

**University of Louisville**  
**Division of Endocrinology, Metabolism and Diabetes**  
**Fellows' Curriculum 2007**

**1. Disorders of the Adrenal Cortex and Medulla**

**A. Background**

A complete understanding of the diseases affecting the adrenal gland is essential for the endocrinologist. Adrenal pathophysiology includes numerous life-threatening conditions ranging from electrolyte disturbances, alterations in blood pressure, and malignancy. Indeed, it is essential that the endocrinologist accurately recognize and promptly manage the patient with adrenal disease.

**B. Goals and Objectives**

Our major goal is to ensure an appropriate knowledge base for this area, including an understanding of the hormonal and neurological regulation of electrolytes and blood pressure, the biosynthesis of steroid hormones and their target tissues/actions, the genetic basis for inherited diseases of the adrenal gland, recognition of adrenal cortical hyper- and hypo-function as well as adrenal medullary hyperfunction, static and dynamic tests of adrenal gland function, adrenal imaging techniques and management of adrenal dysfunction. Many diseases affecting the adrenal gland are common, such as the incidental adrenal mass, primary aldosteronism, and ACTH suppression from exogenous steroid therapy. These will be routinely encountered in most clinical training settings. In contrast, conditions such as a pheochromocytoma are more rare. As noted, however, the latter condition represents an extremely critical medical diagnosis.

**C. Training and Evaluation**

The training program must provide opportunities for the endocrine fellow to develop competence in the clinical evaluation and management of patients with adrenal cortical and adrenal medullary disorders. This clinical experience must include opportunities to diagnose and manage adult outpatients and inpatients of both sexes. The

fellow must be given opportunities throughout the training period to assume responsibility for and follow patients, with increasing level of responsibility to reflect his or her year of training. In addition, the fellow must be given the opportunity to observe the evolution and natural history of these disorders, as well as the efficacy of therapy. Appropriate training in adrenal disease will reflect a combination of both hands-on clinical encounters and an array of additional learning experiences including both formal teaching and self-directed methods. Evaluation will be consistent with those as dictated by the core competencies. Specifically, it will include discussions with faculty on a continuing basis and clinical presentations. In addition, standardized self-learning testing, such as ESAP will be strongly encouraged.

## **2. Program Content**

### **A. Physiology**

The endocrine trainee must have a basic understanding of the normal physiology of the adrenal cortex and medulla. This knowledge base must include:

- (1) adrenal gland embryology, anatomy, and zonation
- (2) adrenal steroid pathways of biosynthesis, specific enzymatic steps, and steroid hormone structures
- (3) steroid metabolism
- (4) hypothalamic-pituitary-adrenal axis and normal patterns of ACTH and cortisol secretion
- (5) regulation of adrenal glucocorticoid, androgen, and estrogen secretion
- (6) factors affecting measured levels of steroids in plasma and urine
- (7) molecular and cellular mechanisms as well as physiologic effects of glucocorticoids, mineralocorticoids, androgens, and estrogens
- (8) renin-angiotensin-aldosterone system and regulation of mineralocorticoid secretion
- (9) catecholamine biosynthetic pathway, physiological effects of catecholamines, excretion of catecholamines and catecholamine metabolites.

The method of education for adrenal physiology should include formal instruction and reading the chapters covering adrenal cortex and adrenal medulla from one of the major endocrine textbooks [1-5] and other resources, becoming progressively more complex as the fellow proceeds through each year of training.

### **B. Evaluation and Management of Adrenal Disorders**

The evaluation and management of the adrenal disorders should be mastered in a progressive fashion for each year of training. For each disorder listed, the trainee must have a thorough knowledge of:

- (1) clinical presentation
- (2) pathophysiology
- (3) physical examination findings
- (4) differential diagnosis
- (5) laboratory findings
- (6) typical imaging findings
- (7) clinical management

Common adrenal disorders include, Cushing's syndrome and disease (adrenal, pituitary, ectopic, and iatrogenic), adrenal insufficiency (primary, including polyglandular, secondary, adrenal crisis and glucocorticoid therapy), non-functioning adrenal mass (benign and malignant), hirsutism and virilization.

The primary methods of education for these disorders should be direct clinical experiences and clinical case discussions. These case discussions would usually take place on hospital rounds or in the outpatient endocrine clinic setting. The training program will provide and document a breadth of adrenal topics in clinical case conferences. The knowledge base should be enhanced with reading appropriate sections of an endocrine textbook [1-5], suggested supplemental articles, and Medline searches.

### **C. Rare Causes of Adrenal Disorders**

The fellow should also be familiar with rare causes of the adrenal disorders including those disorders of mineralocorticoid excess. In addition to primary aldosteronism, the fellow should be familiar with the spectrum of causes from renin-dependent (eg, renovascular disease, coarctation of the aorta) to renin-independent (eg, 11- $\beta$ -hydroxysteroid dehydrogenase deficiency, Liddle's syndrome, hypercortisolism, congenital adrenal hyperplasia). The trainee should be knowledgeable of the special features of Cushing's syndrome, adrenal insufficiency, aldosteronism, and pheochromocytoma in the hospitalized patient.

### **D. Adrenal Hyperplasia; 21-hydroxylase deficiency**

The fellow must have a thorough knowledge of the clinical presentation, pathophysiology, differential diagnosis, laboratory findings, and clinical management of 21-hydroxylase deficiency and should be familiar with other forms of congenital adrenal hyperplasia.

### **E. Hypertension**

With regard to hypertension, the fellow should know when to consider secondary (endocrine) causes of hypertension and how to manage essential hypertension in patients with endocrine disease (eg, diabetes mellitus).

### **F. Glucocorticoid Therapy**

A thorough understanding of glucocorticoid therapy must be achieved.. This part of the curriculum must include:

- (1) knowledge of the different glucocorticoid preparations (oral and parenteral)
- (2) chronic maintenance glucocorticoid dosing
- (3) inpatient and outpatient “stress” coverage dosing
- (4) management of glucocorticoid withdrawal including evaluation of hypothalamic pituitary-adrenal axis function
- (5) recognition of the manifestations of excessive and insufficient glucocorticoid therapy.

### **G. Adrenal Studies and Procedures**

The endocrine fellow must understand the indications for and the interpretation of all of the tests and procedures listed in the Tables below. In addition, the fellow should be able to personally conduct cosyntropin stimulation tests and dexamethasone suppression tests. The fellow should be proficient in identifying normal and abnormal adrenal glands on computerized imaging. Methods of education should include formal instruction, direct clinical experiences, clinical case discussions, and self-directed learning.

### **H. Dynamic Endocrine Tests**

- Cosyntropin stimulation test – 1  $\mu\text{g}$  and 250  $\mu\text{g}$
- Corticotropin-releasing hormone (oCRH) stimulation test
- Dexamethasone suppression tests (DST)
- oCRH/DST protocol

Insulin tolerance test  
Saline suppression test for aldosterone  
Clonidine suppression test for norepinephrine

### I. **Imaging and Radiology Procedures**

Adrenal venous sampling for aldosterone  
Inferior petrosal sinus sampling for ACTH with oCRH stimulation  
Computerized adrenal imaging (CT, MRI)  
CT-guided adrenal FNA biopsy  
<sup>123</sup>I-metaiodobenzylguanidine (MIBG) scintigraphy, where available  
Indium In-111-labeled pentetreotide (OctreoScan®) scintigraphy  
[6β<sup>131</sup>I]iodomethyl-19-norcholesterol (NP-59) scintigraphy

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## 3. Reading List

### *Endocrine Textbooks*

*One of the following general textbooks:*

1. The Adrenal Cortex and the Adrenal Medulla. In: A Grossman, ed. *Clinical Endocrinology*. 2nd ed. London: Blackwell Science Ltd, 1998.
2. Adrenal Cortex. In: DeGroot LJ, Besser M, Burger HG, Jameson JL, Loriaux DL, Marshall JC, Odell WD, Potts JT, Jr, Rubenstein AH, eds. *Endocrinology*. 3rd ed. Philadelphia, Pa: W.B. Saunders Co; 1995.
3. Felig P, Baxter JD, Frohman LA, eds. *Endocrinology and Metabolism*, 3rd ed. New York, NY: McGraw-Hill Inc; 1995.
  - Chapter 12 – The Adrenal Cortex, WL Miller, JB Tyrrell
  - Chapter 13 – Diseases of the Sympathochromaffin System, PE Cryer
  - Chapter 14 – The Endocrinology of Hypertension, JD Baxter, D Perloff, W Hsueh, EG Biglieri
  - Chapter 15 – Glucocorticoid Therapy, JB Tyrrell

4. The Adrenal Glands. In: Becker KL, Bilezikian JP, Bremner WJ, Hung W, Kahn CR, Loriaux DL, Nysten ES, Rebar RW, Robertson GL, Wartofsky L, eds. *Principles and Practice of Endocrinology and Metabolism*. 2nd ed. Philadelphia, Pa: J.B. Lippincott Co; 1995.

5. Wilson JD, Foster DW, Kronenberg HM, Reed Larson P, eds. *Williams Textbook of Endocrinology*. 9th ed. Philadelphia, Pa: W.B. Saunders Co; 1998.

Chapter 12 – The Adrenal Cortex, DN Orth, WJ Kovacs

Chapter 13 – Catecholamines and the Adrenal Medulla, JB Young, L Landsberg

Chapter 14 – Endocrine Hypertension, R.B. Dluhy, GH Williams

### ***CD-ROM***

UpToDate in Endocrinology and Diabetes [CD ROM Series] (ISSN:190-3496). Available at <http://www.uptodate.com/>. Accessed 2005.

### ***Journal Articles***

1. Lamberts, S.W., Bruining, H.A., De Jong, F.H. *Corticosteroid Therapy in Severe Illness*. New England Journal of Medicine. 337(18):1285-92, Oct 30, 1997.

2. Oelkers Wolfgang. *Adrenal Insufficiency*. New England Journal of Medicine. 335(16):1206-12, Oct 17, 1996.

3. Young, William. *The Incidentally Discovered Adrenal Mass*. New England Journal of Medicine. 356(6):601-10, Feb. 8, 2007.

### ***Additional Readings***

#### **Cushing's Syndrome**

Findling JW, Raff H. *Newer diagnostic techniques and problems in Cushing's disease*. Endocrinol Metab Clin North Am. 1999; 28:191-210.

Graham KE, Samuels MH, Nesbit GM, et al. *Cavernous sinus sampling is highly accurate in distinguishing Cushing's disease from ectopic adrenocorticotropin syndrome and in predicting intrapituitary tumor location.* J Clin Endocrinol Metab. 1999; 84:1602-1610.

Newell-Price J, Trainer P, Besser M, Grossman A. *The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states.* Endocrine Rev. 1998; 19:647-672

Raff H, Raff JL, Findling JW. *Late-night salivary cortisol as a screening test for Cushing's syndrome.* J Clin Endocrinol Metab. 1998; 83:2681-2686.

### **Adrenal Insufficiency**

Betterle C, Greggio NA, Volpato M. Clinical review 93: *Autoimmune polyglandular syndrome type 1.* J Clin Endocrinol Metab. 1998; 83:1049-55

Kleerekoper M, Schiebinger R, Gutai JP. *Steroid therapy for adrenal disorders--getting the dose right.* J Clin Endocrinol Metab. 1997; 82:3923-5

Annan D, et al 2002 *Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock.* JAMA 288:862.

### **Pheochromocytoma and Mineralocorticoid Excess**

Dluhy RG, Lifton RP: *Glucocorticoid-remediable aldosteronism.* J Clin Endocrinol Metab. 1999; 84:4341-4

Young WF Jr. *Pheochromocytoma and primary aldosteronism: Diagnostic approaches.* Endocrinol Metab Clin North Am. 1997; 26:801-827.

White PC. *Disorders of aldosterone biosynthesis and action.* N Engl J Med. 1994; 331:250-258

Stratakis CA. 2001 *Genetics of adrenocortical tumors: Carney complex.* Annales d Endocrinologie. 62(2):180-4

Kudva YC, Sawka AM, Young WF Jr. 2003 Clinical review 164: *The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience*. Journal of Clinical Endocrinology & Metabolism. 88(10):4533-9.

Herrmann M. 2003 *Standard and molecular cytogenetics of endocrine tumors*. American Journal of Clinical Pathology. 119 Suppl:S17-38

Bryant J, Farmer J, Kessler LJ, Townsend RR, Nathanson KL. 2003 *Pheochromocytoma: the expanding genetic differential diagnosis*. Journal of the National Cancer Institute. 95(16):1196-204

Ilias I, Pacak K. 2004 *Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma*. Journal of Clinical Endocrinology & Metabolism. 89(2):479-91

### **Nonfunctioning Adrenal Mass**

Angeli A, Osella G, Ali A, et al: *Adrenal incidentaloma: An overview of clinical and epidemiological data from the National Italian Study Group*. Horm Res. 1997; 47:279- 283.

Cook DM. Adrenal mass. Endocrinol Metab Clin North Am. 1997;26:829-852.

Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. *Incidentally discovered adrenal masses*. Endocr Rev. 1995; 16:460-484.

Mantero F, Masini AM, Opocher G, et al. *Adrenal incidentaloma: An overview of hormonal data from the National Italian Study Group*. Horm Res. 1997; 47:284-289.

Anonymous. 2002 *NIH state-of-the-science statement on management of the clinically inapparent adrenal mass ("incidentaloma")*. NIH Consensus & State-of-the-Science Statements. 19(2):1-25

Bugalho MJ, Domingues R, Sobrinho L. 2003 *Molecular diagnosis of multiple endocrine neoplasia Type 2*. Expert Review of Molecular Diagnostics. 3(6):769-79

Sidhu S, Gicquel C, Bambach CP, Campbell P, Magarey C, Robinson BG, Delbridge LW. 2003 *Clinical and molecular aspects of adrenocortical tumourigenesis*. ANZ Journal of Surgery. 73(9):727-38.

### **Hirsutism, Virilization, and Congenital Adrenal Hyperplasia**

Derksen J, Nagesser SK, Meinders AE, Haak HR, van de Velde CJ. *Identification of virilizing adrenal tumors in hirsute women.* N Engl J Med. 1994; 331:968-973.

Franks S. Polycystic ovary syndrome. N Engl J Med. 1995;333:853-861.

Gabrilove JL, Sharma DC, Wotiz HH, Dorfman RI. *Feminizing adrenocortical tumors in the male – A review of 52 cases.* Medicine. 1965; 44:37-44.

Gabrilove JL, Seman AT, Sabet R, Mitty HA, Nicolis GL. *Virilizing adrenal adenoma with studies on the steroid content of the adrenal venous effluent and a review of the literature.* Endocr Rev. 1981; 2:462-470.

Pang S. *Congenital adrenal hyperplasia.* Endocrinol Metab Clin North Am. 1997; 26:853-891.

Hughes I. 2002 *Congenital adrenal hyperplasia: phenotype and genotype.* Journal of Pediatric Endocrinology & Metabolism. 15 Suppl 5:1329-40.

Simard J, Moisan AM, Morel Y. 2002 *Congenital adrenal hyperplasia due to 3beta-hydroxysteroid dehydrogenase/Delta(5)-Delta(4) isomerase deficiency.* Seminars in Reproductive Medicine. 20(3):255-76.

Peter M. 2002 *Congenital adrenal hyperplasia: 11beta-hydroxylase deficiency.* Seminars in Reproductive Medicine. 20(3):249-54.

Hughes IA. 2002 *Congenital adrenal hyperplasia: 21-hydroxylase deficiency in the newborn and during infancy.* Seminars in Reproductive Medicine. 20(3):229-42.

Sultan C, Paris F, Jeandel C, Lumbroso S, Galifer RB. 2002 *Ambiguous genitalia in the newborn.* Seminars in Reproductive Medicine. 20(3):181-8.

Speiser PW, White PC. 2003 *Congenital adrenal hyperplasia.* New England Journal of Medicine. 349(8):776-88

### **Fluid and Electrolytes**

Gennari FJ. *Hypokalemia*. N Engl J Med. 1998; 339:451-458.

*Disturbances in Control of Body Fluid Volume and Composition*. In: BM Brenner, ed. *Brenner and Rector's The Kidney*. 5th ed. Philadelphia, Pa: W.B. Saunders; 1996.

Pitt B, et al 2003 *Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction*. N Engl J Med 348:1309-21

## **Hypertension**

August P. *Hypertension in men*. J Clin Endocrinol Metab. 1999; 84:3451-3454.

August P, Oparil S. *Hypertension in women*. J Clin Endocrinol Metab. 1999; 84:1862-1866.

JNC-VI: *The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*. Rockville, Md: National Institutes of Health; November 1997. NIH Publication 98-4080.

Sibai BM. *Treatment of hypertension in pregnant women*. N Engl J Med. 1996; 335:257-265.

Setaro JF, Black HR. *Refractory hypertension*. N Engl J Med. 1992; 327:543-547.

Pitt B, et al 2001 *The EPHEsus trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction: eplerenone post-AMI heart failure efficacy and survival study*. Cardiovasc Drugs Ther 15:79-87

Bauersachs J, et al 2002 *Addition of spironolactone to angiotensin-converting enzyme inhibitor in congestive heart failure improves endothelial vasomotor dysfunction: role of vascular superoxide anion formation and endothelial nitric oxide synthase expression*. J Am Coll Cardiol 39:351-358

## **Adrenal Studies and Procedures**

Aron DC, Raff H, Findling JW. *Effectiveness versus efficacy: the limited value in clinical practice of high dose dexamethasone suppression testing in the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome.* J Clin Endocrinol Metab. 1997; 82:1780-1785.

Doppman JL, Gill JR Jr. *Hyperaldosteronism: Sampling the adrenal veins.* Radiology. 1996; 198:309.

Oldfield EH, Doppman JL, Nieman LK, et al. *Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome.* N Engl J Med. 1991; 325:897-905.

Torpy DJ, Chenn CC, Mullen N, et al. *Lack of utility of 111-In-pentetreotide scintigraphy in localizing ectopic ACTH producing tumors: follow-up of 18 patients.* J Clin Endocrinol Metab. 1999; 84:1186-1192.

Yanovski JA, Cutler GB Jr, Chrousos GP, et al. *The dexamethasone-suppressed corticotropin-releasing hormone stimulation test differentiates mild Cushing's disease from normal physiology.* J Clin Endocrinol Metab. 1998; 83:348-352.

### ***Self Assessment Tests***

Endocrine Society's Endocrine Self Assessment Program (ESAP). Available at [The Endocrine Society, 2004 most recent edition](#)

American Association of Clinical Endocrinologists (AACE). *Self-Assessment Profile (ASAP) for Endocrinology, Diabetes and Metabolism.* Available at <http://aace.com/asapindex.htm>. Accessed June 5, 2000.

Kudva YC, Sawka AM, Young WF Jr. 2003 Clinical review 164: *The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience.* Journal of Clinical Endocrinology & Metabolism. 88(10):4533-9.

Herrmann M. 2003 Standard and molecular cytogenetics of endocrine tumors. American Journal of Clinical Pathology. 119 Suppl:S17-38



## **Section 3**

### **Disorders of Bone and Mineral Metabolism**

#### **1. Introduction**

##### **A. Background**

A clear understanding of disorders of bone and mineral metabolism is a critical component of the fellowship training in Endocrinology, Diabetes, and Metabolism. Osteoporosis is a major public health problem, accounting for \$13.8 billion in direct health care costs in the United States each year, and primary hyperparathyroidism is the third most endocrine disorder in this area of discipline. Given the widespread prevalence of osteoporosis and frequent nature of primary hyperparathyroidism, the endocrinology fellow needs to learn to work with the patient's primary care and other physicians in providing appropriate consultative and management advice in the care of patients with osteoporosis.

In addition to osteoporosis and primary hyperparathyroidism, the two most common bone & mineral disorders, a number of other disorders of bone and mineral metabolism are commonly referred to the practicing endocrinologist for evaluation and management. These include hypercalcemia of malignancy, Paget's disease, renal osteodystrophy and nephrolithiasis. The remainder of the disorders in this area, while less common, clearly require the knowledge and experience of an endocrinologist to accurately diagnose and manage. These include different varieties of hypoparathyroid states, other forms of hyper- and hypocalcemia, osteomalacia and rickets and their various forms, as well as disorders of other minerals (ie, magnesium and phosphorus), and developmental bone disorders such as osteogenesis imperfecta, fibrous dysplasia, various chondrodysplasias etc.

##### **B. Goals & Objectives:**

It is our intention that the fellow develops the required knowledge base and skills to manage patients with various disorders of bone and mineral metabolism.

- an understanding of the normal mineral homeostasis of calcium, phosphorus and magnesium and of the calcium regulating hormones: parathyroid hormone, calcitonin, and 1,25-dihydroxyvitamin D
- an understanding of the skeletal homeostasis including anatomy, structure, bone remodeling, and of the local and systemic hormones and factors that regulate skeletal homeostasis

- an understanding of the critical and close interrelationship between mineral and skeletal homeostasis.

The overall competencies that an endocrinology fellow needs to acquire in this area must begin with a solid understanding of the anatomy and biology of bone matrix and cellular elements. S/he must also be well versed in the physiology of calcium, magnesium, and phosphorus homeostasis, and understand the biochemistry of the calcium-regulating hormones. With this as a background, the fellow must be competent in the clinical evaluation of bone and mineral disorders, including obtaining a relevant, comprehensive history and performing the relevant physical examination, as well as ordering and interpreting the appropriate laboratory tests in a cost-effective manner. The specific disorders and the management skills needed for each are described in the template and discussed further later. Clinical experience must include opportunities to diagnose and manage patients of both sexes in both the inpatient and outpatient setting. The fellow must also learn to function as a consultant for other physicians in these disorders. To truly understand the evolution and natural history of bone and calcium disorders, as well as the effectiveness of therapeutic interventions, the educational program must have at least 30% of the experience in this area in ambulatory care settings.

The overall training program must facilitate the acquisition of these skills through a number of tools. These include, but are by no means limited to, didactic lectures, interactive computer programs, oral case presentation and discussion, and most importantly, direct and close supervision by the faculty of fellow evaluation and management of patients with as wide a spectrum as possible of bone and calcium disorders.

### **C. Training and Evaluation**

Clear mechanisms must be in place for the evaluation of the fellows and the provision of positive and negative feedback. Evaluation can be in the form of faculty critiques of the fellow's performance, ABIM examinations, or In-Training examinations. Two self-assessment examinations are also available (ESAP and AACE). Feedback should be provided both orally at the end of a specific rotation as well as using written evaluation sheets. In addition, fellows should have an opportunity and a mechanism for providing feedback to the faculty regarding the quality of teaching and mentoring they receive.

In the attached discussion of specific learning areas, the panel recognizes certain essential areas, which each training program must cover. In addition, there are a number of areas which, while desirable and should be covered by the program, are not mandatory, particularly if the relevant patient population is not available or appropriate faculty expertise is not present.

## **2. Program Content**

The following summarizes the key learning areas in disorders of bone and mineral metabolism for the clinical training program in Endocrinology and Metabolism.

### **1. Biology of Bone**

The necessary basic background in this area should include a thorough understanding of the fundamentals of bone biology. Specifically, the fellow must know the macroscopic and microscopic structure of bone, the composition and mineralization of the bone matrix, and the fundamentals of bone remodeling and growth (ie, the processes of intramembranous and endochondral ossification). S/he should also have knowledge of the role and function of the principal cells involved in bone remodeling; osteoblasts, osteoclasts, and osteocytes. Finally, s/he should be familiar with the various systemic and local factors regulating bone development, modeling, and remodeling.

### **2. Physiology of Calcium, Magnesium, and Phosphorus Homeostasis**

A basic understanding of mineral homeostasis should include knowledge of the factors regulating intestinal absorption, renal handling, and flux in and out of bone of these minerals. Included in this is the role of systemic hormones (PTH, calcitonin, 1,25-dihydroxyvitamin D, growth hormone, estrogen, glucocorticoids, and others) as well as dietary factors (intake of these minerals and other factors such as sodium intake). The fellow should also have an understanding of alterations in calcium and phosphorus homeostasis during physiological states such as puberty, pregnancy, lactation, and aging.

### **3. Molecular Biology, Biochemistry, and Mechanism of Action of Calcitropic Hormones**

The fellow should have an understanding of the synthesis and secretion of PTH, its peripheral metabolism, and mechanism of action. S/he should have a knowledge of the role of the calcium-sensing receptor and vitamin D receptor in normal physiology and abnormal pathology. The fellow should understand the role of PTH-rP in malignancy and humoral hypercalcemia of malignancy. S/he should understand the synthesis, metabolism, and action of vitamin D and its key metabolite, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. S/he should be aware of the potential normal

skeletal and non-skeletal actions of PTH-rP and 1,25-dihydroxyvitamin D. Finally, s/he should have an understanding of the synthesis and secretion of calcitonin, as well as its action on bone.

#### **4. Clinical Evaluation of Bone and Mineral Disorders**

The fellow should learn to obtain a comprehensive but relevant history and perform the appropriate physical examination. This should include a detailed musculoskeletal examination, as well as other parts of a comprehensive examination (eg, breast, gonadal and other relevant examination) when appropriate.

#### **5. Laboratory Methods**

The fellow should understand the methods, strengths, and limitations of various measurements s/he will be requesting. S/he should understand issues of assay accuracy, variability (inter and intra assay, individual and biologic) and detection limits. S/he should be able to integrate a number of test results and recognize specific patterns of test abnormalities associated with various disease states.

The fellow should have knowledge of abnormalities in protein binding that might affect serum calcium measurements, as well as possible artifacts/physiological alterations in serum phosphorus and magnesium determinations. S/he should understand issues involved in collection and interpretation of ionized calcium and urinary calcium measurements. S/he should have a full understanding of PTH assays, correct interpretation of the assay result in light of ambient serum calcium concentration including the effects of changes in renal function on the assay. Similarly, s/he should have knowledge of calcitonin assays, as well as the role of stimulated serum calcitonin measurement in the diagnosis of C-cell hyperplasia and medullary thyroid carcinoma. More recently, assays for PTH-rP have become available, and the fellow should have an understanding of when a PTH-rP level may be useful in the evaluation of the patient. S/he should have a knowledge of assays for 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and understand the clinical situations warranting either 25-hydroxyvitamin D measurement (ie, in the evaluation of vitamin D depletion or intoxication) or the 1,25-dihydroxyvitamin D measurement (as in the evaluation of granulomatous hypercalcemia or hypophosphatemic rickets and osteomalacia). The fellow should also understand gonadal steroid and other hormonal measurements as they relate to the evaluation of disorders of bone and mineral metabolism.

The recent availability of biochemical markers of bone turnover has added another tool for the evaluation of osteoporosis and other metabolic bone diseases. The fellow should have a working knowledge of markers of bone formation and resorption, and their indicated uses.

Finally, the fellow should have knowledge of molecular diagnostics, particularly as they apply to disorders of bone and mineral metabolism. This includes understanding the different techniques of molecular diagnostics (ie, mutation identification using single-strand conformational polymorphism, direct DNA sequencing, restriction endonuclease analysis, etc.). While it is acknowledged that the general applicability of these techniques at present is principally for the diagnosis and management of Multiple Endocrine Neoplasia syndromes, clearly they will be increasingly used in the future in the evaluation of other bone and mineral disorders.

## **6 Imaging Techniques/Other Procedures**

The training program should have a close working relationship with a skeletal radiologist who can provide expert interpretation of bone radiographs of adults and children. The fellow should develop the fundamental skills to recognize the typical radiographic appearances of at least common metabolic bone disorders (ie, osteoporosis, hyperparathyroidism (both primary and uremic secondary), rickets and osteomalacia, Paget's disease of bone, etc.). Similarly, s/he should have an understanding of bone scintigraphy and its appropriate use.

Understanding various bone mass measurement techniques is a critical component in the evaluation of osteoporosis. The fellow should have knowledge of the technical aspects of Dual Energy X-ray Absorptiometry (DEXA) measurements, and understand issues of quality control, precision, and interpretation of DEXA measurements, both in terms of diagnosing osteopenia and osteoporosis, as well as in interpreting longitudinal changes. S/he should understand the use of DEXA for assessment of body composition. S/he should also be familiar with other available technologies, such as quantitative CT, ultrasound, and digital radiography.

The fellow should, if possible, acquire the skills to perform and interpret bone biopsies. Bone histomorphometry is useful in the evaluation of difficult metabolic bone diseases, and still remains instrumental for the definitive diagnosis of osteomalacia and renal osteodystrophy.

The fellow should learn the fundamentals of parathyroid imaging (scan and ultrasound), including the appropriate use of these tests in the evaluation of patients with hyperparathyroidism (primary or uremic secondary). S/he should also learn the appropriate use of CT and MR imaging in the evaluation of patients with persistent or recurrent hyperparathyroidism. Finally, the fellow should acquire sufficient working knowledge in interpreting various imaging techniques in the evaluation of patients with kidney stones such as plain x-rays with and without tomography, intravenous pyelography, CT and ultrasound.

## **7 Postmenopausal and Age-Related Osteoporosis**

Post menopausal and age-related osteoporosis is by far the most common bone and mineral disorders and likely the most common reason for referral to an endocrinologist or bone and mineral specialist. Therefore, the fellow should have a thorough understanding of the epidemiology and current concepts in the pathogenesis of both postmenopausal and age-related osteoporosis. The fellow should be familiar with the impact of physical activity and nutrition (in particular, calcium and vitamin D) on bone mass and fractures and of factors such as medications, impaired vision, and propensity to fall on fracture risk. S/he should be sufficiently knowledgeable to advise the patient on appropriate prevention measures, and learn to manage the woman going through menopausal transition. S/he should be well versed in the diagnostic evaluation of osteoporosis, including the correct interpretation of bone density data within the clinical context of the particular patient.

S/he should be able to exclude secondary causes for osteoporosis, including primary and secondary hyperparathyroidism, prolonged and severe vitamin D depletion, exogenous and endogenous glucocorticoid excess, hyperthyroidism, transplant bone disease, osteogenesis imperfecta, multiple myeloma, etc. In addition, the fellow should know how to evaluate and manage patients with idiopathic (both in men and women) osteoporosis and various forms of secondary osteoporosis. The fellow should also be familiar with other skeletal complications of glucocorticoid use, including avascular necrosis.

S/he should be comfortable with the use of both non-pharmacologic (ie, lifestyle changes, calcium and vitamin D supplementation, and, appropriate referral to physiotherapy) and pharmacologic interventions (estrogen/hormone replacement therapy, HRT, Selective Estrogen Receptor Modulators, bisphosphonates, calcitonin, and parathyroid hormone) for management and treatment of a patient with osteoporosis. S/he should be able to evaluate the patient who has sustained an osteoporotic fracture and institute measures to reduce the risk of subsequent fractures. The fellow should also be familiar with issues of pain management in patients with vertebral or other fractures. Finally, s/he should be able to work with the specialists (orthopedist or radiologist) in the management of patients with acute fractures, learn when to seek appropriate referral for a patient with acute fracture for vertebro-, kyphoplasty, as well as in the management of patients with delayed healing of fractures.

## **8. Hypercalcemic Disorders**

The fellow should have a full understanding of the evaluation and management of patients with various types of hypercalcemia. S/he should be able to distinguish the differences and similarities between PTH and non-PTH mediated hypercalcemias and the appropriate use and interpretation of PTH assay (elevated versus non-suppressed in the context of an elevated serum calcium for instance) to make a diagnosis of primary hyperparathyroidism (PHPT) versus non-PTH mediated hypercalcemias (ie, humoral hypercalcemia of malignancy, hyperabsorptive hypercalcemia due to

granulomatous disorders, or other number of miscellaneous causes of hypercalcemia). S/he should also be able and comfortable in differentiating sporadic PHPT from Familial Hypocalcemic Hypercalcemia (sometimes referred to as Familial Benign Hypercalcemia), as well as pursuing, when appropriate, various forms of familial hyperparathyroidism either isolated or as part of MEN syndromes, including an understanding of genetic testing for these syndromes.

If a diagnosis of PHPT is established, the fellow should know the necessary evaluation of these patients leading to a decision regarding surgical versus medical management. If the patient decides to have surgery, the fellow should work with an expert parathyroid surgical team in the peri- and post-operative management of these patients, including post-operative hypocalcemia. Specifically, the fellow should be able to distinguish hungry bone syndrome from post-operative hypoparathyroidism, and manage both appropriately. If a decision is made for medical therapy or conservative observation, the fellow should be familiar with the measures to monitor during follow-up of these patients and the endpoints that would result in recommending surgery. Finally, s/he should be familiar with evolving approaches to the management of patients with PHPT, both surgical (ie, minimal invasive parathyroidectomy, alcohol ablation) and the use of various bisphosphonates, estrogen or raloxifene if the bone density is unacceptably low and the patient refuses surgery and calcimimetic agent, cinacalcet, if the serum calcium is unacceptably high and the patient is unwilling or unable to have parathyroidectomy.

In addition to PHPT, the fellow should know the evaluation and management of patients with parathyroid cancer. S/he should be able to effectively evaluate and manage the patient with hypercalcemia in the setting of a suppressed PTH (ie, hypercalcemia of malignancy and hyperabsorptive hypercalcemia due to granulomatous disorders).

## **9. Paget's Disease of Bone**

The fellow should be familiar with current concepts of pathogenesis, natural history, and treatment of Paget's disease of bone. The evaluation and management of Paget's disease involves an understanding of the appropriate laboratory studies to document the extent and severity of the disease (biochemical markers of bone turnover, scintigraphy, and radiographs), familiarize with the typical radiographic appearance, and learn the characteristic features that distinguish Paget's disease of bone from other similar conditions such as fibrous dysplasia and most importantly osteoblastic metastases. The fellow should be able to combine this data with the patient's symptoms, leading to a decision about appropriate type and duration of therapy. The latter may include observation or pharmacologic therapy with calcitonin, oral, or intravenous bisphosphonates.

## **10. Renal Osteodystrophy**

While primarily managed by the nephrologist, the endocrine fellow should have a clear understanding of pathogenesis and clinical manifestations of renal osteodystrophy in its various forms, including secondary and tertiary hyperparathyroidism. The role of the endocrinologist may be most relevant and important during and following parathyroid surgery in such patients. The fellow should be familiar with pre- and post-operative management of these patients, particularly how to prevent and treat hungry bone syndrome. The fellow should learn the appropriate use of bone biopsy and bone histomorphometry in evaluating patients with various forms of renal osteodystrophy (osteitis fibrosa, adynamic bone disease, mixed uremic osteodystrophy, osteomalacia etc) and if possible, the fellow should make a concerted effort to acquire appropriate training in these techniques.

## **11. Rickets and Osteomalacia**

While much less common than osteoporosis, the fellow should learn how to evaluate and treat various types osteomalacic disorders and to distinguish these from osteoporosis. Nutritional vitamin D deficiency is particularly becoming a growing public health problem in the elderly, and increases significantly the risk of hip fracture. In addition, recognition of vitamin D deficiency often uncovers a previously unsuspected diagnosis, such as celiac sprue, in an otherwise minimally symptomatic patient. The fellow should know the appropriate tests to order in this setting (ie, serum bone specific alkaline phosphatase, 25-hydroxyvitamin D and PTH levels, and urine calcium), including possibly a bone biopsy when needed. The fellow should have appropriate exposure to various inherited disorders of vitamin D action, such as vitamin D dependency, or renal handling of phosphate such as sporadic and familial hypophosphatemic (some times referred to as vitamin D resistant) rickets and osteomalcia. The evaluation of patients with tumor-induced osteomalacia is often extremely difficult, as the underlying tumor may sometimes be impossible to identify. Thus the fellow should also be familiar with medical management of such patients.

## **12.Nephrolithiasis**

The fellow should be able to evaluate a patient with nephrolithiasis. Based on the type of stone and the evaluation (ie, identification of hypercalciuria, hyperoxaluria, hyperuricosuria, or low urinary citrate), the fellow should be able to identify any underlying disorders such as primary hyperparathyroidism or enteric hyperoxaluria. S/he should know the medical management of the patient based on this evaluation, and to work with a dietician in the appropriate dietary management of these patients.

## **13. Hypocalcemic Disorders**

The fellow should know how to manage acute hypocalcemia as, for example, in the post-operative setting. This includes the use of intravenous calcium preparations and when they are indicated. S/he should be able to manage chronic hypocalcemia with oral calcium and vitamin D preparations and, if indicated, a thiazide diuretic. Working with a dietician, s/he should be able to advise the patient with hypoparathyroidism regarding dietary phosphate restriction, and use phosphate binders when indicated. S/he should be able to assess the patient with various forms of hypocalcemia, including that due to acute pancreatitis, acute illnesses, and associated with the use of various medications.

The fellow should know the various types of parathyroid resistance syndromes and the appropriate testing, both biochemical and genetic, necessary to establish a diagnosis of different varieties of pseudohypoparathyroidism. S/he should be familiar with possible resistance to other hormones as well as the non-endocrine disorders that are not uncommon in these patients.

#### **14. Other Mineral Abnormalities**

The fellow should be able to identify the possible causes of hypo- and hypermagnesemia in a patient, and to institute appropriate therapy. S/he should be able to identify situations in which hypomagnesemia is the cause or contributing to hypocalcemia. S/he should also be able to identify the etiology of hyper- or hypophosphatemia in a patient, and to treat these conditions.

#### **15. Genetic, Developmental, and Dysplastic Skeletal Disorders**

The fellow should be familiar with these disorders, which can present both in children and in adults. These include various sclerosing bone disorders and skeletal dysplasias. The fellow should be able to evaluate the patient referred because of an elevated bone density, in the absence of radiographic sclerosis. An experienced skeletal radiologist is a great asset to the training program in the accurate diagnosis of these conditions based on the radiographic findings. The fellow should have exposure to the evaluation and management of patients with osteogenesis imperfecta as well as appropriate medical management of both the skeletal aspects of fibrous dysplasia and, when present, the management of precocious puberty in these patients.

#### **16. Skeletal Neoplasms/Infiltrative Disorders**

The fellow should be able to identify benign and malignant skeletal neoplasms on skeletal radiographs, and institute appropriate referrals to an Orthopedic surgeon or to radiation and/or medical Oncologists. S/he should also be familiar with the various infiltrative disorders of bone, including mast cell disease and histiocytosis X.

### **17. Extraskkeletal Calcification/Ossification**

These include relatively uncommon conditions such as tumoral calcinosis, metastatic and dystrophic calcification, dermatomyositis with calcinosis cutis universalis, and various rare ossification disorders. While the fellow may not necessarily have the opportunity to manage these relatively rare conditions, s/he should be familiar with these disorders and their treatment.

### **D. Suggested Reading**

#### *Testbooks, Primers and Treatise*

J.D. Wilson, D.W. Foster, H.M. Kronenberg & P.R. Larsen, Eds: Williams Textbook of Endocrinology; 9<sup>th</sup> Edition, 1998

Favus MJ, ed. Primer on Metabolic Bone Diseases and Disorders of Mineral Metabolism, Fifth Edition, 2003.

Bonnick, S.L. Bone Densitometry in Clinical Practice: Application and Interpretation, Second Edition, Humana Press.

#### *Useful websites with educational contents and position papers*

[www.asbmr.org](http://www.asbmr.org) American Society of Bone & Mineral Research; Review Bone Curriculum

[www.nof.org](http://www.nof.org) National Osteoporosis Foundation

[www.iscd.org](http://www.iscd.org) International Society for Clinical Densitometry

#### *Selected Topic Specific Additional Reading*

##### **Osteoporosis**

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## **Section 4**

# **Diabetes Mellitus**

### **I. Introduction**

#### **A. Background**

Diabetes is an increasingly common, potentially devastating, extraordinarily expensive, treatable, but incurable, chronic disease. It is by far the most common endocrine disorder that seriously impacts health and limits longevity in those affected. There are 18.2 million people in the United States, or 6.3% of the population, who have diabetes. The World Health Organization projects the worldwide population of people with diabetes will grow to 300 million by the year 2025. Many more have impaired glucose tolerance or impaired fasting glucose and are at high risk for atherosclerotic disease and diabetes. People with diabetes are at 2- to 4-fold increased risk for a myocardial infarction or a stroke. Diabetes is the leading cause of blindness with its onset in working age adults and of non-traumatic amputations, and the most common single cause of end-stage renal disease requiring dialysis and transplantation. The total annual economic cost of diabetes in 2002 was estimated to be \$132 billion, or one out of every 10 health care dollars spent in the United States. Much of this was for the care of long-term microvascular and macrovascular complications of diabetes that are now known to be in large part preventable.

#### **B. Goals and Objectives**

##### *1. Treatment and management goals:*

It is now well-established that treatment makes a long-term difference for people with diabetes. Currently available treatments are far from ideal, but they are demonstrably effective. These treatments involve an integrated care team (eg, an endocrinologist, a diabetes educator, a nutritionist). Among the specific objectives of our training program is to teach our fellows (residents) in Endocrinology, Diabetes and Metabolism to know and understand the evidence that in people with diabetes:

- (1) glycemic control reduces the risk of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardio-, cerebro- and peripheral vascular disease) events;
- (2) treatment of dyslipidemia reduces the risk of macrovascular events;
- (3) treatment of hypertension and even early nephropathy reduces end-stage renal disease and other microvascular as well as macrovascular events;
- (4) aspirin reduces macrovascular events;

- (5) treatment of early retinopathy reduces blindness;
- (6) foot care reduces amputations; and
- (7) implementation of Standards of Care results in better glycemic control and reduces costs.

Additional objectives are to know, understand and pursue the recommended treatment goals (updated by the ADA in each January issue of *Diabetes Care*) and minimum outcome measures shown in the following tables.

### Treatment Goals

	<b>Goal</b>
Hemoglobin A <sub>1c</sub> (%)	≤7
Preprandial Glucose (mg/dL)	80-130
Bedtime Glucose (mg/dL)	100-140
LDL Cholesterol (mg/dL)	<100
Triglycerides (mg/dL)	< 150
Blood Pressure (mm Hg)	≤ 130/80
Urine Microalbumin	Normal

In some individual patients it may be appropriate not to individualize treatment goals, but the rationale for that decision should be made explicit. *These goals need to be modified for children with diabetes.*

### Minimum Outcome Measures

Hemoglobin A <sub>1c</sub>	Semiannually*
Dilated Eye Exam	Annually
Foot Exam	Annually
Blood Pressure	Each visit
Urine Microalbumin	Annually
Fasting Lipid Profile	Annually
Self Management Education	Annually
Medical Nutrition Therapy	Annually
Serum TSH	Annually
Self Blood Glucose Monitoring	Yes
Tobacco Counseling	Yes

\*ADA Recommendation: Quarterly until glycemic control is achieved, then semiannually.

## 2. *Comprehensive Patient Evaluation*

Given this knowledge it is our objective to teach fellows to evaluate patients with diabetes comprehensively including assessments of:

- (1) glycemic control (long-term with HbA<sub>1C</sub>, short-term with the history and the SMBG log including identification of both hyper- and hypoglycemia);
- (2) blood pressure control;
- (3) lipid control (fasting lipid profile);
- (4) the status of microvascular complications (history, dilated eye examination, detailed foot examination including monofilament testing, urine albumin);
- (5) macrovascular complications (history, cardiovascular examination, and nuclear testing for coronary artery disease);
- (6) the need for additional self management education, medical nutrition therapy, or both; and
- (7) smoking status.

These basic principles are emphasized throughout the fellow's training experience in our inpatient and outpatient care settings as well as in our didactic program and our clinical conferences. It is our premise that, while complications of diabetes must be detected and treated in their early stages, the prevention of complications through comprehensive diabetes care is the new paradigm in the management of diabetes.

An additional objective of our program is to provide, through research experience and didactic instruction, insights into the basic and clinical scientific advances that will lead to improvements in the prevention and treatment of diabetes and its complications.

## 3. *Evaluation and Management of Acute and Chronic Complications*

It is also our objective to teach the evaluation and management of acute and chronic complications, including:

- (a) Diabetic ketoacidosis
- (b) Hypersmolar non-ketotic syndromes
- (c) Hypoglycemia
- (d) Microvascular and macrovascular disease, including
  - (i) Diabetic Retinopathy
  - (ii) Diabetic nephropathy
  - (iii) Diabetic neuropathy
  - (iv) Dermatologic aspects of diabetes
  - (v) Coronary heart disease

- (vi) Peripheral vascular disease
- (vii) Cerebrovascular disease
- (e) Infections in the diabetic patient

#### *4. Evaluation and Management of Diabetes and Pregnancy*

Finally, it is also our objective to teach the evaluation and management of all aspects of diabetes and pregnancy, including:

- (a) Preconception counseling of non-gestational diabetes
- (b) Screening and diagnosis of gestational diabetes
- (c) Treatment goals of non-gestational and gestational diabetes
- (d) Antepartum screening for women with diabetes during pregnancy
- (e) Management of labor and delivery in women with diabetes during pregnancy
- (f) Management of the postpartum period on women with diabetes
- (g) Screening for complications during pregnancy in women with diabetes

### **C. Training and Evaluation**

The clinical experiences of our fellows include opportunities to diagnose and manage inpatients and outpatients, representing adolescent and adult patients of both sexes and representing variable acuity, with both types 1 and type 2 diabetes as well as the uncommon types of diabetes. It also includes opportunities for the fellow to function in the role of consultant for patients and other physicians and services in both inpatient and outpatient settings.

Training in comprehensive diabetes care occurs repetitively, and progressively over the first two years of training in the setting of the fellow's supervised inpatient and outpatient care of people with diabetes and in the context of our didactic diabetes teaching program. The latter includes Lectures (eg, Standards of Care for People with Diabetes, Management of Type 1 Diabetes, Management of Type 2 Diabetes, Diabetic Ketoacidosis and Nonketotic Hypersmolar Syndrome, Diabetic Macro- and Microvascular Complications, Dyslipidemia, Hypertension, and Hypoglycemic Syndromes), as well as self-directed and faculty-directed reading about diabetes, including both specific and generic reading. There is no year-specific aspect to the curriculum; rather, the fellow will become more competent with continued exposure to practical and didactic learning.

In addition, our curriculum emphasizes biochemistry and physiology, including cell and molecular biology as they relate to diabetes and its complications. These are fundamental to the management of diabetes. The appropriate utilization and interpretation of clinical laboratory, radionuclide and radiologic studies for the treatment of diabetes is stressed throughout the clinical and didactic program.

Finally, our fellows have clinical experience in multidisciplinary diabetes education and treatment programs related to preventive care. As detailed earlier, our program emphasizes the training of fellows in the preventive aspects of diabetes care (ie, glycemic control, lipid control, blood pressure control, aspirin, use of statins, ACE inhibitors/ARBs, smoking cessation etc. and the identification and treatment of early microvascular and macrovascular complications) in the context of the Standards of Care and Outcome Measures recommended by the American Diabetes Association (updated each January in *Diabetes Care*) [or the Medical Guidelines for the Management of Diabetes Mellitus recommended by the American Association of Clinical Endocrinologists (*Endocrine Practice* 6:43, 2000).] Patient education – by the physician, the diabetes educator, the nutritionist and other specialists – is a fundamental component of diabetes care. Because diabetes is so common, patients with this disease are seen by fellows in virtually all of their inpatient and outpatient encounters and the team approach is also utilized in all of those settings. In addition, multidisciplinary diabetes education and treatment is the central focus of our Diabetes Clinic. This also includes the assistance of social work and ethics consultants, if necessary.

In this context fellows become competent and then expert in the comprehensive management of diabetes through supervised, progressive responsibility for the care of people with diabetes in their inpatient and outpatient activities throughout their fellowship training. This allows them to observe the natural history of diabetes and its complications, as well as the effectiveness of therapeutic interventions. Fellows have experience representing variable acuity and the full spectrum of diabetes. To accomplish these goals, more than 30% of the training in diabetes occurs in ambulatory care settings.

Patient encounters are supervised by a member of the Endocrinology, Diabetes and Metabolism faculty who reviews the historical, physical and other information gathered by the fellow with that fellow at the bed side/examination table and provides immediate confirmatory or corrective feedback. That faculty member then reviews the fellow's diagnostic and therapeutic plans, again providing immediate feedback. Learning is facilitated further by self-directed reading of the literature, reading suggested by the responsible faculty member, or both and by patient follow-up. The latter includes analysis of subsequent laboratory findings and of the patient's course with refinement of the management plan over time, again in consultation with the responsible faculty member. Thus, learning is evaluated by direct observation of the fellow by the faculty member and discussions with that and other faculty and colleagues including presentations at rounds and case conferences as well as by formal written self-assessment (eg, ESAP, MKSAP, or both). Evaluations will be made in all areas of the six core competencies as outlined by the ACGME.

## **II. Program Content**

The ACGME Program Requirements for Residency Education in Endocrinology, Diabetes and Metabolism include a heavy emphasis on diabetes. We include these guidelines for your reference.

- Residents must have clinical experience in a multidisciplinary diabetes and education program.
- Residents must have formal instruction, clinical experience, or opportunities to acquire expertise in the evaluation and management of the following disorders:

Type 1 and 2 diabetes mellitus including

- (1) Patient monitoring and treatment objectives in adolescents and adults
- (2) Acute and chronic complications, including
  - (a) Diabetic ketoacidosis
  - (b) Hypersmolar non-ketotic syndromes
  - (c) Hypoglycemia
  - (d) Microvascular and macrovascular disease, including
    - (i) Diabetic Retinopathy
    - (ii) Diabetic nephropathy
    - (iii) Diabetic neuropathy
    - (iv) Dermatologic aspects of diabetes
    - (v) Coronary heart disease
    - (vi) Peripheral vascular disease
    - (vii) Cerebrovascular disease
  - (e) Infections in the diabetic patient
- (3) Gestational diabetes
- (4) Diabetes mellitus in the pregnant patient
- (5) The surgical patient with diabetes mellitus
- (6) Patient education
- (7) Psychological issues
- (8) Genetics and genetic counseling as it relates to patients with endocrine and metabolism disorders
- (9) Dietary principles

- Provision must be made for the residents to acquire experience and skill in the following areas:

Management of adolescent and adult patients of all ages with diabetes mellitus, including but not limited to the following aspects of the disease:

- (1) The utilization and interpretation of autoimmune markers of type 1 diabetes in patient management and counseling
  - (2) Prescription of exercise program
  - (3) Rationale for and calculation of diabetic diets
  - (4) Oral antidiabetic therapy
  - (5) The use of intravenous insulin in acute decompensated diabetes mellitus
  - (6) Chronic insulin administration, including use of all varieties of insulin delivery systems
  - (7) Glucose monitoring devices, including continuous glucose sensors
  - (8) Funduscopic examination, recognition, and appropriate referral of patients with diabetic retinopathy
  - (9) Foot care
  - (10) Psychosocial effects of diabetes mellitus on patients and their families
  - (11) Patient and community education
- The formal curriculum of the program must, at a minimum, provide instruction in the following:
- (1) Pathogenesis and epidemiology of diabetes mellitus
  - (2) Genetics as it relates to endocrine diseases
  - (3) Developmental endocrinology, including growth and development and pubertal maturation, as it relates to diabetes.
  - (4) Endocrine physiology and its pathophysiology in diabetes and principles of hormone action.
  - (5) Biochemistry and physiology, including cell and molecular biology and immunology, as they relate to diabetes.
  - (6) Signal transduction pathways and biology of hormone receptors.

Provision is also made for the fellows to acquire experience and skill in the management of adolescent and adult patients of all ages with diabetes mellitus, including the utilization and interpretation of autoimmune markers of type 1 diabetes in patient management and counseling, prescription of exercise programs, the rationale for and calculation of diabetic diets, oral antidiabetic therapy, the use of intravenous insulin administration in acute decompensated diabetes, the use of all varieties of insulin delivery systems, glucose monitoring devices, funduscopic examination and recognition and appropriate referral of patients with diabetic retinopathy, foot care, psychosocial effects of diabetes on patients and their families, and patient and community education. They acquire experience and skill in each of these aspects of diabetes care through conferences and their inpatient and outpatient activities. Among the latter, the Diabetes Clinic focuses specifically on diabetes care including the team concept and approaches to the prevention of complications.

### III. Suggested Reading

#### *Textbooks*

Diabetes Mellitus: A Fundamental and Clinical Text, 3<sup>rd</sup> Edition; LeRoith, Simeon, Taylor, Olefsky, Eds.; 2003

Williams Textbook of Endocrinology, 10th ed, Larsen, Ed.;

#### *Journal Articles*

Hirsch, I.B. Insulin analogues. *N Engl J Med* 2005, 352:174-183.

Gestational diabetes mellitus. *Diabetes Care* 2004, 27 Suppl 1:S88-90, 2004.

Standards of Medical Care in Diabetes. *Diabetes Care* 2005 28:S4-S36.

Kitabchi, A.E., Umpierrez, G.E., Murphy, M.B., Barrett, E.J., Kreisberg, R.A., Malone, J.I., and Wall, B.M. Hyperglycemic crises in diabetes. *Diabetes Care* 2004 27 Suppl 1:S94-102.

van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P., and Bouillon, R. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001 345:1359-1367.

Yki-Jarvinen, H. Thiazolidinediones. *N Engl J Med* 2004 351:1106-1118.

The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329:977-986.

The DCCT Research Group. Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *J Am Med Assoc*. 1996; 276:1409-1415.

The UKPDS Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet*. 1998; 352:837-853.

The UKPDS Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet*. 1998; 352:854-865.

The UKPDS Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. *Brit Med J*. 1998; 317:703-713.

The UKPDS Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes. *Brit Med J*. 1998; 317:713-720.

The UKPDS Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes. *Brit Med J*. 1998; 317:720-726.

Pyörälä K, Pederson TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study. *Diabetes Care*. 1997; 20:614-620.

Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without myocardial infarction. *N Engl J Med*. 1998; 339:229-234.

Haffner SM, Alexander CM, Cook TJ, et al. Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels. *Arch Intern Med*. 1999; 159:2661-2667.

Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993; 329:1456-1462.

The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000; 342:145-153.

The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet*. 2000; 355:253-259.

American Diabetes Association. Clinical Practical Recommendations 2000. *Diabetes Care*. 2000; 23(Suppl 1):S1-S116.

Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V 1999 New profiles of diabetic ketoacidosis. Type 1 vs Type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 159:2317-2322.

Golan L, Birkmeyer JD, Welch HG 1999 The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. *Ann Int Med* 131:660-667.

DCCT Research Group 2000 Retinopathy and nephropathy in patients with type I diabetes four years after a trial of intensive therapy. *N Engl J Med* 342:381-9.

Detre KM, Lombardero MS, Brooks MM, et al 2000 The effect of previous coronary-artery bypass surgery on the prognosis of patients with diabetes who have acute myocardial infarction. *N Engl J Med* 342:989-997.

Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253, 2000

Langer O, Conway DL, Berkus MD, et al 2000 A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med* 343:1134-1138.

Mogensen CE, Neldam S, Tikkanen I, et al 2000 Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *Brit Med J* 321:1440-1444.

Skyler J, et al 2001 Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomized proof-of-concept study. *Lancet* 357:331-335.

Malone JL, Pavan PR, Morrison AD, Cuthbertson DD 2001 Prevalence and significance of retinopathy in subjects with type I diabetes of less than 5 years' duration screened for the Diabetes Control and Complications Trial. *Diabetes Care* 24(3):522-526.

Tabaei, B., et al 2001 Does microalbuminuria predict diabetic nephropathy? *Diabetes Care* 24(9):1560-1566

Grundy, S, et al 2002 Efficacy, safety, and tolerability of once daily niacin for the treatment of dyslipidemia associated with type 2 diabetes. *Arch Intern Med* 162:1568-1576.

Miyazaki Y, et al 2002 Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 87:2784-2791

Schneider FS, et al 2002. Effects of pioglitazone in nondiabetic patients with arterial hypertension: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 87:5503-5506.

Rubins HB, et al 2002. Diabetes, plasma insulin, and cardiovascular disease. *Arch Intern Med* 162:2597-2604.

Kanaya A 2003. Glycemic effects of postmenopausal hormone therapy: the heart and estrogen/progestin replacement study. *Ann Int Med* 138:1-9.

Tong PCY, et al 2002. The effects of orlistat-induced weight loss, without concomitant hypocaloric diet, on cardiovascular risk factors and insulin sensitivity in young obese Chinese subjects with or without type 2 diabetes. *Arch Inter Med* 162:2428-2435.

Gaede P 2003. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Eng J Med* 348:383-393.

Effectiveness of Aldosterone blockade in patients with diabetic nephropathy. January, 2003. *Hypertension* p 64-68

Park Y-W, et al 2003 The metabolic syndrome. Prevalence and associated risk factor findings in the US population from the third national health and nutrition examination survey, 1988-1994. *Arch Intern Med* 163:427-436

Delea TE, et al 2003 Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 26:2983-2989.

## **Section 5**

### **Gonadal Disorders**

#### **1. Introduction**

##### **A. Background**

Endocrinology of the reproductive system encompasses normal pubertal development and adult male and female reproductive function and the effects of excesses or deficiencies of reproductive hormones on other body systems. Issues in reproductive endocrinology are extremely prevalent in the population, highlighting the importance of this area in an endocrine training program. Disorders of this system may arise at a hypothalamic, pituitary or gonadal level as a result of a primary abnormality or secondary to abnormalities in other endocrine or non-endocrine organs. These disorders may present as primary or acquired hypogonadism, infertility, or erectile dysfunction or with evidence of hyperandrogenism or hyperestrogenism. In addition, this area of study includes abnormalities of primary or secondary reproductive organs such as skin, penis, prostate, uterus, ovaries and breast. This is an extremely important area of endocrinology, not only due to the prevalence of primary abnormalities of the reproductive system per se, but also because of the profound impact of gonadal hormone abnormalities on other endocrine and non-endocrine systems including bone, thyroid, adrenal, metabolic, dermatologic, cardiovascular, muscle, neurologic and psychiatric. Disorders of non-reproductive systems may be hormone dependent and conversely non-reproductive disorders often affect the reproductive axis.

##### **B. Goals and Objectives**

It is our intention that the fellow develop the following:

1. An understanding of the physiology of: (1) normal male and female adrenarche and puberty; (2) the normal menstrual cycle; (3) normal male reproductive physiology; (4) the physiology of the menopause and the physiology of reproductive aging in men and women; and (5) an understanding of the genetics of disorders of the reproductive system.

2. An understanding of the biochemistry, cell biology, and molecular biology of gonadotropin-releasing hormone, the gonadotropins, gonadal steroids and the inhibin/activin/follistatin family of proteins; an understanding of factors involved in growth and differentiation of the gonads (including germ cell development ), internal genitalia and accessory sex organs, and autocrine/paracrine interactions in reproductive function; knowledge of the mechanism of gonadotropin and steroid hormone action.
3. Familiarity with the types of assays available for the measurement of gonadotropins, steroids, inhibins and insulin and the clinical utility of these assays in the diagnosis and management of patients with reproductive disorders; familiarity with the evaluation and interpretation of semen analysis.
4. An understanding of how to perform, evaluate and determine the utility of dynamic provocative endocrine testing as it applies to the reproductive system.
5. An understanding of how to evaluate and determine the utility of pelvic ultrasonography and hypothalamic/pituitary, adrenal, prostate and testicular imaging, and bone densitometry.
6. A comprehensive understanding of how to evaluate and manage disorders of sexual differentiation, disorders arising in the pediatric age group including congenital adrenal hyperplasias, chromosomal disorders such as Turner and Klinefelter syndromes, and precocious or delayed puberty.
7. A comprehensive understanding of how to evaluate and manage female reproductive disorders including: (1) primary amenorrhea; (2) secondary amenorrhea or oligomenorrhea; (3) galactorrhea; (4) hyperandrogenism; (5) dysfunctional uterine bleeding; (6) ovarian lesions; (7) premenstrual symptoms; (8) peri-menopausal and menopausal symptoms; and (9) infertility. The fellow may also receive training in ovulation induction.
8. A comprehensive understanding of how to evaluate and manage male reproductive disorders including: (1) primary and acquired male hypogonadism; (2) gynecomastia; (3) erectile dysfunction; (4) testicular masses; (6) prostatic disorders; and (7) fertility disorders including induction of spermatogenesis.
9. Due to their prevalence the following areas should receive special attention: (1) the diagnosis, pathophysiology, and genetics of polycystic ovarian syndrome and its metabolic consequences; (2) male subfertility, erectile dysfunction and prostate disorders; and (3) perimenopausal and menopausal management, including decreased libido.

10. An understanding of the clinical presentation and prevalence of hormone producing neoplasms of the testis and ovary and of tumors that affect hypothalamic and pituitary function; familiarity with the treatment of hormone responsive tumors and disorders (breast, prostate, endometrium, neurologic).
11. An understanding of the effects of age on the reproductive axis in men and women and the subsequent effects of hypogonadism on other systems.
12. An understanding of the effects of acute and chronic disease on the reproductive system in men and women.
13. An understanding of the interaction of psychosocial disorders with the reproductive system including premenstrual dysphoric disorder, eating disorders, perimenopausal mood disorders, sexual dysfunction, decreased libido and substance abuse and facility in basic counseling and triage in these areas.
14. An understanding of the physiology and importance of the following drugs as they apply to the reproductive system: (1) GnRH, GnRH agonists/ antagonists, gonadotropins; (2) hormonal contraceptives; (3) selective androgen and estrogen receptor modulators (SARMS and SERMS); (4) hormone replacement therapy in men women; (5) non-hormonal strategies for menopause management; and (6) non-prescription and environmental compounds.
15. An understanding of the emerging technologies and treatment and how they impact on the comprehensive management of reproductive endocrine disorders including assisted reproductive technologies and genetic testing and facility in counseling patients regarding these options.

### **C. Training and Evaluation**

#### **1. Specific Procedures:**

The training program will provide opportunities for the fellow to develop clinical competence in reproductive endocrinology. The opportunity to diagnose and manage male and female adolescent and adult patients with reproductive endocrine disorders will occur primarily in an outpatient setting due to the generally non-acute nature of these problems, but may also include attention to reproductive endocrine issues in inpatients with other endocrine and non-endocrine diagnoses. This training is likely to require interaction with pediatric endocrinology, gynecology, urology, oncology, genetics, surgery, pathology, radiology and/or other subspecialties. Competence in the interpretation of the following procedures/studies is expected:

- a. Hormone assays (peptide and steroid)

- b. Imaging studies
  - i. Pituitary MRI/CT
  - ii. Ovarian ultrasound/CT/MRI
  - iii. Adrenal CT/MRI and functional adrenal scans (e.g. MIBG, NP 59)
  - iv. Hysterosalpingogram
- c. Other radiographic studies
  - i. DXA
  - ii. Mammography
- d. Dynamic hormone testing (e.g. GnRH stimulation test)
- e. Semen analysis
- f. Assisted fertility techniques: IUI, IVF

## 2. Educational Expectations (per year of training)

It is expected that upon completion of the first year of training, fellows will be well versed in the ability to investigate both primary and secondary hypogonadism in men and women. In addition, they will be able to properly interpret radiographic imaging studies of the pituitary and adrenal glands. Moreover, fellows will be facile with the performance and interpretation of hormone assays. By the completion of the second and subsequent years of training, the fellow will be able to identify appropriate patients for medical and/or assisted ovulation induction is needed. They will be able to coordinate therapy for men with hypogonadotropic hypogonadism needing gonadotropin therapy for induction of spermatogenesis. The fellows will recognize the potential advantages and risks of hormone replacement therapy in both women and men and be able to properly prescribe topical, oral or intramuscular hormone treatment as indicated.

## 2. Program Content

See check box forms

## 3. Suggested Reading

### *Textbooks*

Sperling M. *Pediatric Endocrinology*. 1st ed. WB Saunders Co; 1996.

Lifshitz F. *Pediatric Endocrinology*. 3rd ed.. Dekker; 1996.

Tulchinsky B, Little AB, eds. *Maternal-Fetal Endocrinology*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 1994.

Martinez-Mora J. *Textbook of Intersexual States*. Doyma; 1994.

Yee Wm, Rosen G, Cassidenti D. *Transvaginal Sonography in Infertility*. Lippincott-Raven; 1995.

Azziz R, Nestler J, DeWailly D, eds. *Androgen Excess Disorders in Women*. Lippincott-Raven; 1997.

Yen SSC, Jaffe RB, Barbieri RL, eds. *Reproductive Endocrinology*. 4th ed. Philadelphia, Pa: WB Saunders Co; 1999.

### ***Review Articles***

Hayes FJ, Seminara SB, Crowley WF, Jr. Hypogonadotropic Hypogonadism. *Endocrinol Metab Clin North Amer*. 1998; 4:739-763.

Hayes FJ, Welt CK, Martin KA, Crowley WF, Jr. GnRH deficiency: Differential diagnosis and treatment. *Endocrinologist*. 1999;9:36-44.

Taylor AE. Polycystic ovary syndrome. *Endocrinol Metab Clin North Am*. 1998;27(4):877-902.

Dewing P, Bernard P, Vilain E. 2002 Disorders of gonadal development. *Seminars in Reproductive Medicine*. 20(3):189-98

Olive DL. 2003 Medical therapy of endometriosis. *Seminars in Reproductive Medicine*. 21(2):209-22

### ***Journal Articles***

## **1. Hormone Replacement**

Hulley S, Grady D, Bush T, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women. *JAMA*. 1998;280:605-613.

Collaborative Group on Hormonal Factors in Breast Cancer. 1997 Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiologic studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*. 350:1047-1059.

Shifren JL, Braunstein GD, Simon JA, et al 2000 Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med* 343:682-688.

Schairer C, Lubin J, Troisi R, et al. 2000 Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 283:485-491.

## **2. Genetics**

Adashi EY, Hennebold JD. Single-gene mutations resulting in reproductive dysfunction in women. *N Engl J Med*. 1999;340(9):709-718.

Wang N. 2002 Cytogenetics and molecular genetics of ovarian cancer. *American Journal of Medical Genetics*. 115(3):157-63

MacLaughlin DT. Donahoe PK. 2004 Sex determination and differentiation. *N Engl J Med*. 350(4):367-78

## **3. Hypopituitarism**

Miller KK, Sesmilo G, Schiller A, et al 2001 Androgen deficiency in women with hypopituitarism. *J Clin Endocrinol Metab* 86:561-567.

## **4. Polycystic Ovary Syndrome**

Jakubowicz DJ, et al 2002 Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. *J Clin Endocrinol Metab* 87:524-529.

Legro RS. 2003 Polycystic ovary syndrome and cardiovascular disease: a premature association?. *Endocrine Reviews*. 24(3):302-12

Franks S. 2003 Assessment and management of anovulatory infertility in polycystic ovary syndrome. *Endocrinology & Metabolism Clinics of North America*. 32(3):639-51

Tsilchorozidou T. Overton C. Conway GS. 2004 The pathophysiology of polycystic ovary syndrome. *Clin Endocrinol*. 60(1):1-17.

### **5. Testicular failure**

Asklund C. Jorgensen N. Kold Jensen T. Skakkebaek NE. 2004 Biology and epidemiology of testicular dysgenesis syndrome. *BJU International*. 93 Suppl 3:6-11

### ***CD-ROM***

Male and Female Reproductive Endocrinology Sections. *Up-to-Date in Endocrinology & Diabetes* [serial on CD-ROM]. The Endocrine Society, 2000.

### ***Internet sites***

National Center for Biotechnology Information. Online Mendelian Inheritance in Man. Available at <http://www3.ncbi.nlm.nih.gov/Omim/>. Accessed June 5, 2000.

American Association for Clinical Endocrinologists. AACE Guidelines in Male Hypogonadism, Menopause and Sexual Dysfunction. Available at <http://www.aace.com/indexjava.htm>. Accessed June 5, 2000.



- e) Induction of spermatogenesis
- f) Male/Female hormone replacement
- g) Ovulation induction

## **Section 6**

# **Hypothalamic-Pituitary Disorders**

### **1. Introduction**

#### **A. Background**

Growth, development and reproduction are regulated by the interactions of the endocrine and nervous systems. The pituitary regulates endocrine organs under the influence of the hypothalamus. Disorders of the pituitary and hypothalamus may therefore cause isolated or multisystem endocrine hypofunction and hyperfunction. Furthermore, expanding lesions of the pituitary/hypothalamic area may cause neurologic dysfunction.

#### **B. Goals and Objectives**

Fellows will acquire an understanding of (1) neuroendocrine physiology, specifically hypothalamic/pituitary anatomy and morphology, regulation of hormone secretion, cellular and molecular mechanisms of action (receptors, signal transduction pathways, gene interaction); (2) the pathophysiology, clinical manifestations, diagnostic approaches, and treatment of hypothalamic and pituitary dysfunction. By the end of their training, fellows will be competent in the evaluation and management of patients with hypothalamic-pituitary disorders (see below).

#### **C. Training and Evaluation**

##### **1. Specific Procedures**

These objectives will be accomplished through a combination of interdisciplinary conferences, formal lectures, case discussions, direct clinical experience, and self-directed learning. Clinical training will include close interactions with other related disciplines, including neurosurgery, neuroradiology, neurology, neuro-ophthalmology, pathology, and nuclear medicine.

Familiarity with the methods of pituitary surgery is required. This experience includes the pre-operative evaluation, operative approach (e.g. transsphenoidal surgery) and post-operative management. Fellows may obtain this experience through rotations at their primary institution or via collaborative training at other centers where pituitary surgery is performed on a more regular basis.

Fellows will also be familiar with radiotherapy techniques, both standard and stereotactic approaches, for the treatment of pituitary tumors.

## 2. Educational Expectations (per year of training)

It is expected that upon completion of the first year of training, fellows will be well versed in the ability to investigate all forms of hypothalamic and pituitary disease in men and women. In addition, they will be able to properly interpret radiographic imaging studies and dynamic tests of pituitary function. Moreover, fellows will be facile with the performance and interpretation of hormone assays.

## 2. Program Content

In relation to the diseases listed below, residents fellows should have experience in the performance of endocrine clinical laboratory and radiographic studies and basic laboratory techniques, including quality control, quality assurance, and proficiency standards. Provision must be made for the fellow to acquire experience and skill in the following areas:

### *Basal Hormone levels*

- (1) prolactin (PRL)
- (2) insulin-like growth factor-1 (IGF-1)
- (3) growth hormone (GH)
- (4) Free thyroxine (T4)
- (5) thyrotropin (TSH)
- (6) Cortisol (plasma and urine, including metabolites)
- (7) adrenocorticotrophic hormone (ACTH)
- (8) luteinizing hormone (LH)
- (9) follicle stimulating hormone (FSH)
- (10) testosterone/estradiol
- (11) serum osmolality
- (12) urine osmolality.

### *Dynamic Hormone Testing*

- (1) Insulin-hypoglycemia stimulation (insulin tolerance test)

- (2) Thyrotropin Releasing Hormone (TRH) stimulation test
- (3) Gonadotropin Releasing Hormone (GnRH) stimulation test
- (4) Corticotropin Releasing Hormone (CRH) stimulation test
- (5) GH stimulation tests (L-dopa, arginine, clonidine, exercise, glucagon, GH Releasing Hormone [GHRH], insulin-hypoglycemia)
- (6) ACTH (cosyntropin) stimulation test
- (7) Metyrapone test
- (8) Dexamethasone suppression test
- (9) Oral glucose suppression test
- (10) Water deprivation test.

### *Neuroradiology*

- (1) Magnetic Resonance Imaging (MRI)
- (2) Computed Tomography (CT)
- (3) Inferior Petrosal Sinus Sampling

### *Neuroophthalmology*

The fellow will understand the indications for and interpretation of formal visual field examinations

### *Other Tests*

- (1) Growth charts
- (2) Radiologic bone age)

### *Pituitary Adenomas*

#### Prolactinomas

- (1) Manifestations (galactorrhea, amenorrhea, infertility, erectile dysfunction, osteopenia, neurologic mass effects)
- (2) Diagnostic tests (basal PRL, assessment for hypopituitarism when indicated, exclusion of other causes of hyperprolactinemia, MRI)
- (3) Management options (dopamine agonists, surgery, irradiation)
- (4) Special considerations for pregnancy and MEN1

#### GH-secreting adenomas

- (1) Manifestations (acromegaly, gigantism, neurologic mass effects)
- (2) Diagnostic tests (IGF-1, glucose suppression test of GH, assessment for hypopituitarism when indicated, MRI)
- (3) Management options (surgery, somatostatin analogs, GH antagonists, dopamine agonists, irradiation)
- (4) Special considerations - ectopic GHRH syndrome, assessment for co-secretion of PRL, TSH, ACTH, association with MEN1

#### ACTH-secreting adenomas

- (1) Clinical manifestations – Cushing’s syndrome
- (2) Diagnostic tests (urinary free cortisol, ACTH, dexamethasone suppression testing, CRH testing, MRI, Inferior Petrosal Sinus Sampling, assessment for hypopituitarism when indicated)
- (3) Management options (surgery, irradiation, medical [ketoconazole, mitotane, metyrapone, and other agents])
- (4) Special considerations - differential diagnosis from ectopic ACTH and ectopic CRH is critical; Nelson’s syndrome

#### TSH-secreting adenomas

- (1) Clinical manifestations - hyperthyroidism
- (2) Diagnostic tests (Free T4, TSH, alpha-subunit, consideration for TRH testing, MRI, assessment for hypopituitarism when indicated)
- (3) Management options (surgery, irradiation, somatostatin analogs)
- (4) Special consideration - differential diagnosis from thyroid hormone resistance is critical

#### Gonadotropin cell adenomas

- (1) Clinical manifestations - mass effects (neurologic dysfunction, hypopituitarism)
- (2) Diagnostic tests (LH, FSH, glycoprotein subunits, TRH test, assessment for hypopituitarism, MRI, visual field assessment when indicated)
- (3) Management options (surgery, irradiation)

#### Non-secreting tumors

- (1) Clinical manifestations - mass effects (neurologic dysfunction, hypopituitarism)
- (2) Diagnostic tests (assessment for hypopituitarism, MRI, visual field assessment when indicated)
- (3) Management options (surgery, irradiation)

#### *Space-occupying and Infiltrative Disorders of the Pituitary and Hypothalamic Region*

Space occupying lesions (Craniopharyngiomas, Rathke’s cleft cysts, meningiomas, arachnoid cysts, chordomas, dysgerminomas, hamartomas, gangliocytomas, abscess, metastases)

Infiltrative/inflammatory disorders (sarcoidosis, tuberculosis, Langerhans cell histiocytosis, lymphoma, lymphocytic hypophysitis, hemochromatosis)

### *Hypopituitarism*

#### Panhypopituitarism

(1) Clinical manifestations (growth failure, fatigue, decreased strength, body hair loss, fine facial skin wrinkling, infertility, amenorrhea, erectile dysfunction, constipation, cold intolerance, bradycardia, orthostatic hypotension)

(2) Etiology

*Congenital* (gene, receptor, embryopathic)

*Acquired* (tumors, infiltrative, trauma, apoplexy and Sheehan's, irradiation, metabolic [weight loss, anorexia nervosa, malnutrition, hemochromatosis, critical illness], drug (corticosteroids, dopamine))

#### Selective hormone deficiencies

(1) Gonadotropins (Kallmann's syndrome, weight loss, idiopathic)

(2) ACTH (iatrogenic from glucocorticoid suppression, idiopathic very rare)

(3) TSH (rare)

(4) Growth Hormone

*Child onset* (congenital or acquired)

(i) Manifested as growth failure

(ii) Differential diagnosis (hypothalamic vs pituitary, GH insensitivity syndrome, differentiate from non GH deficiency causes of short stature [systemic disease, dyschondroplasias, Turner's syndrome, psychosocial, etc. ])

*Adult onset* is usually associated with other hormone deficiencies in panhypopituitarism. See above.

#### Treatment

(1) Growth hormone administration - dose adjusted by IGF-1 levels Special consideration - IGF-1 treatment for GH insensitivity

(2) Thyroxine -dose adjusted clinically and by Free T4 levels

(3) Glucocorticoids - dose adjusted clinically

(4) Estrogen/Progestin - oral, transdermal

(5) Testosterone - injection, transdermal

(6) GnRH - possible utility with hypogonadotropic hypogonadism of hypothalamic etiology

(7) HCG and HMG/FSH - for fertility in men and women

*Posterior Pituitary Disorders*

Diabetes Insipidus

(1) Clinical Manifestations - polyuria, polydipsia, thirst, dehydration

(2) Differential diagnosis

*Central vs. nephrogenic*

*Congenital (familial) vs. acquired* (see causes of hypopituitarism plus drug induced [cisplatin, carbamazepine, lithium, vincristine, etc.] plus metabolic [hypercalcemia, hypokalemia], sickle cell anemia)

*Psychogenic polydipsia*

*Others causes of polyuria*

(3) Diagnostic testing

*Overnight water deprivation test*

*Measurement of vasopressin*

*Diagnostic trial of desmopressin*

*MRI*

*Assessment of anterior pituitary function*

(4) Treatment

*Desmopressin* - nasal, oral, parenteral

*Chlorpropamide*

*Thiazide diuretics* (esp. nephrogenic)

(5) Special considerations

*Coexistent thirst center damage*

*Pregnancy* - DI may be transient, may be associated with acute fatty liver of pregnancy

Hyponatremia

(1) Clinical manifestations (nausea, vomiting, headache, confusion, seizures, coma, death) - symptoms dependent upon degree and speed of onset

(2) Differential diagnosis

*Hypovolemic* - appropriate vasopressin (ADH) secretion

*Euvolemic* - inappropriate ADH secretion (SIADH) {need to exclude hypothyroidism, hypoadrenalism}

*Hypervolemic* - (intravascular hypovolemia, eg, cirrhosis, CHF)

(3) Diagnostic tests

*Urine and serum osmolality and urine sodium*

*Exclude other causes of hyponatremia (high triglycerides, glucose)*

(4) Treatment

*Mild* - water restriction

*Severe* - saline, hypertonic saline, furosemide, monitor closely to avoid central pontine myelinolysis

*Miscellaneous Hypothalamic Syndromes*

(1) Laurence-Moon-Biedl Bardet

(2) Prader-Willi Syndrome

(3) Sotosí Syndrome (cerebral gigantism)

(4) Pineal region tumors

(5) Empty sella syndrome

### 3. Suggested Reading

#### General

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## **Section 7**

# **Lipid Metabolism Disorders**

### **1. Introduction**

#### **A. Background**

Hyperlipidemia refers to elevations in plasma cholesterol, triglycerides or both. These are usually due to an increase in the concentration of very low density lipoprotein (VLDL) and/or low density lipoprotein (LDL) in plasma and result from disturbances in lipoprotein metabolism. The term dyslipidemia is generally used to describe abnormalities in plasma lipoproteins that include low levels of high density lipoprotein (HDL), and/or abnormalities of lipoprotein composition or distribution. The lipid section requires an understanding of the physiology and pathophysiology of lipoprotein metabolism, the clinical impact of disorders of lipoprotein metabolism, and their treatment. An understanding of the pathobiology of the dyslipidemias requires a fundamental understanding of lipoprotein physiology, and the various sites at which defects can occur in these metabolic pathways. This includes an appreciation of the pathogenesis and diagnosis of both genetic disorders and secondary forms of dyslipidemia that result from the presence of several endocrine and other diseases, lifestyle variations, and/or the use of a variety of drugs. The area of lipids also requires training in the therapy of these disorders. Therapeutic options include both lifestyle (diet and physical activity) and pharmacological therapy.

Many forms of dyslipidemia are associated with an increased risk of cardiovascular disease (CVD), especially coronary artery disease. These include those that have high levels of LDL, and some forms of hypertriglyceridemia, which can be a marker of other abnormalities associated with increased cardiovascular risk. Low levels of HDL in plasma also can be associated with increased CVD risk. Epidemiological studies have demonstrated that the major importance of dyslipidemia is that they are associated with an increased risk of developing accelerated or premature CVD. Clinical trials have shown that CVD symptoms and cardiovascular events can be markedly attenuated by appropriate therapy of these disorders. However, not all forms of dyslipidemia are associated with increased CVD risk. An understanding of the relationship between various forms of dyslipidemia and other cardiovascular risk factors in determining overall cardiovascular risk is important in the prevention and treatment of accelerated or premature CVD.

Marked elevations of plasma triglycerides also can result in pancreatitis and other features of the chylomicronemia syndrome. An understanding of the multiple factors that may contribute to marked hypertriglyceridemia and the appropriate management, which dramatically reduce the risk of pancreatitis in these patients.

#### **B. Goals and objectives**

By the completion of their training, fellows should be competent in the diagnosis of the various common genetic and acquired forms of dyslipidemia. They should have a good understanding of the various laboratory tests that are available to aid in their diagnosis, and should be aware of the strengths and limitations of these diagnostic tests. Fellows also should be competent in the management of these disorders. This includes an understanding of the dietary principles and other life style modifications involved in the treatment of dyslipidemia and in atherosclerosis prevention. The fellow also should be competent to prescribe the major classes of drugs used to treat dyslipidemia, singly and in combination, and be aware of their major side effects.

### **C. Training and Evaluation**

1. Specific Procedures: None

### **2. Educational Expectations (per year of training):**

These skills should be acquired through a variety of means, which may vary between different programs, depending on the size and specific interest of the faculty, and whether or not the program includes a clinic dedicated to the diagnosis and treatment of lipid disorders. By completion of their first year of training, the fellow should be facile with the following areas of practice:

- (1) Familiarity with the latest guidelines for the diagnosis and management of hyperlipidemic patients that are issued by the National Cholesterol Education Program. These are updated periodically
- (2) Evaluation and follow-up of outpatients with various genetic and acquired forms of dyslipidemia
- (3) Selection of the appropriate pharmacological agent in the management of hyperlipidemic/dyslipidemic patients

By completion of the second year of training, the fellow will have further improved their skills to include interdisciplinary practice with cardiologists, nuclear medicine (e.g. stress tests) and thoracic/cardiovascular surgeons.

### **3. Program Content**

#### *Triglyceride*

chylomicrons (risk for pancreatitis)

LPL deficiency

Mix of two common disorders: chylomicronemia syndrome

VLDL (with low HDL)

familial hypertriglyceridemia (FHTG)  
familial combined dyslipidemia (FCHL)  
diabetic dyslipidemia

Type III, remnant removal disease

*Cholesterol*

With increased triglyceride: FHTG, FCHL, diabetes

LDL: defective LDL receptor or ligand

Lp(a)

*Other Endocrine Dyslipidemia*

Hypothyroidism

Cortisol excess

Acromegaly

Estrogen, testosterone

(Other) drugs, alcohol

*Management*

Severe hypertriglyceridemia and pancreatitis

Atherosclerosis risk: LDL level and heterogeneity, Lp(a), low HDL with and without high triglyceride

*Special considerations*

One area that requires special emphasis is the approach to the diagnosis and management of diabetic dyslipidemia and the dyslipidemia that frequently accompanies insulin resistance. The focus in many diabetic clinics is on management of hyperglycemia, which has been convincingly shown to be of benefit to the prevention of microvascular complications of diabetes. However, the major cause of morbidity and mortality in this disease is due to complications of macrovascular disease. An approach to the prevention and treatment of the macrovascular complications of diabetes is often inadequately emphasized in the management of the diabetic patient. With the increasing awareness of the importance of treatment of dyslipidemia and other modifiable risk factors in addition to hyperglycemia, special emphasis on the management of diabetic dyslipidemia, and the dyslipidemia that accompanies the insulin resistant syndrome, should be included as part of the lipid curriculum. This includes knowledge of the specific changes in lipids and lipoproteins that occurs in diabetes and the insulin resistance syndrome, how these changes are affected by the management of hyperglycemia, specific approaches to the management of these lipid abnormalities in diabetes, and a global approach to CVD risk factor management in diabetes and the insulin resistance syndrome.

Another area that requires emphasis is the management of the patient with marked hypertriglyceridemia. Elevation of plasma triglycerides to levels that put a patient at risk of pancreatitis usually results from a combination of a

common genetic form of hypertriglyceridemia with one or more acquired forms of hypertriglyceridemia, and/or the use of lipid raising drugs. Marked hypertriglyceridemia is one of the most common causes of recurrent pancreatitis, but frequently is not diagnosed and treated appropriately. It is important that fellows understand the interaction of genetic and secondary forms of hypertriglyceridemia in the etiology of marked hypertriglyceridemia. At the completion of their fellowship, fellows should be able to identify the major genetic and acquired conditions that are involved in the causation of marked hypertriglyceridemia. They also should be competent in the management of this condition, with a view to the prevention of recurrent pancreatitis.

A uncommon condition that fellows should be competent with the diagnosis and treatment of is remnant removal disease (type III hyperlipoproteinemia), or remnant removal disease. General internists or primary care physicians usually do not correctly diagnose this genetic form of dyslipidemia. The clinical and laboratory features that lead to the diagnosis of this relatively uncommon condition should be part of the lipid curriculum for endocrinology fellows. Fellows also should be aware of the different therapeutic options in this condition.

With the advent of newer and improved lipid-lowering agents, combinations of drugs that affect lipid metabolism are being used more frequently. Some of these combinations are rational, effective, safe and cost effective. Others are associated with potentially dangerous side effects. It is important that fellows understand the relative risks and benefits of combination therapy for the treatment of dyslipidemia. In rare instances with high LDL that is resistant to therapy, apheresis may be indicated.

There are a number of rare disorders of lipid and lipoprotein metabolism, which have provided considerable insight into our understanding of lipid and lipoprotein metabolism. These include lecithin cholesteryl acyl transferase deficiency, hepatic lipase deficiency, cholesterol ester transport protein deficiency, apolipoprotein CII deficiency, abetalipoproteinemia and Tangier disease. For example, the recent identification of the molecular defect in Tangier disease has provided important insight into the understanding of reverse cholesterol transport. However, most practicing endocrinologists and even lipid specialists are unlikely to see any of these conditions in their lifetime. Therefore, a detailed working knowledge of these conditions should not be a requirement for the lipid curriculum. A less rare condition is hypobetalipoproteinemia. Fellows should be familiar with this condition, its diagnosis and implications.

#### **4. Suggested Reading**

##### ***Textbooks***

Chapters 56-64. In: Scriver et al, eds. *The Metabolic Basis of Inherited Disease*. 7th ed. McGraw-Hill; 1995.

***Review Articles and Position Statements***

AACE Medical Guidelines for Clinical Practice: Diagnosis and Treatment of Dyslipidemia and Prevention of Atherogenesis. *Endocrine Practice*. 2000; 6:162-213.

Ridker PM, Hennekens CH, Buring JE, Rifai N 2000 C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women.



# **Section 8**

## **Nutrition and Obesity**

### **1. Introduction**

#### **A. Background**

Endocrinology is concerned with the actions of hormones and the organs and tissues in which the hormones are formed. A number of hormones are particularly involved with fuel, vitamin, and mineral metabolism. They are profoundly involved in substrate flux and the utilization of food for energy production and storage. Their importance in nutrition is therefore great. A practicing endocrinologist must have a basic knowledge of nutrition to understand the endocrine interactions that occur. At a minimum, there must be in an endocrinology subspecialty training curriculum a core knowledge in nutrition (including nutrition support), and an understanding of eating disorders (including obesity, anorexia nervosa and bulimia).

#### **B. Goals and Objectives**

The goals for the training of Endocrine Fellows in Nutrition are to have a working knowledge of the above conditions, both basic pathophysiology and treatment modalities.

#### **C. Training and Evaluation**

##### 1. Specific Procedures:

- (1) Metabolic Cart - Energy Expenditure
- (2) DEXA for Body Composition
- (3) Bioelectrical Impedance Analysis
- (4) Total Parenteral Nutrition Formulation/Management

##### 2. Educational Expectations (per year of training):

By completion of their first year of training, the fellow should be facile with the following areas of practice:

- (1) Familiarity with the latest guidelines for the diagnosis and management of obese patients.
- (2) Medical and surgical approaches to the management of obesity
- (3) Sequelae of diet, malabsorption and weight loss
- (4) Nutritional management of the hospitalized patient
- (5) Manifestations of nutritional deficiencies

By completion of the second year of training, the fellow will have further improved their skills to include interdisciplinary practice with bariatric surgeons, gastroenterologists and physical therapists.

## **2. Program Content**

### i. Fuel Metabolism

Role of hormones and peptides in the regulation of fuel metabolism

*Central Nervous System Regulation*

*Micronutrient Requirements*

Vitamins: A, D, E, K folate, ascorbate, thiamine, riboflavin, niacin, B12, biotin, pantothenic acid, pyridoxine

Antioxidants

Inositol, choline, carnitine

Minerals: Ca, P, Mg, Mn, Fe, Zn, Cu, Se, iodine

*Vitamins and Minerals*

- (1) Sources in the diet: bioavailability and absorption
- (2) Parenteral preparations
- (3) Metabolism
- (4) Antagonists
- (5) Drug/nutrient interactions
- (6) Deficiency syndromes
- (7) Excess syndrome
- (8) DRIs (normal requirements)
- (9) Dietary supplements

*Macronutrient Utilization:* carbohydrates, proteins and fats

*Modulation of Disease Processes* by nutrients in food and by dietary supplements (carcinogenesis, diabetes mellitus, cardiovascular disease, pregnancy, metabolic bone disease)

*Eating Disorders*

### ii. Obesity

*Who Are the Obese?*

- (1) body composition
- (2) prevalence

### *What Causes Overweight?*

- (1) gene/environment interactions
- (2) energy balance
- (3) neuro-endocrine causes: rare hypothalamic obesity syndromes, pituitary, adrenal, thyroid, PCO, insulin resistance, leptin deficiency
- (4) drug induced
- (5) primary psychiatric

### *Health Hazards*

- (1) insulin resistance leading to the metabolic syndrome
- (2) mechanical complications

### *Clinical Classification and Natural History*

#### *Clinical Evaluation*

#### *Treatment*

- (1) behavior modification
- (2) diet treatments including:
  - high protein, high fat, low carbohydrates,
  - protein-supplemented modified fast, liquid diets
  - low fat, high carbohydrate diets
  - traditional diet (ADA, AHA)
  - non-traditional diets
- (3) physical activity
- (4) pharmacological treatment
- (5) surgery
- (6) setting up a weight management practice
- (7) complications of treatment (eg, gallstones, electrolyte abnormalities, arrhythmias, vitamin deficiency)

### *Obesity Clinical Trials – evaluation and interpretation*

### iii. Anorexia/Bulimia

#### *The Clinical Syndromes*

- (1) anorexia: diagnosis, full blown syndrome, pre-"syndrome"
- (2) bulimia: purging, exercise, laxative, exercise as purging

#### *Neuro-Endocrine Metabolic Abnormalities*

- (1) gonadotropin abnormalities

- (2) hypo metabolic manifestations
- (3) HPA axis interrelations
- (4) other pituitary abnormalities: GH, prolactin
- (5) estrogen abnormalities

*Clinical Sequelae*

- (1) osteoporosis
- (2) amenorrhea
- (3) dentition
- (4) CVD

*Psychological Characteristics*

*Treatment*

iv. Nutrition Support

*Protein Calories Malnutrition (Marasmus)*

head and neck cancer, malabsorption, CNS disease, anorexia and bulimia, GI obstruction, iatrogenic, drug induced, senescence

*Protein Malnutrition (Adult Kwashiorkor-Like Syndrome)*

critical illness acute vs sustained/chronic, trauma, burn, protein-losing enteropathy, HIV, cancer, nephrotic syndrome

*Nutritional Assessment*

history, physical exams, including anthropometrics, laboratory assessment, body composition: bia dexta, metabolic cart

*Treatment*

- (1) enteral: oral and tube feeding
- (2) parenteral
- (3) pharmacological (anabolics)
- (4) combined modalities
- (5) monitoring treatment

*Interpretation of Clinical Trials in Nutrition Support*

v. Emergencies

*Extreme Obesity*

- (1) decompensated respiratory failure
- (2) decompensated cardiovascular failure
- (3) cellulitis and other skin disorders
- (4) complications of treatment (acute cholecystitis, arrhythmias)

*Anorexia/Bulimia*

- (1) cardiac arrhythmia
- (2) sepsis
- (3) hypotension
- (4) hypoglycemia
- (5) psychosis
- (6) electrolyte abnormalities

*Parenteral Nutrition*

- (1) catheter related sepsis
- (2) thrombus or emboli
- (3) bleeding
- (4) hypo and hyperglycemia

*Re-feeding Syndrome*

- (1) volume overload and heart failure
- (2) electrolyte abnormalities and arrhythmia

### **3. Suggested Reading**

*Texts*

*Biochemical and Physiological Aspects of Human Nutrition*. Martha Stipanuk, editor. W.B. Saunders Company.  
A comprehensive textbook focusing on biochemistry and metabolism. It is appropriate for the human nutrition curriculum in an endocrine training program setting.

George Bray. *Contemporary Diagnosis and Management of Obesity*. Newtown, Pa: Handbooks in Health Care Co.  
An excellent introduction to obesity.

Jeffrey S. Flier, Daniel W. Foster. Eating Disorders: Obesity, Anorexia Nervosa, and Bulimia Nervosa. In: *Williams Textbook of Endocrinology*.

Disorders of Fuel Metabolism. In: Kenneth L. Becker, ed. *Principles and Practice of Endocrinology*. 2nd ed. Philadelphia, Pa: J.B. Lippincott Company.

*Physicians Desk Reference*: Dietary Supplements.

*Aspen Guidelines For Enteral and Parenteral Nutrition*

### ***C-D ROMS***

Nutrition in Medicine (NIM) Series. Steven Zeisel, M.D., Ph.D., editor. Website: [www.med.unc.edu/nutr/nim](http://www.med.unc.edu/nutr/nim)  
Commercial: [www.medeorinteractive.com](http://www.medeorinteractive.com)

This is an initiative to incorporate innovative, effective, and transportable nutrition education into the standard pre-clinical medical school curriculum. These programs incorporate the biochemical, clinical and epidemiological elements of nutrition science, and include preventive and therapeutic perspectives in nutrition. The NIM series can be used either as a supplement to a regular textbook or the series can serve as a complete reference source, it is indexed. Each CD-ROM in the series provides approximately 3-4 hours student contact time (if grades are assigned we find students take longer than this to complete a CD, but remember that the CD provides the lecture, clinical modeling, review from the reading and the exam). A web-based examination system (Nutraquiz) is available at no charge. This is an excellent nutrition introduction for endocrine residents.

### ***Additional Reading***

Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease*. 9<sup>th</sup> edition, Williams and Wilkins.

Carolyn D. Berdanier. *Advanced Nutrition. Micronutrients*. CRC Press.

*For an introduction to alternative medicine products that an endocrinologist will be faced with in practice:*

Jeffrey I. Mechanick. *Report of the AACE Nutrition Guidelines Task Force: The Use of Nutraceuticals in Clinical Medicine.*

Vitamin E supplementation and cardiovascular events in high risk patients. *N Engl J Med* 342:154-159, 2000.

Shultz. *Rational Phytotherapy*

US Food and Drug Administration website

Dr. Zeisel, *SCIENCE*, 1998 for understanding safety

US Office of Dietary Supplements website

Tufts website for dietary supplements



## **Section 9**

# **Thyroid Disorders**

### **1. Introduction**

#### **A. Background**

Thyroid specific disorders include both anatomical defects of the thyroid gland as well as disorders due to the effects of thyroid hormones on extrathyroidal tissues. Thyroid disorders are among the most common diseases encountered by the endocrine consultant; they occur in the population with a prevalence greater than 10% in some studies. Furthermore, the incidence of thyroid disorders is rising, in part because our diagnostic tools are much more sensitive and sophisticated. Thyroid disorders account for a significant amount of morbidity in our society and the fellow should be competent in their diagnoses and treatment.

#### **B. Goals and Objectives**

It is our intent that the fellow develop the following:

1. The training program will provide opportunities for the fellow to develop clinical competence in the area of thyroid disease. Clinical experience must include opportunities to diagnose and manage (1) adolescent and adult inpatients and outpatients of both sexes with (2) a variety of thyroid diseases of (3) varying acuity. The program also must include opportunities to function in the role of an endocrinology consultant for patients and other physicians and services in both inpatient and outpatient settings.
2. In relation to the diseases listed below, there should be formal instruction in: (1) thyroid physiology and pathophysiology in systemic diseases and principals of hormone action, (2) biochemistry and physiology, including cell and molecular biology and immunology, as they relate to thyroid disease, and (3) signal transduction pathways and biology of thyroid hormone receptors and their interaction with other hormone receptor pathways. The appropriate utilization and interpretation of clinical laboratory, radionuclide, and radiologic studies for the diagnosis and treatment of thyroid diseases should be stressed.

3. Fellows will have formal instruction, clinical experience, or opportunities to acquire expertise in the evaluation and management of the disorders listed below as well as aspects of those disorders that relate to: (1) psychiatric disease, (2) aging, with particular emphasis on the care of geriatric patients and thyroid related changes associated with aging, and (3) adaptations and maladaptations to systemic diseases with respect to effects on the hypothalamic-pituitary-thyroid axis.

### **C. Training and Evaluation**

#### **1. Specific Procedures:**

The training program will provide opportunities for the fellow to develop clinical competence in thyroidology. Specific procedures needed include:

(1) The fellow must perform a sufficient number of fine needle aspiration biopsies of a thyroid nodule to be deemed competent. The fellow is expected to review the cytology with a pathologist who has expertise in interpretation of thyroid cytopathology.

(2) The fellow is expected to review imaging studies with individuals who have expertise in interpreting these images. Such studies include thyroid ultrasound and nuclear imaging studies.

Experience in the two following areas is encouraged.

(1) The opportunity to become proficient in the performance of thyroid ultrasound, including ultrasound-guided fine needle aspiration biopsy of the thyroid and lymph node tissue. This opportunity may occur at the fellow's training site or through a sponsored course.

(2) The opportunity to fulfill the Nuclear Regulatory Commission and state requirements for administration of radio-iodine for hyperthyroidism and thyroid cancer. This opportunity may occur at the fellow's training site or through a sponsored course.

### **D. Educational Expectations (per year of training)**

It is expected that upon completion of the first year of training, fellows will be well versed in the ability to investigate all forms of thyroid disease in men and women. In addition, they will be able to properly interpret radiographic imaging studies and nuclear scans of the thyroid gland. Moreover, fellows will be facile with the

performance and interpretation of hormone assays. During the initial year of training, the fellow will gain significant experience in needle biopsy of thyroid nodules. By the completion of the second year of training, the fellow will be able to independently perform a fine needle aspiration of a thyroid nodule.

## **2. Program Content**

In relation to the diseases listed below, fellows should have experience in the performance of endocrine clinical laboratory and radionuclide studies and basic laboratory techniques, including quality control, quality assurance, and proficiency standards. Provision must be made for the fellow to acquire experience and skill in the following areas:

- (1) the interpretation of laboratory tests; immunoassays; and radionuclide, ultrasound, radiologic, and other imaging studies for the diagnosis and treatment of thyroid diseases;
- (2) the effects of a variety of non-endocrine disorders on laboratory and imaging studies and performance and interpretation of stimulation and suppression tests as related to thyroid disease; and
- (3) thyroid related emergencies, including:
  - (a) severe hypo- and hyperthyroidism (thyroid storm and myxedema coma);
  - (b) severe thyroid dysfunction during and after pregnancy;
  - (c) tracheal compression from a goiter or from the treatment of thyroid disease;
  - (d) agranulocytosis secondary to anti-thyroid drug therapy.

1. The fellow will have a comprehensive understanding of all causes of thyrotoxicosis and will be familiar with Graves' Disease, thyroiditis, and toxic nodular goiters.
2. The fellow will have a comprehensive understanding of all causes of hypothyroidism including the conditions of auto-immune and post-ablative hypothyroidism .
3. The fellow will have a comprehensive understanding of thyroid cancer including:
  - Differentiated epithelial thyroid cancer
  - Medullary thyroid cancer
  - Thyroidal lymphoma
4. The fellow will have a comprehensive understanding of the causes of nodules and goiters including the single nodule, multinodular goiter, and a diffuse goiter.

5. The fellow will be familiar with other causes of thyroid dysfunction. These include pregnancy related thyroid dysfunction, polyglandular autoimmune syndrome, and thyroid dysfunction in non-thyroidal disease.

### **3. Suggested Reading**

#### ***Review Articles:***

Cooper DS. 2003 Hyperthyroidism. *Lancet*. 362(9382):459-68

#### ***Journal Articles:***

Parle JV, et al 2001 Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet* 358:861-865.

Sachmechi I, Miller E, Varatharajah R, et al 2000 thyroid carcinoma in single cold nodules and in cold nodules of multinodular goiters. *Endocr Pract* 6:5-7.

Hak, AE, Pols HAP, Visser TJ, et al 2000 Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam study. *Ann Intern Med* 132:270-278.

Canaris GJ, Manowitz NR, Mayor G, Ridgway EC 2000 The Colorado thyroid disease prevalence study. *Arch Intern Med* 160:526-534.

Machens A, et al 2003 Early malignant progression of hereditary medullary thyroid cancer. *N Engl J Med* 349:1517

Pacini F, et al. 2001 Prediction of disease status by recombinant human TSH-stimulated serum Tg in the post-surgical follow-up of differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 86:5686-5690.

Alexander EK, et al 2002 Assessment of nondiagnostic ultrasound-guided fine needle aspirations of thyroid nodules. *J Clin Endocrinol Metab* 87:4924-4927.

Wiersinga WM, Bartalena L. 2002 Epidemiology and prevention of Graves' ophthalmopathy. *Thyroid*. 12(10):855-60

Biondi B. Palmieri EA. Lombardi G. Fazio S. 2002 Effects of subclinical thyroid dysfunction on the heart. *Annals of Internal Medicine*. 137(11):904-14

Sawin CT. 2002 Subclinical hyperthyroidism and atrial fibrillation. *Thyroid*. 12(6):501-3

Osman F. Gammage MD. Franklyn JA. 2002 Hyperthyroidism and cardiovascular morbidity and mortality. *Thyroid*. 12(6):483-7

Papini, E, et al. 2000 Risk of malignancy in nonpalpable thyroid nodules : predictive value of ultrasound and color-doppler features. *J Clin Endocrinol Metab* 87:1941-1946.

Langley RW. Burch HB. 2003 Perioperative management of the thyrotoxic patient. *Endocrinology & Metabolism Clinics of North America*. 32(2):519-34

Helfand M. U.S. Preventive Services Task Force. 2004 Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Annals of Internal Medicine*. 140(2):128-41

Fazio S. Palmieri EA. Lombardi G. Biondi B. 2004 Effects of thyroid hormone on the cardiovascular system. *Recent Progress in Hormone Research*. 59:31-50

# Thyroid Disorders

## Method of Education

	Formal Instruction	Direct Clinical Experiences		Clinical Case Discussions		Self-directed learning
		In-patient	Out-patient	Attd. Rds	Conferences	
<b>1. Hyperthyroidism</b>						
a) Grave's Disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Thyroiditis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Toxic nodule	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Toxic multinodular goiter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Struma Ovaril	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
f) Thyrotoxicosis factitia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
g) Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>2. Hypothyroidism</b>						
a) Thyroiditis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Post-ablative	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>3. Thyroid Cancer</b>						
a) Pappillary thyroid cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Follicular thyroid cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Medullary thyroid cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Anaplastic thyroid cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
e) Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>4. Nodules</b>						
a) Simple nodule	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Multinodular goiter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Diffuse goiter	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
d) Other	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>5. Other</b>						
a) Polyglandular autoimmune syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
b) Pregnancy-related thyroid disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
c) Non-thyroidal illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>6. Disease Specific Studies/ Procedures</b>						

- a) Fine needle aspiration
- b) Thyroid ultrasound
- c) Thyroid scan-iodine
- d) Thyroid scan-Tcm