new information about the diagnosis and natural history of acromegaly by providing the first direct measurements of the hypersecretion of this hormone by the pituitary, which enabled clinicians to follow the effects of treatment quantitatively. This assay also provided a reliable means for diagnosis of pituitary dwarfism, which had assumed a new importance because of the purification of human somatotropin from cadaver pituitaries by Maurice Raben in 1957 (4). Precise diagnosis and therapy for the pituitary dwarf thus became available.

The technique of radioimmunoassay has been applied to measure very many hormones and intermediary products of endocrine glands. The magnificent armamentarium of the clinical laboratory places the burden of wise choice on the clinical endocrinologist. Those of us who remember the days, only a quarter of a century ago, when direct hormone measurements were limited to the serum protein-bound iodine, plasma cortisol by Porter–Silber chromogens, and urinary gonadotropins, think we have come a long way. There have been many refinements of radioimmunoassays; techniques have been developed for limiting damage to the tracer by the radiation. Perhaps the most promising method is that of labeling the antibody. The recent use of monoclonal antibodies provides a major advance in the field. Because of the problems inherent in the use of radioisotopes, such as radiation safety and disposal of radioisotope waste, the technique of enzyme-labeled immunoassay, which does not involve radioisotopes, is in a phase of exciting development. Each month’s issue of this journal seems to contain an article about a new enzyme-labeled immunoassay that has been developed. I think it safe to predict that these assays, combining monoclonal antibodies and enzyme-labeled immunoassay, will be the assays of the future.

Quantification of Advances in Endocrinology

There are about 25 English-language endocrinology journals today. In addition, dozens of journals such as Clinical Chemistry publish articles in the field of endocrinology and metabolism. The explosion of information in endocrinology is not reflected only in the large number of journals in the field. Figure 1 shows the number of pages published annually in the two leading journals, Endocrinology and The Journal of Clinical Endocrinology and Metabolism. Until 1941, Endocrinology included basic studies and clinical research. The Journal of Clinical Endocrinology began in 1941. Within the past 25 years, the size of these journals has become ponderous, despite a continuous attempt by the editors to limit the size of the articles and increase the rejection rate of manuscripts. Threefold as many pages were published in these journals in 1981 as were published 20 years ago.

Advances in Thyroid Disease

Now I would like to turn to specific advances in the field of my special interest, thyroid disease.
Although the physical deformity and short stature of congenital hypothyroidism are reversed by treatment in early childhood, treatment must be instituted within the first few postnatal months if the mental deficiency of cretinism is to be prevented. The diagnosis is difficult to make in newborns on clinical criteria alone. The pioneering studies of Jean Dussault in Quebec in the early 1970s showed that screening of newborns could be done effectively. Table 1 is a compilation of North American data based on screening of a blood sample, usually obtained at three days of age, by measurement of thyroxin and thyrotropin (5). The prevalence of hypothyroidism was 2.7 per 10,000 newborns. Note that only eight of 277 hypothyroid newborns were diagnosed on the basis of clinical findings alone. Treatment within the first month results in normal intelligence in these children. Because the disorder is mainly the result of maldevelopment of the thyroid gland, prevention may not be possible. Future work in this field should be directed at diagnosis in utero and possible prenatal therapy.

RIA of serum thyroxin (T4) and serum thyrotropin makes diagnosis of hypothyroidism a simple matter. The increased serum thyrotropin value confirms that the low serum T4 is due to primary hypothyroidism. What is the prevalence of hypothyroidism in the geriatric population? A recently completed screening of the Framingham Study population by my colleague Clark Sawin and myself confirmed previous reports from screening of geriatric subjects. Serum thyrotropin is above normal in 5.9% of women and 2.3% of men over age 60; and 39% of those with an increased value for serum thyrotropin have a subnormal serum T4 concentration. Therefore, the prevalence of primary hypothyroidism is 4.4% of the geriatric population. The cause is mainly chronic lymphocytic thyroiditis, an autoimmune disorder. Hypothyroidism in the elderly is 160-fold more prevalent than in the newborn. Is it not reasonable to recommend that elderly persons be regularly screened for hypothyroidism?

One problem clinicians have encountered recently is the severely ill patient, usually in the intensive-care unit, who has very low serum T4, free T4, and triiodothyronine (T3) concentrations, well into the hypothyroid ranges (6). Usually, their serum thyrotropin concentration is normal. These patients have been termed the "euthyroid low-T4 sick"—but are they euthyroid or hypothyroid? Clinical evaluation is very difficult. To explain this problem, I suggest that reversible hypothyroidism may be a selective adaptation to severe systemic illness. Unfortunately, this hypothesis cannot be readily tested, because there is no sensitive method for measuring the metabolic action of thyroid hormone.

T3 binds to a nuclear receptor and thus influences synthesis of messenger RNA in many tissues. Although synthesis of many proteins is altered by T3, none (except thyrotropin) yet serves as a sensitive marker for the effect of thyroid hormone. The challenge is obvious. We need a sensitive and specific marker of the metabolic action of thyroid hormone for use in diagnosis of abnormalities of thyroid function and for a guide to therapy of disorders of thyroid function.

Precise measurements of T4 and T3 concentrations in serum by immunoassay make the diagnosis of hyperthyroidism relatively simple at the present time. Graves' disease is the most common cause of hyperthyroidism. The hyperthyroidism of Graves' disease is caused by an immunoglobulin G thyroid stimulator, discovered about 25 years ago as a result of bioassays of serum of hyperthyroid patients in guinea pigs and mice. This stimulator displaces thyrotropin from its specific receptor on the thyroid cell membrane. It also activates thyroid adenylate cyclase (EC 4.6.1.1) and increases cyclic AMP, leading to secretion of thyroid hormones. Tests for the thyroid-stimulating immunoglobulin by use of human thyroid tissue are specific and sensitive but also difficult. If one of these new tests were readily available to the clinician, it could be used as a marker for the activity of the disease and as a guide to therapy of hyperthyroidism with anti-thyroid drugs. Such therapy, developed 40 years ago by E. B. Astwood, leads to a remission in about half the patients, but there are no readily available tests to show which patients have gone into remission and which will relapse when the thionamide drug is stopped. Only the long-acting thyroid stimulator bioassay in mice and the assay of thyrotropin-displacing activity have been marketed by reference laboratories, but these tests are not sensitive or specific. The direction of the future for the clinical chemist is

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**Table 1. Screening for Congenital Hypothyroidism by Measurement of T4 and Thyrotropin in Spot or Cord Blood (5)**

<table>
<thead>
<tr>
<th>No. screened</th>
<th>Primary</th>
<th>Secondary</th>
<th>Transient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,046,000</td>
<td>239</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Incidence/1000</td>
<td>2.3</td>
<td>0.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Missed 7. Only 8 of these 277 hypothyroid newborns were suspected clinically.*

<table>
<thead>
<tr>
<th>Hypothyroid glands</th>
<th>Aplastic or hypoplastic</th>
<th>Ectopic</th>
<th>Normal or enlarged</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>23%</td>
<td>14%</td>
<td></td>
</tr>
</tbody>
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**Fig. 1. Number of pages published annually in Endocrinology and The Journal of Clinical Endocrinology and Metabolism**

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The pathological types that make up 80% of the cases are well-differentiated carcinomas that have many of the biochemical as well as histological features of normal thyroid tissue. These tumors have receptors for thyrotropin on their cell membranes, and they secrete thyroglobulin. Therapy consists of removing the carcinoma surgically and destroying functional remnants with iodine-131. Enough thyroid hormone is given to the patient to suppress thyrotropin, which is a growth factor for these neoplasms. Therefore, it is valuable to have available radioimmunoassays for thyrotropin that are very sensitive and can differentiate suppressed thyrotropin concentrations from low-normal concentrations. With just a little extra effort, this is now achievable in the RIA laboratory (7). The high-sensitivity assay for thyrotropin in serum should replace the less-sensitive assays now commonly marketed.

Differentiated thyroid cancers secrete thyroglobulin, a characteristic of normal thyroid tissue. After all thyroid tissue presumably has been destroyed, a measurable thyroglobulin concentration indicates metastatic disease. A sensitive thyroglobulin radioimmunoassay showed that serum thyroglobulin concentrations exceeding 4 ng/mL during thyroid-suppression therapy indicated the presence of functional metastases; in the thyrotropin-stimulated state after thyroid-hormone therapy was stopped, concentrations exceeding 10 ng/mL also indicated metastases (8). Thus, measurement of serum thyroglobulin is very useful for following these cases if the assay is sufficiently sensitive and precise.

Neuroendocrinology

Progress in neuroendocrinology has been very rapid. For many years, the concept that hypothalamic factors controlled the release of pituitary hormones was considered a fanciful hobby. Through a combination of persistence, brilliance, and serendipity, the Nobel duelists, Roger Guillemin and Andrew Schally, discovered the tripeptide structure of thyroliberin, the thyrotropin-releasing hormone, in 1969. My colleagues and others rapidly exploited its clinical utility—and new applications are still under development (9-11). Thyroliberin is most concentrated in the hypothalamus, but it is found throughout the brain and spinal cord, in the gastrointestinal tract, pancreas, retina, and in the reproductive tract (12, 13). This tripeptide may serve as a neurotransmitter in many tissues, but its functions outside of the hypothalamus have not been defined.

Schally and his colleagues discovered the decapetide structure of luteinizing hormone-releasing hormone, in 1971 and showed that it also releases follicitropin (14). Because luteinizing hormone down-regulates its receptor, a long-acting analog has great potential as a contraceptive and inhibitor of sex-steroid secretion. Only two years later, Guillemin and his team responded with the discovery of somatostatin, a tetradecapeptide that inhibits the secretion of somatotropin (15). It also inhibits secretion of thyrotropin, insulin, glucagon, and gastrin. Somatostatin is found throughout the brain, pancreas, and gastrointestinal tract.

The releasing factor for somatotropin was the target of the work resulting in the discovery of somatostatin in an inhibitory fraction of hypothalamic extract. The recent description of the structure of somatoliberin, the growth hormone-releasing factor, originated from a microscopic observation. Acromegaly in a few patients was found to be the result of hyperplasia of somatotropin-secreting cells rather than a pituitary adenoma. This in turn was attributed to uncontrolled secretion of a releasing factor for somatotropin in a pancreatic tumor in two patients and a carcinoid tumor of the lung in a third patient. Purification of the growth hormone-releasing factor from these tumors showed that it was a peptide containing about 44 amino acid residues. The team from Guillemin’s laboratory has determined the amino acid sequence of this peptide and, in fact, synthesized it (16). The synthetic material has full activity. Its therapeutic potential is fascinating. I leave it to the reader to consider uses in farm animals and potential professional athletes.

The first of the releasing factors for which there was good physiological evidence was corticotropin-releasing factor, or corticotropin. Its structure eluded definition for over 25 years. Last year, another team at the Salk Institute reported that it is a 41-amino-acid peptide, which releases corticotropin and its sister molecules, beta-endorphin and melanotropin (17). Its role in the mediation of stress should prove interesting. Measurements of it in human serum are underway and will, I believe, become an important tool in the study of mental disease.

In the realm of neuroendocrinology, there has been an explosion of discoveries related to the synthesis of corticotropin, which arises in the pituitary corticotrophs from a large glycosylated precursor with a molecular mass of 31,000 Da (18). Processing of this precursor yields both corticotropin and beta-lipotropin, a molecule still in search of a function. Within the structure of beta-lipotropin are beta-endorphin and gamma-endorphin; both are potent opiate agonists. This system provided the first demonstration of the importance of precursors processing in pituitary cells. Differential processing yields different quantities of each of these biologically important peptides. Precise measurements of these peptides in the next few years may provide important insights into control of behavior, appetite, the response to pain, and even psychic trauma.

Some of the other peptides found in the hypothalamus and in other regions of the brain include neurotensin, substance P, metenkaphalin, leu-enkephalin, vasoactive intestinal peptide, cholecystokinin, and bombesin. The functions of these peptides are still unclear. Measurements of them may indeed show they have important roles in the complex chemistry of the brain.

The purification of human prolactin by Henry Friesen in 1971 led to the development of a radioimmunoasay for human prolactin (19). This, in turn, led to the discovery that the most common functioning pituitary tumor is the prolactinoma. Before the development of the prolactin RIA, these tumors were considered to be nonfunctional. The prolactinoma is a common cause of amenorrhea, with or without galactorrhea, in women and of impotence in men. Long-acting dopaminergic drugs are a new form of treatment for prolactinomas and actually cause shrinkage of the tumors. The decrease in tumor mass parallels the decrease in the concentration of prolactin in serum.

There still remains a small proportion of pituitary adenomas that are considered nonfunctional because they do not secrete measurable hormones: they do not cause infertility, acromegaly, Cushing’s disease, or hyperthyroidism. Are they secreting hormones we do not yet know how to measure? I believe we will find this to be the case.

Mental Disease

The ability to measure hormones has provided new insights into understanding mental disease. The neuroleptic
drugs that have caused such great improvement in the therapy of psychosis are central dopamine blockers. As such, they increase the secretion of prolactin, which is under chronic dopaminergic inhibition. Measurement of serum prolactin serves to indicate the effect of these drugs.

Depression is one of our most common miseries. Differentiation of endogenous depression from situational depression can be difficult. Psychiatrists have used two hormonal markers for diagnosis of endogenous depression. One is the failure of normal suppression of afternoon cortisol concentrations by dexamethasone in depressed patients (20). The other marker of depression is the response of thyrotropin to thyroliberin (21). Patients with endogenous depression often exhibit a suppression of this response, the basis for which is unclear. I believe it is related to increased cortisol concentrations and increased dopamine. Both of these hormones inhibit thyrotropin secretion. Reduced noradrenergic tone would also inhibit thyrotropin secretion. Perhaps some of the peptides not yet measured, such as somatostatin or other neuropeptides, inhibit thyrotropin release in depressed patients. Measurement of these peptides in serum may yet serve as a more direct marker for depression.

Hyperparathyroidism

Our bountiful new measurement capabilities have created new problems. We now have direct assays for each part of the parathyroid molecule in serum. In patients with minimal hypercalcemia—usually discovered by screening serum calcium—measurement of serum parathyrin confirms the diagnosis. The clinician’s problem then is to determine whether a patient with a biochemical disorder (and often no apparent clinical symptoms) will benefit from surgical removal of the parathyroid adenoma. The paradox is that the sophistication of modern hormone measurements creates such an early diagnosis that the treatment may be worse than the disorder, in contrast with Fuller Albright’s patients in the 1930s, who usually were seen with severe hypercalcemia, kidney stones, and bone disease.

In hospital populations, severe hypercalcemia is usually caused by malignant tumors that secrete substances that have the effect of parathyrin but do not react in the RIA for it. Parathyrin increases production of 1,25-dihydroxy-vitamin D3 because the hormone increases 1α-hydroxylase activity in the kidney. Measurement of 1,25-dihydroxy-D3 may be useful in differentiating the patient with cancer from patients with hyperparathyroidism, because those with cancer and hypercalcemia have low concentrations of 1,25-dihydroxy-D3, while those with hyperparathyroidism have above-normal concentrations of it (22). The rapid progress in this field will probably clarify within a few years the nature of the parathyrin-like factor secreted by neoplasms.

Many clinical problems remain to be solved. The future of clinical endocrinology is closely linked to the cutting edge of physiological and biochemical research. Advances in clinical endocrinology will continue to occur in tandem with advances in clinical chemistry.

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References