History of the Clinical Endocrinology Branch of the National Institute of Diabetes and Digestive and Kidney Diseases: Impact on Understanding and Treatment of Diseases of the Thyroid Gland

Marvin C. Gershengorn

IN 1955, THE NATIONAL INSTITUTE of Arthritis and Metabolic Diseases, the predecessor of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), established the Clinical Endocrinology Branch (CEB).¹ A multidisciplinary group of scientists were brought together to collaborate in the study of the physiology and diseases of the thyroid gland. During the next 55 years, this area of research was expanded to include many aspects of the hypothalamic-pituitary-thyroid axis from the very basic molecular, cellular, and structural biology through translational research to patient-oriented clinical studies. Members of CEB, and the off-shoot Molecular, Cellular and Nutritional Endocrinology Branch, made important contributions to many of these areas of research (Table 1). In this commentary, I will describe a few of these many accomplishments and attempt to demonstrate the importance of multidisciplinary collaborations in these studies.²

During the initial two decades, a number of studies that used radioactive iodine (RAI), which was at the time newly available, were performed by CEB scientists. Dr. Joseph Edward (Ed) Rall, the founding Chief of CEB, and Dr. Jacob (Jack) Robbins, who later became CEB Chief, performed a series of studies, which they had been begun with Dr. Rulon Rawson at Memorial-Sloan Kettering Cancer Center in New York, on the use of RAI in the diagnosis and treatment of thyroid diseases, in particular of thyroid cancer. Drs. Rall and Robbins established the safety and efficacy of RAI usage and in collaboration with computational biologists, in particular Dr. Mones Berman of another NIDDK laboratory, developed a kinetic model of iodine metabolism that was used to optimize the effective RAI dose administered, while reducing its suppressive effects on the bone marrow (1). Simultaneously,

Drs. Rall and Robbins began their studies of serum thyroid hormone (TH) binding proteins that led to the breakthrough “free” TH hypothesis in which they elucidated the role of free (or unbound) TH, as opposed to total TH in blood, as the biologically relevant TH component (2). These studies were part of one of the most successful collaborations in the history of thyroid research.

Another early recruit to CEB was Dr. Jan Wolff. While in the laboratory of Dr. I.L. Chaikoff at the University of California, Berkeley, Dr. Wolff discovered the inhibitory effect of high concentrations of iodide on iodine organification in the thyroid, a major regulator of thyroid gland function (“Wolff-Chaikoff effect”). Dr. Wolff, in some studies in collaboration with Drs. Rall and Robbins, made a number of seminal contributions to our understanding of the transport of iodide and other anions in the thyroid gland that predicted the discovery of the sodium-iodide symporter (3). A related finding by Drs. Wolff and Robbins was that lithium ion was an inhibitor of iodide uptake by the thyroid. This finding, as with so many basic discoveries by NIDDK investigators, was translated into clinical use of lithium in the treatment of hyperthyroidism and as an adjunct in the RAI treatment of thyroid cancer (4).

The initial studies of TH binding proteins were extended by a collaboration within CEB between Dr. Robbins and Dr. Harold Edelhoch. In these experiments, the structure and binding properties of thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin (transthyretin) were elucidated. For example, the single polypeptide chain functional unit of TBG, which binds a single molecule of TH, was shown to be different than the oligomeric transthyretin, which binds two molecules of TH in a negatively cooperative manner and binds retinol-binding protein. Another important area of collaboration amongst Drs. Rall, Robbins, and Edelhoch involved studies of thyroidal iodoproteins, in particular thyroglobulin. For example, in a series of elegant studies, they delineated the structure of thyroglobulin and its role as a substrate for iodination as the precursor of THs (5). Studies of thyroglobulin and other iodoproteins were joined by Dr. Hans Cahnmann who delineated the coupling mechanism within

¹The CEB was disbanded as part of a re-organization of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Intramural Research Program in 2010.

²Although investigators in the CEB performed research in other areas of endocrinology, this commentary is limited to research performed in thyroid-related areas.

TABLE 1. AREAS OF STUDY OF THE HYPOTHALAMIC–PITUITARY–THYROID AXIS BY MEMBERS OF THE CLINICAL ENDOCRINOLOGY BRANCH

1. Use of RAI for the diagnosis and treatment of thyroid disease
2. TH binding proteins and development of the “free” TH hypothesis
3. Iodide uptake by the thyroid and iodine metabolism
4. Thyroid cancer
5. Synthesis and structure of thyroglobulin and other iodoproteins
6. TH nuclear receptors
7. Effects of radioactive fallout on the thyroid and the use of potassium iodide for prophylaxis
8. TH synthesis and metabolism
9. Effects of lithium on thyroid function and its use in patients with thyroid cancer and hyperthyroidism
10. Causes of congenital goiter
11. Use of fine-needle aspiration biopsy in the diagnosis of thyroid lesions
12. Studies of TSH-secreting pituitary tumors and pituitary resistance
13. Studies of TH resistance syndromes
14. TSH synthesis, structure-function relationships and development of TSH analogs with higher potencies and efficacies
15. TSH regulation of thyroid gland function
16. TH in development of the auditory and visual systems
17. TH deiodinases
18. TRH-R and TSH-R structure and function
19. Development of drug-like ligands for TSH-R and TRH-R

RAI, radioactive iodine; TH, thyroid hormone; TRH, thyrotropin releasing hormone; TRH-R, TRH receptor; TSH, thyrotropin; TSH-R, TSH receptor.

thyroglobulin that led to TH synthesis and also synthesized many TH analogs that were used to study TH metabolism (6).

At the same time the structural studies of TBG were being performed, experiments to elucidate the site and regulation of the biosynthesis of TBG were ongoing. For example, Dr. Robbins' laboratory showed conclusively that TBG is synthesized in the liver and both the synthesis and secretion of TBG are enhanced by estrogen (7).

Clinical research collaborations that included Drs. Rall, Robbins, and Wolff involved their participation in studies of RAI fallout after hydrogen bomb testing in the Pacific Ocean near the Marshall Islands and after the Chernobyl accident, and of reactor protection measures in the United States (8).

Initially in collaboration with Dr. Rall, Dr. Vera M. Nikodem and then Dr. Sheue-yann Cheng performed studies of TH nuclear receptors. Their research, in which they used triiodothyronine (T_3) derivatives to covalently label the receptor, provided early insights into the structure and function of the nuclear receptor by showing that it was a single polypeptide chain that binds either T_3 or thyroxine (9). More recently, Dr. Douglas Forrest continued studies of the molecular biology of THs. His continuing research focuses on the roles of THs, TH deiodinases, and TH receptors in development of mammalian sensory systems. In particular, Dr. Forrest has described the critical role of local generation of T_3 in the development and homeostasis of the mammalian retina (10).

Dr. Bruce D. Weintraub performed research on several aspects of the biology of the pituitary–thyroid axis. He studied the regulation of thyrotropin (TSH) gene transcription and cloned the complementary DNA (cDNA) for the TSH beta-subunit. He produced biologically active, dimeric TSH in cells in tissue culture that led to a series of collaborations in which recombinant human TSH was developed for use in patients. Dr. Weintraub studied the structure–function relationships of TSH and created novel TSH mutants that exhibited increased activities (11). His translational and clinical research also included studies of pituitary (12) and TH resistance syndromes and TSH-secreting pituitary tumors in collaboration with many extramural investigators (13).

Upon returning to the CEB, I continued my studies of the thyrotropin releasing hormone (TRH)/TRH receptor (TRH-R) and the TSH/TSH receptor (TSH-R) systems. Our studies focus on understanding how the TRH-R and the TSH-R function at the molecular level and on the development of small molecule ligands (SMLs) for these receptors. Our studies involve collaborations with computational chemists, organic chemists, molecular pharmacologists, and neuroscientists. For the TRH-R and the TSH-R, we characterized molecular details of their signaling and regulation in *in vitro* models, of their biology in intact animal models (14–16), and developed SMLs as probes of extra-pituitary functions of the TRH-R (17) and extra-thyroidal functions of the TSH-R (18). We think that SMLs for the TRH-R may be used in the future as treatment for several nervous system disorders, SML agonists for the TSH-R may be used in clinical practice to stimulate radioiodine uptake by residual thyroid cancer cells in the diagnosis and treatment of patients with thyroid cancer, and SML antagonists for the TSH-R to treat Graves' disease, especially ophthalmopathy.

In summary, there have been wide-ranging studies of the hypothalamic–pituitary–thyroid axis conducted by CEB investigators,³ which have impacted our understanding and treatment of diseases of the thyroid gland. The success of these collaborations amongst multidisciplinary teams of scientists, which began in CEB more than 50 years ago, is still a model for biomedical research into the future.

Acknowledgment

The author thanks Dr. Jan Wolff for his thoughtful comments regarding this commentary.

References

1. Rall JE 1956 The role of radioactive iodine in the diagnosis of thyroid disease. *Am J Med* 20:719–731.
2. Robbins J, Rall JE 1960 Proteins associated with the thyroid hormones. *Physiol Rev* 40:415–489.
3. Wolff J 1964 Transport of iodide and other anions in the thyroid gland. *Physiol Rev* 44:45–90.

³In addition, thyroid researchers from around the world spent time as trainees or visiting scientists at CEB. These scientists made important contributions to the research performed in CEB and were among the many scientists who collaborated with CEB investigators when at their home institutions. The trainees subsequently filled many senior medical school and research institute positions throughout the world.

4. Gershengorn MC, Izumi M, Robbins J 1976 Use of lithium as an adjunct to radioiodine therapy of thyroid carcinoma. *J Clin Endocrinol Metab* **42**:105–111.
5. Edelhoch H 1965 The structure of thyroglobulin and its role in iodination. *Recent Prog Horm Res* **1**:1–31.
6. Gavaret JM, Cahnmann HJ, Nunez J 1981 Thyroid hormone synthesis in thyroglobulin. The mechanism of the coupling reaction. *J Biol Chem* **256**:9167–9173.
7. Robbins J, Cheng SY, Gershengorn MC, Glinioer D, Cahnmann HJ, Edelhoch H 1978 Thyroxine transport proteins of plasma. Molecular properties and biosynthesis. *Recent Prog Horm Res* **34**:477–519.
8. Robbins J, Dunn JT, Bouville A, Kravchenko VI, Lubin J, Petrenko S, Sullivan KM, Vanmiddlesworth L, Wolff J 2001 Iodine nutrition and the risk from radioactive iodine: a workshop report in the Chernobyl long-term follow-up study. *Thyroid* **11**:487–491.
9. Nikodem VM, Cheng SY, Rall JE 1980 Affinity labeling of rat liver thyroid hormone nuclear receptor. *Proc Natl Acad Sci USA* **77**:7064–7068.
10. Swaroop A, Kim D, Forrest D 2010 Transcriptional regulation of photoreceptor development and homeostasis in the mammalian retina. *Nat Rev Neurosci* **11**:563–576.
11. Szkudlinski MW, Teh NG, Grossmann M, Tropea JE, Weintraub BD 1996 Engineering human glycoprotein hormone superactive analogues. *BioTechnology* **14**:1257–1263.
12. Gershengorn MC, Weintraub BD 1975 Thyrotropin-induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone. A new syndrome of “inappropriate secretion of TSH”. *J Clin Invest* **56**:633–642.
13. Beck-Peccoz P, Brucker-Davis F, Persani L, Smallridge RC, Weintraub BD 1996 Thyrotropin-secreting pituitary tumors. *Endocr Rev* **17**:610–638.
14. Gershengorn MC 1986 Mechanism of thyrotropin releasing hormone stimulation of pituitary hormone secretion. *Annu Rev Physiol* **48**:515–526.
15. Sun Y, Zupan B, Raaka BM, Toth M, Gershengorn MC 2009 TRH-receptor-type-2-deficient mice are euthyroid and exhibit increased depression and reduced anxiety phenotypes. *Neuropsychopharmacology* **34**:1601–1608.
16. Neumann S, Huang W, Titus S, Krause G, Kleinau G, Alberobello AT, Zheng W, Southall N, Inglese J, Austin CP, Celi FS, Gavrilova O, Thomas CJ, Raaka BM, Gershengorn MC 2009 Small molecule agonists for the thyrotropin receptor stimulate thyroid function in human thyrocytes and mice. *Proc Natl Acad Sci USA* **106**:12471–12476.
17. Engel S, Skoumbourdis AP, Childress J, Neumann S, Deschamps JR, Thomas CJ, Colson AO, Costanzi S, Gershengorn MC 2008 A virtual screen for diverse ligands: discovery of selective G protein-coupled receptor antagonists. *J Am Chem Soc* **130**:5115–5123.
18. Neumann S, Raaka BM, Gershengorn MC 2009 Human TSH receptor ligands as pharmacological probes with potential clinical application. *Expert Rev Endocrinol Metab* **4**:669

Address correspondence to:
Marvin C. Gershengorn, M.D.

Laboratory of Endocrinology and Receptor Biology
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
50 South Drive, Room 4134
Bethesda, MD 20892-8029

E-mail: marving@intra.niddk.nih.gov