CONTENT OUTLINE

Pediatric Endocrinology

Subspecialty In-training, Certification, and Maintenance of Certification Examinations
INTRODUCTION

This document was prepared by the American Board of Pediatrics Subboard of Pediatric Endocrinology for the purpose of developing in-training, certification, and maintenance of certification examinations. The outline defines the body of knowledge from which the Subboard samples to prepare its examinations. The content specification statements located under each category of the outline are used by item writers to develop questions for the examinations; they broadly address the specific elements of knowledge within each section of the outline.
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I. Carbohydrate Metabolism

A. Integrated hormone effects on metabolism

1. Physiology

Know the sources of glucose from digestion and absorption of dietary carbohydrates and endogenous release of glucose from the liver

Know the enzyme systems (glycogenolysis, glycogen synthesis, glycolysis, gluconeogenesis, tricarboxylic acid cycle, and pentose phosphate shunt) involved in the storage, oxidation, and production of glucose

Understand the processes and regulation of nutrient and substrate metabolism in the fasted and fed states with regard to glycogen, glucose, fatty acids, ketone bodies, amino acid, and protein metabolism

Know effects of insulin on protein synthesis and proteolysis, lipolysis and ketogenesis, and glucose production and utilization

Understand the mechanisms of action of cortisol, growth hormone (GH), epinephrine, and somatostatin on carbohydrate, fat, and protein metabolism

Be familiar with the endocrine and metabolic responses to fasting

Know the effects of lipotoxicity and glucotoxicity on beta cell function and insulin resistance

2. Homeostasis

Know the criteria for a normal blood glucose concentration in children, and adolescents, and the definitions of biochemical hyperglycemia and hypoglycemia at these ages

Know the rate of glucose production (expressed as glucose infusion rate) in normal neonates, children, and adolescents, and the factors which regulate it

Know the duration of time glycogen stores and gluconeogenesis can maintain normal blood glucose concentrations in normal neonates, children and adolescents

B. Insulin
1. Physiology

   a. Ontogeny/embryology

      Know the genes that are responsible for pancreatic development

   b. Synthesis/processing/storage

      Know biochemistry of insulin biosynthesis and post-translational processing

      Know the structural homology of insulin-like growth factor (and other growth factors) with insulin

   c. Secretion

      Understand physiologic regulation of insulin secretion including the effects of blood glucose, amino acids, glucagon, adrenergic mechanisms, gastric inhibitory peptide (GIP), and somatostatin

      Know the importance of the sulfonylurea receptor, chromium picolinate, the potassium channel, and the role of calcium flux in insulin secretion

      Understand the role of glucokinase in insulin secretion

      Know the interactions of medications and other exogenous substances that regulate insulin secretion with beta cell receptors and channels

   d. Receptor/action

      (1). Tissue/organ specific

      Know the plasma membrane location, structure, and function of the insulin receptor

      Know the role or lack thereof of insulin on glucose transporters in different tissues

      Know that different glucose transporters are expressed in different tissues

      Know the relationship of the structures of IGF-I and insulin receptors and the related membrane molecules

      Understand insulin receptor signaling mechanisms

2. Pathology

   a. Insulin deficiency with hyperglycemia
(1). Type 1 diabetes

(a). Pathophysiology (classification/etiology)

Know the association of HLA and DR loci in the etiology of type 1 diabetes

Recognize histologic appearance of islets early and late in the course of type 1 diabetes with preferential destruction of beta cells and late persistence of alpha and delta cells

Know the current concepts of the role of autoimmunity including cell-mediated immunity and cytoplasmic and surface autoantibodies and insulin autoantibodies in the pathogenesis and prediction of type 1 diabetes

Know the rationale for the use of immunomodulating agents for the treatment of early type 1 diabetes

Know the prevalence of glutamic acid decarboxylase, islet cell, and insulin antibodies in recent-onset type 1 diabetes and in individuals of various ages

(b). Epidemiology and clinical manifestations

Know the different prevalence rates of type 1 diabetes in people of different ethnicities

Know the risk of type 1 diabetes development in identical twins, other siblings, offspring, and parents of patients who have type 1 diabetes

Understand the clinical differentiation of ketoacidosis from other causes of altered states of consciousness, such as hypoglycemia and nonketotic hyperosmolar coma, in diabetes mellitus

Understand the pathogenesis of ketoacidosis and disturbances in body fluid, electrolytes, substrates, and acid-base balance (pH, O2 dissociation), and the significance of relevant laboratory findings in type 1 diabetes

Recognize the mechanism, presentation, and natural history of neonatal diabetes

(c). Diagnosis

Recognize the stages of clinical development of type 1 diabetes with progressive carbohydrate intolerance, and the pathophysiology of the polyuria, polydipsia, weight loss, and fatigue

(d). Treatment of diabetic ketoacidosis
Know the methods, rationale, consequences, and principles of administration of insulin (bolus and iv infusion) in the treatment of diabetic ketoacidosis

Know the rationale and strategy for monitoring blood glucose, serum electrolytes, acid-base balance and ketone concentrations in the management of patients with diabetic ketoacidosis

Know when and how to change to subcutaneous insulin and oral intake in patients recovering from diabetic ketoacidosis

Know the complications (cerebral edema, hyperkalemia, hypokalemia, renal failure, hyperchloremia, hypoglycemia, persistent hyperglycemia, thrombosis, and/or ketonemia), pathophysiology, clinical manifestations and management in the treatment of diabetic ketoacidosis

Recognize that repeated episodes of ketoacidosis in a child or adolescent are most likely a result of failure to administer insulin regularly rather than dietary indiscretions or infectious illness

Know the methods, rationale, consequences, and principles of administration of fluid and electrolytes in the treatment of diabetic ketoacidosis

Know the methods, rationale, consequences, and principles of administration of glucose in the treatment of diabetic ketoacidosis

Know the risk factors for cerebral edema in diabetic ketoacidosis

(e). Daily management

Understand the effects of the insulin counter-regulatory hormones glucagon, epinephrine, cortisol, and GH in type 1 diabetes

Know the formulations and action profiles of rapid, short, intermediate, and long-acting insulins

Recognize blood glucose values requiring insulin dose adjustments in patients with diabetes using home glucose monitoring

Understand the effects of meals, exercise, illness, trauma, and surgery on blood glucose concentration and insulin requirements of patients who have diabetes

Know the use and significance of glycosylated hemoglobin and factors other than blood glucose concentration (eg, hemolytic anemia) that affect or alter its value in the management of patients with diabetes

Know the carbohydrate content of common foods
Know how to calculate an insulin-to-carbohydrate ratio for determination of insulin dosing for patients with diabetes

Be able to identify patients with type 1 diabetes who will succeed with insulin infusion pump therapy and know the steps required to prepare a patient for insulin pump therapy

Know how to calculate an initial basal and bolus insulin dose for a patient beginning insulin pump therapy

Know the pros and cons of intensification of diabetes management with both multiple daily insulin doses and with continuous subcutaneous insulin infusion therapy

Know how to make insulin dose adjustments in patients with type 1 diabetes using home glucose monitoring

Understand the rationale and appropriate use of continuous glucose monitoring devices in children with type 1 diabetes, including clinical indications and limits

Know how to convert insulin dose from intermediate/rapid-acting insulin regimens to basal-bolus regimens using long-acting insulin analogues

Know the limitations of the available methods of home blood glucose monitoring

Know the role for measurement of fructosamine in the management of diabetes mellitus

Know what conditions require temporary adjustments in basal and bolus insulin doses

Understand the effects of puberty on blood glucose concentrations and insulin requirements in patients who have type 1 diabetes

(f). Prognosis and complications

Know the clinical situations leading to complications of insulin treatment, including lipohypertrophy local reactions, and insulin edema in patients who have diabetes

Know the relationship of A1c to the microvascular complications of diabetes

Know the tests for early detection of the microvascular complications (retinopathy, nephropathy, peripheral neuropathy, and macrovascular disease) in patients with diabetes
Know the effects of poor control of type 1 diabetes on pubertal growth and development

Understand the disturbed physiology of the polyol pathway and its consequences in type 1 diabetes
Know that glycosylation of hemoglobin and other proteins is non-enzymatic and irreversible

Recognize the association of other autoimmune endocrine disease (eg, thyroid, celiac, adrenal, gonadal) with type 1 diabetes

Know the mechanisms for insulin resistance in children with diabetes

Know the signs, symptoms, and management of mild, moderate, and severe hypoglycemia in children with type 1 diabetes

Understand the risks of hypoglycemia while driving a motor vehicle and know the strategies for preventing hypoglycemia during driving

Know the strategies for preventing hypoglycemia during driving

Know the effect of tobacco use on micro and macro vascular complications of diabetes

Know the signs and symptoms of celiac disease in a child with type 1 diabetes

Know the tests that may be useful for diagnosis of celiac disease

Understand the treatment of celiac disease and when treatment should be recommended

Know the effects of blood pressure on later development of complications

Know target lipid values for children with diabetes

Recognize that recurrent hypoglycemia in type 1 diabetes may be associated with adrenal insufficiency

Know the effect of alcohol on blood glucose concentration in type 1 diabetes

Know the risk for impotence in a patient with poorly controlled diabetes mellitus

(g). Gestational diabetes

Understand the clinical significance of gestational diabetes for the fetus and the child
Understand the risk for both type 1 and type 2 diabetes in the mother and child following gestational diabetes

Understand the different laboratory findings that indicate the risk for type 1 diabetes and type 2 diabetes in the mother, following gestational diabetes

Know the importance of counseling patients about driving safety (medic alert, checking blood glucose, glucose availability)

(h). Pregnancy in a woman with diabetes

Know the effects of pregnancy on carbohydrate metabolism in pregnant women with and without diabetes

Know the importance of careful glucose control in a pregnant woman with diabetes

Know the metabolic effects of maternal hyperglycemia on the offspring in the neonatal period

Understand the importance of preconception counseling for a woman with type 1 diabetes, and know at what age this counseling should begin

Know the types of congenital malformations that can occur as a result of poorly controlled diabetes mellitus during each of the trimesters of pregnancy

Know the effects of poorly controlled diabetes mellitus on conception, fetal anomalies, fetal loss, and birth weight

(i). Prevention

Know the strategies to attempt to interrupt the destruction of the pancreatic beta cell in individuals who are statistically at risk to develop type 1 diabetes

(2). Type 2 diabetes

Know the roles of insulin resistance, obesity, and insulin deficiency in the pathophysiology of type 2 diabetes

Recognize the clinical and laboratory findings in type 2 diabetes and differentiate from other types of diabetes

Recognize the various presentations of type 2 diabetes

Recognize that the co-morbid conditions associated with type 2 diabetes are the same as those associated with metabolic syndrome
(eg, hypertension, hyperlipidemia, polycystic ovary syndrome, non-alcoholic fatty liver disease), and their treatment

Understand the treatment of type 2 diabetes, including the mechanisms of action of the medications used

Understand the inheritance of type 2 diabetes and its implications for testing and counseling of family members

Recognize the public health implications of type 2 diabetes in youth and possible public health interventions aimed at the prevention of type 2 diabetes

Know the effect of adiponectin, leptin, IL-6, and TNF-alpha on insulin sensitivity and markers of insulin resistance

Know the cellular origin of adiponectin, ghrelin, amylin, glucagon-like peptide-1 (GLP-1) and leptin

Know the effects of exogenous obesity on adiponectin and leptin levels

Know the association between insulin resistance and amylin levels

Understand the actions of glucagon-like peptide-1 (GLP-1) on the GI system, pancreas, and brain

Know when to monitor for lipids, blood pressure, and urine microalbumin in patients with type 2 diabetes at diagnosis

Know the implications of large, pivotal diabetes trials

Understand that a reduced calorie diet and exercise are more effective than metformin in slowing the progression of type 2 diabetes

Know screening criteria for type 2 diabetes in youth

Know the treatment of co-morbid conditions associated with type 2 diabetes and metabolic syndrome

(3). Other forms of diabetes

Recognize carbohydrate intolerance in children with pancreatic disorders, eg chronic pancreatitis or cystic fibrosis

Recognize drug-induced (glucocorticoids, L-asparaginase, somatostatin, diazoxide, etc) hyperglycemia and approaches to management

Recognize factors which may result in hyperglycemia in neonates
and children

Know the management of transient and persistent diabetes of the newborn

Recognize the clinical and biochemical findings, various etiologies, and management of MODY

Know other conditions associated with type 2 diabetes (e.g., Turner syndrome, Prader-Willi syndrome)

Know the management of CF-related diabetes mellitus

Know how to differentiate MODY from other forms of diabetes that occur in young patients

Know the association of diabetes mellitus with mitochondrial defects including clinical features and inheritance

b. States of insulin resistance other than type 2 diabetes

Know the conditions, diagnosis, and management associated with diminished insulin receptor number or insulin receptor defect that can result in insulin resistance with or without hyperglycemia

Know the effects of somatostatinoma, glucagonoma, pheochromocytoma, Cushing disease, and GH producing tumors on carbohydrate and substrate metabolism

c. Hypoglycemia - general

Recognize the frequent lack of correlation of symptoms of hypoglycemia with blood glucose concentrations

Know the different symptomatology of hypoglycemia in newborn infants (tremors, cyanosis, lethargy, poor feeding, convulsions, or no symptoms)

Know the neuroglycopenic manifestations of hypoglycemia in older children

Know the requirements for history and physical examination in the diagnosis of hypoglycemia

Recognize the need for determination of plasma insulin and insulin counter-regulatory hormone concentrations, plasma free fatty acid, ketone body and carnitine concentrations, urine organic acid, serum cortisol, and plasma lactate and alanine at the time of hypoglycemia

Understand the administration of glucagon and significance of blood glucose measurements after its injection in the diagnosis of
d. **Hypoglycemia without hyperinsulinism**

(1). **Physiology**

Know the normal physiology of fasting (absorption, gluconeogenesis, glycogenolysis, lipolysis, and ketogenesis)

(2). **Clinical implications**

Know the history, physical examination, and laboratory findings for glucose-6-phosphate deficiency

Know the enzyme defects in the syndromes of glucose underproduction and means of testing for them

Know the diagnosis and treatment of defects in glycogen metabolism (Debrancher enzyme, phosphorylase activation defects, glycogen synthetase)

Know the clinical findings, diagnosis, and treatment of genetic conditions that result in a functional defect in gluconeogenesis

Know the history, physical examination, and laboratory testing for hormone deficiencies (glucagon, cortisol, GH) that can present with hypoglycemia

Know the history, physical examination, and laboratory testing for defects in fatty acid metabolism (defects in fatty acid transport, defects in carnitine metabolism, defects in fatty acid oxidation, defects in amino acid catabolism)

Know the management and prognosis of children with defects in glycogen metabolism that are relevant to endocrinology

Know the mechanism of hypoglycemia induced by alcohol ingestion

Know the time to hypoglycemia after eating in disorders of absorption, gluconeogenesis, glycogenolysis, lipolysis, and ketogenesis

Know age of presentation of hypoglycemia in disorders of absorption, gluconeogenesis, glycogenolysis, lipolysis, and ketogenesis

Know the clinical findings in disorders of gluconeogenesis

Know the laboratory findings in disorders of gluconeogenesis, including the finding of increased lactate concentrations
e. Hypoglycemia secondary to hyperinsulinism

(1). Clinical

(a). Transient hyperinsulinemia

Recognize that hyperinsulinemia and beta cell hyperplasia are associated with infants of diabetic mothers, erythroblastosis, and Beckwith-Wiedemann syndrome

Know the treatment of hypoglycemia due to hyperinsulinemia in infants of diabetic mothers, and infants with erythroblastosis and Beckwith-Wiedemann syndrome

Know the prognosis of hypoglycemia due to hyperinsulinemia in infants of diabetic mothers, or in infants with erythroblastosis and Beckwith-Wiedemann syndrome

Know that hypoglycemia with hyperinsulinism can be associated with stress and sepsis in newborn infants

(b). Sustained hyperinsulinemia

Know that hypoglycemia secondary to hyperinsulinism is due to overutilization and underproduction of glucose

Recognize decreased plasma concentrations of ketones, free fatty acids, and IGFBP-1 as a feature of hyperinsulinemia

Understand the administration of glucagon and significance of blood glucose measurements after its injection in the diagnosis of hypoglycemia

Recognize the various names previously used to describe congenital hyperinsulinism (e.g., nesidioblastosis, islet cell hyperplasia, islet cell dysplasia, islet cell dysmaturity) represented in the pathological findings of pancreatic beta cells in pancreatic ductal tissue

Recognize that certain amino acids aggravate hyperinsulinemia

Recognize the clinical settings in which hypoglycemia may be due to islet cell tumors

Know how to diagnose islet cell tumors

Know how to treat islet cell tumors

Recognize the clinical findings in hyperinsulinemia, including the requirements for increased glucose infusion

Know the most appropriate initial steps in identifying the etiology
Recognize hyperinsulinemia as a likely cause of intractable hypoglycemia in a neonate

Know the acute management of persistent hypoglycemia due to hyperinsulinism

Understand the chronic management of hyperinsulinism in young infants and children including mechanisms of action of medications used

Know the association of islet cell tumors with other endocrine tumors

Know the effects of hyperinsulinemia on hepatic glucose production

Know the genetic etiology and inheritance of congenital hyperinsulinism

Know that glutamate dehydrogenase deficiency produces hyperinsulinemic hypoglycemia, and understand the mechanism by which hypoglycemia and hyperammonemia are produced

Know the genetic syndromes associated with islet cell tumors, including MEN I

Know the pathophysiology of the genetic mutations that result in congenital hyperinsulinism

Understand the difference between focal and diffuse causes of congenital hyperinsulinism and know the diagnostic tests used to differentiate between them

Recognize that hypoglycemia secondary to hyperinsulinism may be due to exogenous insulin and sulfonylureas

C. Glucagon

1. Physiology

   a. Secretion

      Know the biochemistry of glucagon biosynthesis and the factors that regulate glucagon release

   b. Receptor/action

      (1). Tissue/organ specific (receptor/post receptor)

      Understand mechanisms of action of glucagon on glycogenolysis and the role of glucagon in the regulation of the blood glucose
(2). Integrated hormone effects on metabolism

2. Pathology

a. Hormone deficiencies
   (1). Pathophysiology (classification/etiology)
   (2). Clinical implications

b. Hormone excess
   (1). Pathophysiology (classification/etiology)
   (2). Clinical implications

c. Other
   (1). Pathophysiology (classification/etiology)
   (2). Clinical implications

Understand the use of glucagon as a diagnostic and therapeutic tool in hypoglycemia

II. Bone and Mineral Metabolism

A. Minerals: physiology and homeostasis

1. Calcium

   a. Total versus ionized calcium

      Know that some extracellular calcium is bound to serum proteins, primarily albumin, while some extracellular calcium is ionized or free

      Know that ionized calcium is biologically active

      Know that in hypoalbuminemia, the total serum calcium concentration is often low despite a normal ionized calcium

      Know that acidosis decreases binding of calcium to serum proteins and thus, in acidosis, the total serum calcium is often low despite a normal ionized calcium

      Recognize the preanalytical factors (eg, prolonged exposure to air, temperature, excess heparin) which may affect accurate laboratory measurement of ionized calcium
b. Maintenance of eucalcemia

(1). Intestinal handling of calcium

Understand the difference between passive and active intestinal calcium absorption and identify the factors (calcium load, hormonal regulation) affecting each

(2). Renal handling of calcium (for regulation by PTH see II.B.1.c.(1))

Recognize that in hyperparathyroidism, hypercalciuria is due to the effect of increased extracellular calcium concentration on the kidney and is not due to increased parathyroid hormone concentration

Know the effects of thiazide diuretics, corticosteroids, and furosemide on renal excretion of calcium

(3). Skeletal handling of calcium

c. Role of calcium in cell biology

(1). Calcium channels

(2). Intracellular messenger

Know that calcium is an intracellular second messenger

(3). Neurotransmission

Know that calcium is important for neural function, particularly at the neuromuscular junction, and that decreased extracellular calcium concentration causes increased neuromuscular excitability, accounting for many of the symptoms of hypocalcemia

2. Phosphate

a. Mechanisms of absorption, excretion, and compartmentalization

(1). Kidneys (for regulation by PTH, see II.B.1.c.(1))

Know that phosphate homeostasis is regulated predominantly by the kidney

(2). Bone

Recognize that phosphate is a major constituent of bone mineral
(3). **Intracellular exchange**
Recognize that phosphate shifts between extracellular and intracellular compartments and know which factors influence this movement

3. **Magnesium**

Know that serum magnesium is composed of free and protein-bound components

a. **Intestinal absorption**

Understand that magnesium is actively absorbed in the intestinal tract

b. **Renal handling of magnesium**

Understand that the kidney acts to conserve magnesium during magnesium depletion

c. **Effect of PTH secretion, action**

Know how hypomagnesemia can affect parathyroid secretion and action

Know that hypocalcemia may be refractory to therapy when serum magnesium concentration is decreased

Recognize the suppressive effect of hypermagnesemia on parathyroid hormone secretion

B. **The calcitropic hormones**

1. **PTH**

a. **Glandular origin**

(1). **Anatomy and embryology**

Recognize the embryonic derivation of the parathyroid glands

b. **Biochemistry, physiology**

(1). **Synthesis and secretion**

Know that PTH is derived from proteolytic processing of pre-pro-PTH

Know that the classical bioactivity of PTH resides in the first 34 N-terminal amino acid structure

Know that calcitriol can directly suppress parathyroid hormone
synthesis

Know that PTH secretion is regulated by extracellular ionized calcium via G-protein-coupled calcium-sensing receptors in parathyroid cells

(2). **Mechanism of action**

Know that PTH acts through the PTH/PTHrP receptor and that this receptor is a seven-transmembrane receptor that signals through Gs to increase cAMP

(3). **Metabolism**

Recognize that PTH is rapidly cleaved after secretion into amino- and carboxy-terminal fragments

c. **Effect on target organs**

(1). **Kidney**

Know that PTH inhibits phosphate reabsorption in the proximal renal tubule and increases Ca reabsorption in the distal tubule

Recognize that PTH is an important stimulus to renal 1 alpha-hydroxylase activity and synthesis of calcitriol

(2). **Bone**

Know mechanisms by which PTH increases calcium resorption from bone by activating osteoclastic activity

Know that PTH is involved in the recruitment and differentiation of osteoclasts from monocytic cells

(3). **Intestinal tract**

Recognize that PTH effects upon intestinal calcium absorption are mediated indirectly by its stimulation of calcitriol synthesis
d. **Measurement of PTH**

(1). **Region specific assays**

Understand the physiologic and diagnostic importance of PTH assays which are specific for the N-terminal, C-terminal and mid-region fragments and intact molecule

(2). **Cytochemical assay**

(3). **Ancillary studies (cyclic AMP, urine calcium)**
Know the uses and limitations of assays for PTH and vitamin D metabolites and other calcitropic hormones

Know that nephrogenous cyclic AMP, assessed by measuring plasma and urinary cyclic AMP, is a measure of parathyroid hormone activity

e. PTH-related abnormalities

(1). PTH insufficiency or resistance

(a). Primary hypoparathyroidism

Be aware that congenital hypoparathyroidism may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive trait

Know the syndromes associated with hypoparathyroidism

Know that acquired hypoparathyroidism may be a complication of thyroid surgery or, rarely, radioactive iodine therapy

Know the pathophysiological consequences of hypoparathyroidism

Know that hypocalcemia that occurs in hypoparathyroidism is partly due to decreased synthesis of calcitriol

Recognize the characteristic laboratory abnormalities in hypoparathyroidism

Know the clinical features of hypoparathyroidism including ectopic (particularly intracranial) calcification

Know the differential diagnosis of hypoparathyroidism

Know that functional hypoparathyroidism can result from activating mutations or antibody-mediated stimulation of the calcium-sensing receptor of the parathyroid cells

Know which medications are used to treat children with hypoparathyroidism and how to adjust doses

(b). Resistance to PTH (pseudohypoparathyroidism)

Recognize the phenotype known as Albright hereditary osteodystrophy (AHO) that occurs in PHP I

Distinguish between PHP I and PHP II

Recognize the findings in patients with pseudohypoparathyroidism
Recognize that PHP IA is due to a mutation in the gene encoding Gs-alpha, which is involved in PTH receptor signal transduction, and that PHP IB is due to abnormal imprinting of Gs-alpha.

Know that maternal inheritance of inactivating Gs-alpha mutations leads to AHO plus resistance to various hormones, whereas paternal inheritance leads to AHO alone.

Recognize the laboratory findings, including gene analysis, in patients with pseudohypoparathyroidism.

Know how to treat children with pseudohypoparathyroidism.

(2). Hyperparathyroidism

(a). Etiology

Be aware that hyperparathyroidism may occur sporadically or as an inherited trait, particularly in MEN I or MEN IIA.

Know the causes of hyperparathyroidism.

(b). Familial hypocalciuric hypercalcemia

Be familiar with the diagnosis of familial hypocalciuric hypercalcemia and know how to distinguish it from other forms of hypercalcemia.

Know the molecular cause and inheritance pattern for familial hypocalciuric hypercalcemia and its relationship to severe neonatal hyperparathyroidism.

(c). Treatment

Know the appropriate treatments for hyperparathyroidism.

Recognize the biochemical profile consistent with "hungry bone syndrome" after parathyroidectomy for severe hyperparathyroidism.

2. Vitamin D

a. Biochemistry, physiology

(1). Biosynthesis

(a). Photosynthesis in skin

Know that vitamin D is produced in the skin by the action of ultraviolet light on 7-dehydrocholesterol.
Know that the photocatalyzed conversion of 7-dehydrocholesterol to vitamin D proceeds faster in light-skinned persons than dark-skinned persons

Know that ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) can be derived from plant and animal dietary sources respectively and that the two molecules are metabolized similarly

(b). Hydroxylation in liver

Know that the liver is the site of 25-hydroxylase activity

(c). Hydroxylation in kidney

Understand the regulation of 1-alpha hydroxylase activity by phosphate, parathyroid hormone, and 1,25-dihydroxyvitamin D

(d). Synthesis in inflammatory tissue

Know that 1-alpha hydroxylase activity exists in some neoplastic and inflammatory monocytes and in macrophages, particularly in sarcoidosis

(2). Circulating metabolites

Know that serum 25-hydroxyvitamin D concentrations primarily reflect vitamin D nutritional status

Know that 1,25-dihydroxyvitamin D concentrations may be elevated in children with rickets due to phosphate or vitamin D deficiency

Know that 25-hydroxyvitamin D can cross the placenta from mother to fetus

(3). Mechanism of action

(4). Effects on target tissues

Know that 1,25-dihydroxyvitamin D binds to a cytoplasmic receptor that is a member of the steroid receptor superfamily and that the receptor binds to promoters to alter transcription of the target genes

(a). Intestine

Recognize that 1,25-dihydroxyvitamin D is the primary stimulator of intestinal calcium transport

(b). Bone
(c). Kidney

(5). Vitamin D-related disorders

(a). Vitamin D deficiency (nutritional)

Understand that nutritional vitamin D deficiency occurs only if there is both insufficient dietary intake of vitamin D and insufficient sun exposure.

Recognize that nutritional vitamin D deficiency can cause rickets, and less commonly, hypocalcemia.

Recognize that anticonvulsant therapy may be associated with vitamin D deficiency.

Know the typical pattern of biochemical abnormalities in vitamin D deficiency rickets.

Know how to treat nutritional vitamin D deficiency.

Recognize the high prevalence of subclinical 25-hydroxyvitamin D deficiency in U.S. children and its association with increased levels of parathyroid hormone.

(b). Vitamin D deficiency (gastrointestinal etiology)

Understand the importance of the intestinal mucosa, biliary tract, and pancreatic enzymes in the absorption of dietary vitamin D, and that vitamin D metabolites undergo enterohepatic circulation.

Recognize the gastrointestinal causes of childhood vitamin D deficiency: short-bowel syndrome, celiac disease, biliary obstruction, and other causes of fat malabsorption.

Know how to treat vitamin D deficiency due to malabsorption.

(c). Vitamin D abnormalities in renal insufficiency

Understand the pathophysiology of the secondary hyperparathyroidism that accompanies renal insufficiency.

Recognize that 1,25-dihydroxyvitamin D values are decreased in patients with chronic renal insufficiency and understand the pathophysiological basis for the decreased concentrations.

Understand the rationale for use of calcimimetic agents.

(d). Deficient 1 alpha-hydroxylase activity
Know that deficiency of calcidiol 1 alpha-hydroxylase results in rickets (previously termed Vitamin D-dependent rickets type 1) which is inherited in an autosomal recessive pattern.

Recognize the laboratory abnormalities in 1 alpha-hydroxylase deficiency.

Know the treatment for 1 alpha-hydroxylase deficiency.

(e). **Hereditary resistance to vitamin D**

Know that vitamin D insensitivity is associated with mutations in the gene encoding the vitamin D receptor.

Recognize that insensitivity to calcitriol causes vitamin D-dependent rickets type 2 (hereditary vitamin D-resistant rickets) and know the phenotype of that condition, which includes alopecia.

(f). **Hypervitaminosis D**

Recognize various causes of Vitamin D excess.

Recognize the clinical and laboratory manifestations of hypervitaminosis D.

3. **Calcitonin**

   a. **Physiology -- effects on target tissue**

      (1). **Bone**

      Know that calcitonin, given pharmacologically, inhibits bone resorption.

C. **Other clinical disturbances of mineral homeostasis**

1. **Hypocalcemia**

   a. **Neonatal**

   Know the symptoms of infantile hypocalcemia.

      (1). **Early onset**

      Recognize that early onset neonatal hypocalcemia frequently reflects intrauterine and postnatal insults such as type 1 diabetes, toxemia of pregnancy, or premature or traumatic delivery.

      (2). **Late onset**

      Know that late onset neonatal hypocalcemia may be due to excessive
phosphate intake, hypomagnesemia, or congenital hypoparathyroidism

(3). With hypomagnesemia

Know that hypomagnesemia is associated with hypocalcemia and decreased secretion of PTH

Know that, in patients with hypomagnesemia, eucalcemia is achieved by administration of magnesium

(4). Maternal hypercalcemia

Know that maternal hypercalcemia can cause neonatal hypocalcemia and the mechanism involved

(5). Transient

Recognize that hypoparathyroidism in the newborn and early infancy periods may spontaneously abate, particularly when it is caused by maternal hypocalcemia

b. Nutritional calcium deprivation

Know that hypocalcemia can be due to inadequate calcium intake, particularly in infants

c. Evaluation of hypocalcemia

Know the various causes of hypocalcemia and how to determine the etiology of hypocalcemia by clinical and laboratory evaluation

Recognize the signs and symptoms of hypocalcemia

d. Treatment

Know appropriate therapy for individual causes of hypocalcemia

Know the available therapies for children with hypoparathyroidism and their potential adverse effects

Recognize the therapeutic usefulness of various forms of vitamin D (vitamin D, calcidiol, 1-alpha hydroxyvitamin D, calcitriol, and dihydrotachysterol), including vitamin D metabolites or analogs which do not raise serum calcium

Know the indications for intravenous administration of calcium

2. Hypercalcemia

a. Malignancy associated
Know the various mechanisms by which malignant diseases increase serum calcium concentrations

Know that PTH-related peptide is a major cause of humoral hypercalcemia of malignancy

b. **Williams syndrome**

Know that Williams syndrome is associated with developmental delay, supravalvular aortic stenosis and a characteristic facies

Know that Williams syndrome is caused by a contiguous gene deletion

Know that Williams syndrome is associated with infantile hypercalcemia that usually resolves spontaneously

c. **Hypervitaminosis A**

Know that vitamin A causes hypercalcemia by increasing bone resorption

d. **Immobilization**

Know that immobilization can cause hypercalcemia because of increased bone resorption

e. **Evaluation**

Know the various causes of hypercalcemia and how to determine the etiology of hypercalcemia by clinical and laboratory evaluation

Recognize the signs and symptoms of hypercalcemia

f. **Management**

Be able to appropriately treat hypercalcemia

Recognize the importance of correcting dehydration in acute hypercalcemia

3. **Hypophosphatemia**

Know that hypophosphatemia is most often due to renal phosphate wasting

Recognize the association of hypophosphatemic rickets and mesenchymal tumors of bone and soft tissue (oncogenic osteomalacia) and understand the clinical and pathophysiological similarities between this disorder and X-linked hypophosphatemic rickets
Know what is meant by the "Fanconi syndrome" and recognize its causes

Know that hypophosphatemia may be due to acute redistribution of phosphate
Recognize that hypophosphatemia can be caused by primary or secondary hyperparathyroidism

Recognize the clinical signs and symptoms of hypophosphatemia

Be familiar with X-linked autosomal dominant and autosomal recessive hypophosphatemic rickets, including clinical characteristics, mode of inheritance, biochemical characteristics, pathophysiology, and molecular genetic etiology

Understand that, in patients with X-linked hypophosphatemic rickets, there is both urinary phosphate wasting and decreased 1-alpha hydroxylation, often resulting in a 1,25-dihydroxyvitamin D level that is inappropriately normal in the presence of hypophosphatemia

Be familiar with hereditary hypophosphatemic rickets with hypercalciuria and understand how the phosphaturia causes increased 1-alpha hydroxylation that leads to increased calcium absorption and hypercalciuria

Understand the role of increased FGF-23 in disorders of phosphate wasting, such as autosomal dominant hypophosphatemic rickets or McCune-Albright syndrome

a. **Evaluation**

Know the various causes of hypophosphatemia and how to determine the etiology of hypophosphatemia by clinical and laboratory evaluation

Understand the concepts of reabsorbed fraction of filtered phosphate and the renal phosphate threshold

b. **Therapy**

Understand the treatment of hypophosphatemic disorders and recognize renal calcification and secondary hyperparathyroidism as complications of therapy

4. **Hyperphosphatemia**

a. **Neonatal**

Know the causes of increased serum phosphate concentrations in the neonate

b. **Renal insufficiency**
Recognize the relationship between calcium and phosphate in renal disease

Understand the pathogenesis and clinical manifestations of renal osteodystrophy including the role of hyperphosphatemia, decreased 1,25-dihydroxyvitamin D, and secondary hyperparathyroidism

c. **Idiopathic (tumoral calcinosis)**

Recognize different causes of hyperphosphatemia, including the syndrome of tumoral calcinosis

Understand the role of decreased FGF-23 function, such as in the syndrome of tumoral calcinosis

d. **Hypoparathyroidism**

Recognize that hypoparathyroidism causes hyperphosphatemia

e. **Phosphate loading**

Recognize that hyperphosphatemia can be a cause of hypocalcemia

(1). **Endogenous**

Know that acute hyperphosphatemia and hypocalcemia can be caused by massive cell lysis, either neoplastic cell lysis (due to cytotoxic therapy) or lysis of normal cells (e.g., rhabdomyolysis, hemolytic anemia, crush injuries, etc)

(2). **Exogenous**

Know that acute hyperphosphatemia and hypocalcemia can be caused by phosphate administration (intravenous, oral, or rectal)

f. **Evaluation**

g. **Treatment**

Know when to use a low phosphate diet and phosphate-binding agents to treat hyperphosphatemia

5. **Hypomagnesemia**

a. **Clinical presentation**

Recognize the clinical consequences of hypomagnesemia

b. **Etiology**
Know the causes of hypomagnesemia

c. **Evaluation**

Know how to evaluate hypomagnesemia

d. **Treatment**

Know how magnesium salts should be administered and the specific drawbacks of each route of administration

6. **Hypermagnesemia**

a. **Treatment**

Know how to treat a hypermagnesemic patient

7. **Disorders of other trace minerals**

D. **Bone biology**

1. **Anatomy and structure**

a. **Matrix**

Know that the organic matrix of bone contains collagen (particularly type I) and osteocalcin and that unmineralized bone matrix is called osteoid

b. **Mineral phase**

Know that bone mineral is deposited in the matrix and consists principally of hydroxyapatite, which contains calcium and phosphate

c. **Bone cells**

Understand the origins and roles of osteoblasts, osteoclasts, and osteocytes

d. **Trabecular and cortical bone**

Understand the differences between trabecular bone and cortical bone

2. **Physiology**

a. **Bone formation**

Know factors that stimulate bone formation (eg, mechanical load, GH/IGF-I, intermittent PTH) and factors that inhibit bone formation (eg, glucocorticoid)
b. **Bone resorption**

Know factors that stimulate bone resorption (eg, continuous PTH, thyroid hormone) and factors that inhibit bone resorption (eg, estrogen, androgen and calcitonin)

Understand the interplay among RANK, RANK ligand, and osteoprotegerin (OPG) in the regulation of osteoclast function

c. **Bone mineralization**

Know that bone mineralization requires sufficient extracellular calcium and extracellular phosphate and is promoted by osteoblasts

Know that alkaline phosphatase is an enzyme essential for normal mineralization of bone

Know that alkaline phosphatase in liver and bone are biochemically distinguishable and that bone alkaline phosphatase is a marker of bone formation

d. **Bone turnover**

Be aware that bone is continually remodeled through the combined actions of osteoblasts and osteoclasts and that an imbalance between formation and resorption can lead to osteoporosis or osteopetrosis

e. **Skeletal growth**

Understand that longitudinal bone growth occurs at the growth plate by endochondral bone formation in which cartilage is created and then remodeled into bone tissue

Be familiar with the mechanisms of replacement of cartilage with ossification centers

Understand the process of longitudinal growth at the growth plate

Know that apoptosis is a mechanism of growth regulation

Know that growth in bone width occurs at the periosteum

Know that IL-1 alpha, TNF-alpha, and TNF-beta are potent stimulators of bone resorption and inhibitors of bone formation

E. **Clinical disorders of the skeleton**

1. **Osteopenic disorders in childhood**

   a. **Juvenile osteoporosis**
Recognize idiopathic juvenile osteoporosis

Recognize the causes of acquired osteoporosis in childhood, particularly disuse and glucocorticoid therapy

Know the treatment options for childhood osteoporosis

Know the foods rich in calcium so as to properly advise the optimal dietary calcium intake

b. Osteogenesis imperfecta

Recognize that osteogenesis imperfecta can be due to mutations of the type I collagen gene

Recognize the clinical features of osteogenesis imperfecta and the clinical spectrum of the disease

Know the treatment options for osteogenesis imperfecta

2. Sclerosing disorders of childhood

a. Osteopetrosis

(1). Primary

Know the various forms of osteopetrosis

Know that "malignant" osteopetrosis is a recessively inherited disorder of osteoclasts

(2). Secondary

Know the various forms of therapy for osteopetrosis (including calcitriol, bone marrow transplantation)

3. Rickets and osteomalacia

Know the biochemical features of various types of rickets

Be able to recognize the clinical and radiographic features of rickets

Know the various causes of rickets and be able to determine the cause in a patient based on clinical and biochemical features

Know how to treat the various types of rickets

a. Hypophosphatasia
Know the principal clinical and biochemical manifestations of hypophosphatasia, an inherited deficiency of alkaline phosphatase leading to rickets-like bone disease and craniosynostosis

b. **In low-birth-weight infants**

Know that rickets and osteopenia may occur in premature infants as a result of dietary phosphate and/or calcium deficiency

c. **Renal tubular acidosis**

Know that distal type renal tubular acidosis may lead to rickets in childhood and eventually to dense nephrocalcinosis

4. **Skeletal manifestations of systemic disease**

a. **Parenteral hyperalimentation**

Recognize that aluminum toxicity may occur with parenteral nutrition of neonates

Recognize that osteopenia may occur with parenteral nutrition

5. **Miscellaneous**

6. **Investigation of bone disease**

a. **Assessment of bone mineral density**

Know the techniques used to assess bone mineral density in children (especially DEXA and quantitative CT)

Know the advantages and disadvantages of bone mineral density techniques

Be aware that bone density measured by DEXA scans should be interpreted using Z-scores (SD score for age) and not T-score (SD score compared to young adults) and that bone density by DEXA will appear artifactually low in a child with short stature

b. **Biochemical markers of bone metabolism**

Be able to distinguish between benign and clinically significant forms of hyperphosphatasemia

Know that bone formation and resorption can be assessed by serum and urinary markers

7. **Miscellaneous disorders of mineralized tissue**
a. **Nephrolithiasis**

Understand the pathophysiology of calcium-related kidney stones

b. **Soft-tissue calcification**

Know the etiologies of soft-tissue calcification

Know the difference between soft-tissue calcification and ectopic bone formation

### III. Thyroid Hormones (Thyroxine (T4) and Triiodothyronine (T3))

**A. Physiology**

1. **Ontogeny/embryology**

   Know the embryology of the formation and migration of the thyroid gland and the developmental genes involved

   Know the pattern and timing of hypothalamic-pituitary-thyroidal function in the fetus

2. **Synthesis/processing**

   Understand the synthesis of thyroid hormones, including iodide metabolism, uptake, organification, incorporation into thyroglobulin, coupling, and proteolytic secretion

3. **Regulation and secretion**

   Be aware of the changes in thyroid hormone concentrations in the immediate neonatal period and the first weeks after birth

   Appreciate the occurrence of the immediate TSH surge in the first hours of postnatal life

4. **Transport**

   Know whether thyroidal hormones cross the placenta

   Be aware of the various proteins in blood which bind thyroid hormones and their relative clinical importance

5. **Metabolism**

   Know that thyroid hormone transport into tissues is facilitated by thyroid hormone transporters, including MCT8

   Understand the metabolism of thyroid hormone, its regulation, and its
physiologic significance

6. **Receptors/action**

Know that TSH acts through the a seven-transmembrane receptor that signals through Gs alpha to increase cAMP

Know that thyroid hormone receptors belong to the nuclear (steroid) hormone receptor superfamily, and that multiple isoforms exist

Understand the role of the surge of thyroid hormone in thermal homeostasis, especially in the newborn period

**B. Pathology**

1. **Thyroid hormone deficiencies**

   a. **Fetal hypothyroidism**

      (1). **Pathophysiology**

      Be aware that transplacental passage of certain substances including radioiodine, iodides, propylthiouracil and methimazole administered to the mother may affect fetal thyroid development and/or function

      (2). **Clinical implications**

      Know the concentrations of thyroid hormones and their metabolites throughout fetal development

      Know the value of ultrasonography in detecting thyroidal enlargement in the fetus

      Know the efficiency of fetal brain deiodination in the face of fetal hypothyroidism

      Know that maternal hypothyroidism is associated with increased fetal loss and with mild cognitive delay in the infant

      Know that when there is hypothyroidism in the mother and the fetus, severe mental retardation is likely in the fetus

   b. **Congenital hypothyroidism**

      (1). **Pathophysiology**

      Be aware of potential effects on the breast-fed infant of antithyroidal agents ingested by the mother

      Recognize that worldwide iodide deficiency is the most common cause of congenital primary hypothyroidism and of preventable mental
(2). Clinical implications

(a). Clinical manifestations

Know the pattern of osseous maturation in the neonate and the impact of thyroid hormone deficiency on the process

Recognize that congenital central hypothyroidism is often associated with other pituitary hormone deficiencies

Be aware of intracranial anatomical defects which may accompany TRH or TSH deficiencies

Be aware that congenital hypothyroidism is the most common disease screened for in newborns

Be familiar with the clinical significance of the effect of prematurity on thyroid function in the neonate

Know the clinical characteristics and inheritance patterns of TSH unresponsiveness syndromes

Know the clinical findings of congenital hypothyroidism and when they become manifest

Know the clinical findings of Pendred syndrome and recognize that mutations in the affected gene are an important cause of sensorineural deafness

(b). Diagnosis
Know the changes in hormonal concentrations suggesting deficiency of either TRH or TSH

Be aware of procedures for delineating errors of thyroid hormone synthesis

Be aware of techniques for defining the anatomy of the thyroid (scans and ultrasound)

Be aware that maternally transmitted TSH receptor-blocking antibodies can be a cause of transient congenital hypothyroidism

Be aware of laboratory findings suggesting agenesis of the thyroid

Be aware that maternally transmitted TSH-receptor-blocking antibodies can inhibit TSH-induced iodine uptake and therefore result in apparent absence of the thyroid gland on scanning

**c. Treatment**

Be aware of the half-life of transferred blocking antibodies

Be able to develop a safe management plan for infants born to mothers with TSH receptor blocking antibodies

Be aware that the recommended dosage of thyroxine per kg of body weight for congenital hypothyroidism changes with the age of the child

Know how to interpret concentrations of thyroxine and TSH in monitoring treatment of congenital hypothyroidism

Recognize the variability of TSH suppression in the young infant receiving treatment for congenital hypothyroidism with thyroxine

Be aware of the advantages of maintaining high-normal concentrations of thyroxine in serum for optimal outcome in treating congenital hypothyroidism

Know potential side effects of overtreatment of congenital hypothyroidism (premature craniosynostosis and advanced bone age)

Know that soy formula, fiber, and iron can inhibit thyroid hormone absorption

Know that mild hypothyroidism frequently normalizes and that treatment may not be necessary

**d. Prognosis**
Be familiar with the prognosis for future cognitive development in congenital hypothyroidism and the factors that affect this prognosis.

Recognize the features of congenital hypothyroidism that may affect outcome (osseous maturation - thyroxine concentrations before treatment; absence of thyroid tissue) and requires higher initial doses of thyroid hormone.

(e). Prevention

Know how to apply the genetics of biosynthetic errors in counseling.

Know the methodology involved in thyroid screening of the neonate including measurement of thyroxine and TSH concentrations.

Be able to cite advantages and disadvantages of various systems of neonatal thyroid screening.

Know the appropriate diagnostic approaches for children with various abnormalities on newborn screening.

Be aware of various transient abnormalities in thyroid function which may be detected by neonatal screening.

Recognize that congenital hypothyroidism may not be detected in a small number of infants by neonatal screening.

c. Acquired Hypothyroidism

(1). Pathophysiology

Be aware of the intracranial abnormalities (and their treatments) which may affect TRH and TSH production.

Be aware that thyroid hormone deficiency may develop during treatment of growth hormone deficiency.

Know which drugs may interfere with thyroid function (eg, iodides, lithium, and amiodarone) and the clinical correlates of these drugs in thyroid physiology.

Be aware that neck irradiation can cause hypothyroidism and thyroid neoplasia.

Know that some chromosomal disorders (Down syndrome, Turner syndrome) predispose a patient to the development of autoimmune endocrine diseases.

Recognize the importance of iodide deficiency as a
cause of hypothyroidism in some parts of the world

Know the frequency and manifestations of thyroid disease in cystinosis

Recognize that iodine excess in topical anti-sepsis therapy (eg, beta dine to open umbilical wounds), medications, radiographic dyes, and other forms can inhibit thyroid function

(2). Clinical implications

(a). Clinical manifestations

Be aware of the clinical findings of acquired hypothyroidism including typical impact on growth patterns

Recognize the unusual type of sexual precocity which may accompany severe acquired primary hypothyroidism and the pathophysiology of this problem

Recognize the characteristics of the thyroid gland on physical examination or imaging studies in autoimmune acquired hypothyroidism

Be aware of association of the autoimmune acquired hypothyroidism with other autoimmune endocrine diseases, including the autoimmune polyglandular syndromes

Know the clinical significance of the changes in thyroid hormone concentrations that occur during severe illnesses such as euthyroid sick syndrome

Know that clinical features of secondary or tertiary hypothyroidism are milder than primary hypothyroidism

(b). Diagnosis

Be aware of the laboratory measurements for documentation of primary hypothyroidism as well as the antibody determinations which will indicate its autoimmune nature

Understand that a substantial fraction of the population has measurable thyroid auto-antibodies, and that if T4, TSH, and thyroid exam are normal, treatment is not indicated for antibody titer alone

(c). Treatment

Know the dosage of thyroxine for replacement therapy for acquired hypothyroidism

Know the techniques for monitoring the adequacy of thyroid hormone replacement in primary hypothyroidism and in central hypothyroidism,
including the need to delay thyroxine monitoring for at least five half-lives (5 weeks) after dose adjustment

Know the effects of age and size on thyroid hormone replacement dosage in patients with secondary or tertiary hypothyroidism

Be aware of the effects on thyroid function tests of treatment with large doses of thyroxine

Know the effects of medication on thyroid function tests

Know that thyroid hormone is not indicated as a weight loss drug in individuals with normal thyroid function test results

(d). Prognosis

Be aware of the effects of the treatment of acquired hypothyroidism on the patient's school performance and be able to counsel parents

Be aware that delay in the treatment of acquired hypothyroidism and overzealous replacement therapy may have an adverse effect on ultimate height

Be aware of ultimate outcome of acquired hypothyroidism, including impact of the disorder on the patient's growth and mental development

Recognize that treatment of acquired hypothyroidism may be required indefinitely

Recognize the occurrence of pseudotumor cerebri in some hypothyroid children treated with thyroxine

d. Thyroid hormone resistance

(1). Pathophysiology

Be aware that mutations in the thyroid hormone receptor beta are associated with thyroid hormone resistance

Be aware that the presence of different thyroid hormone receptor types in different tissues produce variable effects of this condition upon different tissues of the body

(2). Clinical implications

(a). Clinical findings

Be aware of the clinical findings in thyroid hormone resistance, including attention deficit hyperactivity disorder
(b). Diagnosi

Be aware of the diagnostic approach to thyroid hormone resistance

(c). Treatment

Be aware of the treatments for thyroid hormone resistance

2. Thyroid hormone excess

a. Neonatal Graves disease

(1). Pathophysiology

Understand the mechanism of neonatal Graves disease in relation to maternal thyroid disease

(2). Clinical implications

Know the clinical presentation of neonatal Graves disease

Know the course of neonatal Graves disease

Be aware of the management of neonatal Graves disease

b. Childhood Graves disease

(1). Pathophysiology

Know about the autoimmune mechanisms involved in the pathogenesis of Graves disease including the various types of TSH receptor antibodies

Recognize the relationship of Graves disease to other autoimmune diseases of the thyroid with and without hyperthyroidism

(2). Clinical implications

(a). Clinical manifestations

(b). Diagnosis

Differentiate between Graves disease and other conditions involving hyperthyroidism

Know the usefulness of the measurement of T4, free T4, and T3 concentrations in hyperthyroidism
Recognize and identify the various forms of nonthyrotoxic hyperthyroxinemia

Understand that low iodine uptake in the face of negative stimulatory antibodies with high T4, T3, and low TSH may be indicative of a temporary form of hyperthyroidism, such as subacute thyroiditis

Understand that, after the neonatal period, children's serum T3 concentrations exceed those of adults, and that with normal TSH do not indicate hyperthyroidism, and that obese children may have slightly increased serum T3 concentrations

Understand that the reference ranges for thyroid function tests provided by many laboratories are often specific to adults, and not children

Understand that a mildly increased TSH concentration with normal T4 and T3 concentrations cannot account for excessive weight gain or other symptoms

Understand the usefulness of measuring TSH receptor antibodies and the different tests available

(c). Treatment

Understand the medical management of Graves disease with antithyroid drugs, including dosage, monitoring, and side effects

Understand the medical management of Graves disease with antithyroid drugs including pharmacologic actions

Understand the medical management of Graves disease with antithyroid drugs including indication for seeking alternative treatments

Know how to use beta-blocking agents for immediate control of the symptoms of Graves disease

Know the indications for surgery to treat Graves disease

Know the medical preparation for surgery to treat Graves disease

Know the intra and post-operative complications of surgical treatment of Graves disease

Know the risks of radioactive iodine therapy

Know the indications and use of radioiodine in the treatment of Graves disease

Know the likelihood of remission with medical management and the
duration of therapy required for this to occur

(d). Prognosis

Be aware of the natural course of Graves disease

Understand that stimulatory antibodies may persist for years after treatment in a subset of women with Graves disease, and be unrecognizable if thyroid ablation has occurred, increasing the risk for neonatal hyperthyroidism in their offspring

c. Hyperthyroidism--other causes

(1). Pathophysiology

Be aware of the occurrence but rarity of the "hot nodule" as a cause of thyrotoxicity

Be aware of the occurrence of thyrotoxicosis following ingestion of ground beef with a high thyroxine content due to inclusion of neck strap muscles

Be aware of subacute thyroiditis (silent thyroiditis) as a cause of hyperthyroidism and of its clinical cause

Be aware of activating mutations of the TSH receptor as a cause of familial (autosomal dominant) congenital or acquired hyperthyroidism

(2). Clinical implications

Be aware of the biochemical findings in various types of hyperthyroidism

Recognize clinical and laboratory findings suggesting hyperthyroidism

Know the radiographic and MRI findings associated with longstanding primary hypothyroidism

Know the diagnostic evaluation of patients with hyperthyroidism due to TSH excess

3. Other

a. Thyroid hormone binding protein abnormalities

(1). TBG deficiency

Be aware of the clinical significance of low total thyroid hormone concentrations due to a low thyroxine-binding globulin (TBG)
Know the changes in thyroid hormone concentrations in blood which suggest a deficiency of TBG

Know the genetics of TBG deficiency and how to apply the genetics of TBG deficiency when counseling families

Be aware of the impact of nonthyroidal illnesses, which alter protein concentrations, on thyroid hormone binding by proteins such as in nephrosis

Know that certain drugs and hormones will alter the concentration of thyroid binding proteins with subsequent impact on laboratory measurements of total thyroid hormones

(2). **TBG excess**

Recognize the characteristic findings on laboratory measurements which suggest increased concentrations of TBG

Know the clinical significance of excess TBG

Know the genetics of TBG excess and how to counsel families

Know the common clinical conditions (eg, estrogen therapy, oral contraceptives, pregnancy) that will increase TBG concentration

(3). **Dysalbuminemia**

Know the clinical significance of dysalbuminemia and the characteristic laboratory findings

b. **Thyroiditis**

(1). **Acute suppurative**

Be aware of the clinical and laboratory findings in acute suppurative thyroiditis

Know the appropriate treatment of acute suppurative thyroiditis

(2). **Subacute (de Quervain)**

(a). **Pathogenesis**

Recognize the relationship of subacute (de Quervain) thyroiditis to viral diseases such as mumps

Recognize the rarity of subacute (de Quervain) thyroiditis
in children

(b). Clinical implications

Be aware of the clinical picture of subacute (de Quervain) thyroiditis

Understand the natural course of subacute (de Quervain) thyroiditis

Know how to manage subacute (de Quervain) thyroiditis

(3). Subacute (lymphocytic)

Be aware that subacute (lymphocytic) thyroiditis may be a cause of transient hyperthyroidism followed by transient hypothyroidism and then by euthyroidism

Be aware of the propensity for transient abnormalities caused by subacute (lymphocytic) thyroiditis to recur in affected individuals

(4). Chronic

Be aware of the variable clinical course of chronic thyroiditis including the effects of pregnancy and the postpartum period

c. Thyroid gland neoplasms

(1). Single nodule

(a). Pathophysiology

Understand the histologic types of thyroid carcinoma

Know the predisposing factors to the development of thyroid carcinoma such as irradiation and the increased risk in children less than 10 years of age

(b). Clinical manifestations

Recognize the clinical manifestations of carcinoma involving the thyroid

Recognize the clinical manifestations of thyroid carcinoma involving sites other than the thyroid

Be familiar with the clinical and laboratory manifestations of medullary carcinoma

Understand the importance of and techniques for studying other family members' medical histories in patients with medullary
canceroma

Recognize that natural history of medullary carcinoma of the thyroid varies, depending on the specific mutation

Know that C cell hyperplasia is a precursor of medullary carcinoma of the thyroid

(c). Diagnosis

Know the diagnostic strategies and implications of a single thyroid nodule

Be able to devise a plan for diagnosis of a single thyroid nodule

Know the indications for biopsy, including fine needle aspiration biopsy, of a single thyroid nodule

Be familiar with various techniques for biopsy of a single thyroid nodule

Be familiar with the laboratory manifestations of medullary carcinoma

Know the value of calcitonin measurements for diagnosis of medullary carcinoma

Recognize that basal calcitonin levels may not be elevated in patients with medullary carcinoma of the thyroid or C-cell hyperplasia

(d). Treatment

Know the indications for excision of a single thyroid nodule

Know the protocol for medical management following surgery for thyroid carcinoma

Know the indications for use of I-131 in treating thyroid carcinoma

Know the value of calcitonin measurements for monitoring medullary carcinoma

Be aware of the principles of management of medullary carcinoma

Know the protocol for rhTSH stimulation, imaging and thyroglobulin testing following surgery for thyroid cancer

(e). Prognosis
Understand the features of thyroid carcinoma affecting prognosis

Understand that metastases of follicular and papillary thyroid cancer may be curable with radioiodine

Understand that distant metastases of medullary thyroid carcinoma are not currently curable but that long-term survival is still possible

(f). Prevention

Understand the importance of genetic testing at an early age and prophylactic thyroidectomy in individuals with a family history of medullary carcinoma

d. Diffuse enlargement

(1). Pathophysiology

Know that diffuse enlargement of the thyroid is most commonly due to chronic lymphocytic thyroiditis

Be familiar with the mechanisms of diffuse enlargement of the thyroid

Be aware of causes of diffuse thyroid enlargement other than chronic lymphocytic thyroiditis
Know that lymphoma and teratoma may rarely involve the thyroid gland

Know that Hodgkin disease and other infiltrative hematologic diseases (eg, histiocytosis) and their treatment may involve the thyroid gland

(2). Clinical implications

Be familiar with the clinical methods for diagnosis of diffuse enlargement of the thyroid

Be familiar with the laboratory tests used to evaluate diffuse enlargement of the thyroid

Know the indications for treatment of diffuse thyroid enlargement

IV. Adrenal Disorders

A. Cortisol

1. Physiology

   a. Ontogeny/Embryology
Know neonatal changes in the secretion of adrenocortical hormones

Understand the placental control of steroid production

Understand effects of maternal glucocorticoids cortisol on fetal adrenal function

Know the normal histology and zonality of the adrenal cortex in the fetus, newborn, and child

Understand the origin and significance of maternal estriol during pregnancy

Know the maturational pattern of synthesis and secretion of adrenal cortical hormones in the fetus, neonate, and throughout early life

**b. Synthesis/processing/storage**

Know the enzymatic steps and genes encoding the enzymes in the pathway of cortisol synthesis from cholesterol

**c. Secretion and regulation (See also V.C.3.a.(3))**

Know the normal rate of production of cortisol in children

Know how cortisol production in children is affected by body mass index

Know cortisol production in children is affected by stress

Know the diurnal pattern of cortisol secretion and understand the role of ACTH in cortisol secretion

Recognize the clinical implications of diurnal variations in cortisol secretion

Know the main clinical applications of measurement of free cortisol in urine

Know which hormones and cytokines regulate ACTH and glucocorticoid production

Know that intravascular volume depletion and vasopressin stimulates ACTH secretion

**d. Transport**

Know that under physiologic circumstances about 80% to 90% of plasma cortisol is tightly but reversibly bound to cortisol-binding globulin (CBG) or transcortin
Know the conditions in which transcortin cortisol-binding globulin concentrations are increased or decreased

Understand the metabolism of cortisol

Know that most synthetic steroids have low relative binding to cortisol-binding globulin compared to cortisol

Understand the role of cortisol-binding globulin and albumin in the transport of cortisol

e. Receptor/Action

Know that adrenal steroids passively enter the nucleus to bind with nuclear receptors

Know that the steroid-receptor binds DNA to stimulate transcription of messenger RNA and protein synthesis

Know the effects of glucocorticoids on carbohydrate metabolism

Know the effects of glucocorticoids on fat metabolism

Understand the interactions between glucocorticoids and the immune system

Understand the effects of glucocorticoids on bone and mineral metabolism and connective tissue

Understand that cortisol may activate both the glucocorticoid and mineralocorticoid receptors

Know that 11-beta hydroxysteroid dehydrogenase type 2 enzyme efficiently inactivates cortisol to cortisone, which prevents hypertension caused by cortisol's binding to the mineralocorticoid receptor in the kidneys

Understand that steroid hormone receptors are part of a superfamily of nuclear receptors that share homologies and mechanisms of action

2. Pathology

a. Cortisol deficiency

(1). Pathophysiology

Understand the recovery of H-P-adrenal axis after chronic suppression with exogenous glucocorticoids

Recognize the possibility of isolated ACTH
deficiency

Know the clinical characteristics, inheritance, and genetic etiology of ACTH unresponsiveness syndromes

Know that adrenal insufficiency can result from adrenal hemorrhage

Understand the hypothalamic pituitary abnormalities that can cause secondary adrenocortical insufficiency

Know the association of hypoadrenalism with adrenoleukodystrophy and related disorders

Know that adrenal insufficiency may occur in AIDS

Know that adrenal hypoplasia congenita may be due to an X-linked DAX-1 (NROB1) gene mutation and may be associated with hypogonadotropic hypogonadism

Know that congenital adrenal hypoplasia may be part of an x-linked contiguous gene deletion associated with glycerol kinase deficiency, retardation, and muscular dystrophy

Understand that adrenal cortical insufficiency may result from congenital adrenal hypoplasia or hyperplasia of various etiologies

Understand that adrenal hypofunction (cortisol deficiency) may occur after high dose glucocorticoid therapy for as little as 2-3 weeks, and understand symptoms and signs of glucocorticoid withdrawal

Know that adrenocortical insufficiency may occur after removal of adrenal or ACTH secreting pituitary tumors

Know that certain chemotherapeutic agents may cause adrenal insufficiency

Know which single gene defects cause hypopituitarism that includes ACTH deficiency

(2). Clinical implications

Know that the anti-inflammatory potency of glucocorticoids may differ from their capacity to suppress the HPA axis

Understand the diagnosis and laboratory evaluation of decreased adrenal cortical function

Understand the cause of hyperpigmentation in primary glucocorticoid deficiency

Know the mild increase in serum TSH present in adrenal insufficiency
Plan replacement therapy for hypoadrenocorticism with glucocorticoids and mineralocorticoids as indicated

Understand that aldosterone secretion can be normal in secondary adrenal deficiency

Understand the clinical and laboratory features of cortisol resistance

Distinguish the key features of classic and nonclassic congenital adrenal hyperplasia

Understand the risk to a patient or relative of a patient or of having a child affected with congenital adrenal hyperplasia

Understand concept of prenatal diagnosis of congenital adrenal hyperplasia

Understand the medical and surgical management of the different forms of congenital adrenal hyperplasia

Understand that girls with virilizing classic CAH may have certain play preferences and behaviors

Know the expected internal genital structures in girls with virilizing classic CAH

Understand the signs and symptoms of glucocorticoid deficiency

Understand the management of cortisol deficiency at times of increased stress

Know the differential diagnosis of adrenal calcification

Know that adrenoleukodystrophy is an x-linked condition associated with increases of C22-C26 very long chain fatty acids due to a defect in peroxisomal beta oxidation

Recognize that Addison disease (autoimmune) may occur in association with other non-endocrine disorders

Know that familial glucocorticoid deficiency (ACTH resistance) may be associated with achalasia and alacrima

Understand newborn screening for congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency

Know the long-term outcome of the disorders associated with cortisol deficiency
Recognize the pros and cons of adrenalectomy as treatment for congenital adrenal hyperplasia (CAH)

Know that anti-adrenal antibodies in Addison's are often directed at the 21-hydroxylase enzyme

Understand the clinical presentation and treatment of the most common forms of CAH

Know the likely causes of false positive newborn screening test results for CAH

Understand why hydrocortisone or prednisone cannot be used for prenatal treatment of congenital virilizing adrenal hyperplasia (CAH)

Understand the relative merits of low and high dose ACTH tests in evaluating the hypothalamic-pituitary-adrenal axis

Understand the primary clinical and biochemical features for the various genetic defects in the cortisol biosynthetic pathway causing CAH

Know that long-standing elevation of ACTH can result in the formation of adrenal rest tissue

Understand the advantages and disadvantages of prenatal treatment of CAH

b. Cortisol excess

(1). Pathophysiology

Understand that cortisol excess may be pituitary ACTH-dependent (Cushing disease)

Know that cortisol excess may result from ectopic ACTH or CRH secretion

Know that cortisol excess may result from a functioning adrenal cortical tumor

Know that Cushing syndrome may be produced by systemic or topical (inhaled and dermal) glucocorticoid administration

(2). Clinical implications (See also IV.A.1.e.)

Recognize that the diurnal secretory pattern of ACTH is altered in patients with Cushing disease

Recognize the clinical signs and symptoms of excessive CRF secretion
Know how to appropriately administer glucocorticoids to ACTH-deficient individuals during both normal and stressful periods

Recognize clinical and laboratory findings of patients with Cushing disease

Understand the clinical and laboratory evaluation needed to determine the etiology of hypercortisolism

Know how to differentiate Cushing syndrome from exogenous obesity

Understand effects of glucocorticoid and androgen excess on growth in patients with Cushing syndrome

Know appropriate therapy of patients with Cushing disease

Know the relative growth suppressive effects of synthetic glucocorticoids

Recognize the characteristic fat distribution in cortisol excess problems

Know the clinical features of Cushing syndrome

Know the diagnostic methods to distinguish among causes of Cushing syndrome

Know the characteristic cortisol excretion rate in Cushing syndrome

Know the disturbance in pattern and significance of serum urine, and salivary concentrations in Cushing syndrome

Know diagnostic tools available to detect pituitary tumors in Cushing syndrome and the indications

Know the indications for adrenalectomy

Know indications and contraindications for removal of pituitary microadenomata in Cushing syndrome

Know indications for pituitary radiation therapy, either alone or in combination with other therapeutic modalities

Know the syndromes associated with adrenal cortical tumors

Understand methods of reducing or discontinuing hydrocortisone therapy after surgical treatment of Cushing syndrome

Know the medical management of Cushing syndrome
Know the role of cortisol in the hypertension and hypokalemia of ectopic ACTH production

Know that excess glucocorticoids induce protein catabolism

Know the outcome of Cushing syndrome of various etiologies

Understand that radiation therapy is not immediately effective in controlling cortisol secretion, and that other modalities must be used in the interim

c. **Other**

(1). **Pathophysiology**

Understand that alteration in the HPA axis occurs in pseudo-Cushing syndrome

(2). **Clinical implications**

Know that cortisol excess may be found with obesity and depression

**B. Androgens**

1. **Physiology**

a. **Ontogeny/Embryology (See also IV.A.1.a.)**

Know that 3-beta-hydroxysteroid dehydrogenase activity is normally decreased in infancy

Know that prematurity is associated with higher levels of Delta 5 steroid hormones than observed in full-term infants

Know the maturational pattern of synthesis and secretion of the adrenal gland (androgens) in the fetus, infant, prepubertal and pubertal child

b. **Synthesis/Processing/Storage**

Understand the role of ACTH in adrenal androgen synthesis

Know the pathways of adrenal androgen synthesis and extra-adrenal conversion of androstenedione to testosterone and DHT

Know the enzymes involved in sex hormone metabolism

Understand the importance of aromatase in sex hormone metabolism in the fetus and older individuals

c. **Secretion**
Understand the role of ACTH in adrenal androgen secretion

Understand the measurement of circulating adrenal androgens

d. **Transport**

Understand that the adrenal androgens are largely bound to albumin and to a small extent to sex hormone-binding globulin

Understand the metabolism of the adrenal androgens

Understand the relative abundance of various androgens and their biologic sources

e. **Receptor/action**

Understand that adrenal androgens exert their effect through peripheral conversion to more potent androgens

Understand the role of the adrenal androgens at adrenarche in the development of pubic and axillary hair

2. **Pathology**

a. **Adrenal androgen deficiency**

(1). **Pathophysiology**

Know the differential diagnosis of adrenal androgen deficiency

(2). **Clinical implications**

Know that adrenal androgen deficiency or resistance may contribute to paucity of pubic and axillary hair

Know that androgen replacement can be used to treat adrenal androgen deficiency

b. **Adrenal androgen excess**

(1). **Pathophysiology**

Know the pathophysiology of adrenal androgen excess in congenital adrenal hyperplasia (CAH)

Know that 17-hydroxyprogesterone is a precursor to androgens

Know that adrenal androgen excess can be due to an adrenal tumor

Know that adrenal androgen excess can occur in Cushing syndrome
Know that a mild increase in adrenal androgens occurs in premature adrenarche

Know the expected age ranges for pubarche in boys and girls

Understand the difference between isolated pubarche and puberty

Know that elevated adrenal androgens can suppress pituitary secretion of gonadotropins

(2). **Clinical implications (See also IV.A.2.a.(2))**

Know the clinical features, differential diagnosis, and laboratory diagnosis of the various forms of classic and nonclassic CAH

Know the diagnostic evaluation of an adrenal tumor

Know the clinical features, differential diagnosis, and laboratory diagnosis of premature adrenarche

Understand the treatment of virilizing adrenal tumors

Understand the long-term outcome of classic and nonclassic congenital adrenal hyperplasia in terms of growth and reproductive function

Know the long-term outcome of premature adrenarche in that it may be associated with later ovarian hyperandrogenism and/or insulin resistance

Know the long-term outcome of adrenal adenomas and carcinomas

Know the clinical features of P450 oxidoreductase deficiency

c. **Other**

(1). **Pathophysiology**

Understand the causes of infertility in males and females with classic CAH

(2). **Clinical implications**

Know that androgen excess may be found in girls with insulin resistance syndrome

Understand the therapeutic options for androgen excess of adrenal and ovarian derivation

C. **Estrogens**

1. **Physiology**
a. Ontogeny/embryology

b. Synthesis/processing/storage

c. Secretion

Know that the adrenal cortex synthesizes and secretes minimal amounts of estrone and estradiol

Know that most adrenal estrogens are derived indirectly from peripheral conversion of adrenal androgens

Understand the biosynthetic pathway of adrenal estrogens from androgens

d. Transport

e. Receptor/action

2. Pathology

a. Estrogen excess

(1). Pathophysiology

(2). Clinical implications

Know the clinical and laboratory findings in patients with feminizing adrenal tumors

Know the treatment and long-term outcome of feminizing adrenal tumors

Understand that there is relative estrogen excess in virilizing forms of CAH; this contributes to premature epiphyseal fusion

D. Aldosterone

1. Physiology

a. Ontogeny/embryology

Know the maturational pattern of synthesis and secretion of aldosterone

Know that the zona glomerulosa synthesizes aldosterone

Understand that there is relative aldosterone insensitivity in newborn infants

b. Synthesis/processing/storage
Know the pathways by which cholesterol is transformed to aldosterone; understand how this is different from cortisol synthesis.

Know the enzymes and the genes encoding these enzymes necessary for the synthesis of aldosterone from cholesterol.

c. **Secretion**

Understand the factors that regulate aldosterone secretion, including the renin-angiotensin system.

Know the effect of ACTH on aldosterone secretion.

Know how plasma potassium concentration affects aldosterone secretion.

Know that vasopressin has a transient stimulatory effect on aldosterone secretion.

d. **Transport**

Understand that aldosterone circulates in either a non-protein bound form or bound to cortisol-binding globulin or albumin.

e. **Receptor/action**

Understand the metabolism and excretion of aldosterone.

Understand that the aldosterone-receptor complex enters the cell nucleus to stimulate DNA-directed messenger RNA synthesis.

Know that the renin-angiotensin aldosterone system regulates sodium and potassium homeostasis.

Understand the role of 11-beta-hydroxysteroid dehydrogenase in controlling corticosteroid action on aldosterone-responsive tissues.

Understand that aldosterone passively crosses cell membranes to bind with receptors.

Understand that the mineralocorticoid receptor mediates aldosterone action.

Understand that aldosterone promotes active sodium reabsorption and potassium excretion in its major target tissues.

2. **Pathology**

a. **Aldosterone deficiency**
(1). Pathophysiology (See also IV.A.2.a.(1))

Know that aldosterone deficiency may occur without cortisol deficiency

Know the differential diagnosis of hypoaldosteronism

Know the various causes of salt-losing syndromes and how to differentiate among them

Know that salt wasting crisis may be due to aldosterone resistance (mineralocorticoid receptor defect) rather than aldosterone deficiency

Know that adrenal hypoplasia congenita is a cause of hypoaldosteronism

Know the enzymatic deficiencies and genetic defects resulting in hypoaldosteronism in CAH and isolated hypoaldosteronism

Know the molecular basis of pseudohypoaldosteronism and related salt-losing syndromes

(2). Clinical implications

Know how to differentiate mineralocorticoid deficiency from mineralocorticoid unresponsiveness

Understand the clinical presentations of pseudohypoaldosteronism and the variability in aldosterone resistance of different target tissues

Know the clinical features and laboratory findings in hypoaldosteronism

Know how to manage hypoaldosteronism

Understand the prognosis in aldosterone deficiency and aldosterone resistance

b. Aldosterone excess

(1). Pathophysiology

Know that secondary aldosteronism results from angiotensin stimulation of the zona glomerulosa

Know the differential diagnosis of low-renin hypertension

Understand the pathophysiology of hypertension due to excess mineralocorticoid secretion or action

(2). Clinical implications
Know that renin production is characteristically suppressed in hyperaldosteronism.

Know that the standard treatment for primary aldosteronism is surgery.

Understand the medical treatment of unilateral aldosteronoma.

Know the appropriate diagnostic steps for hyperaldosteronism.

Know the clinical presentation of patients with excess mineralocorticoid secretion or action.

Understand the medical treatment of hyperaldosteronism due to bilateral adrenal hyperplasia.

Know the treatment of dexamethasone suppressible (glucocorticoid remediable) hyperaldosteronism.

Know the prognosis of hyperaldosteronism due to unilateral aldosteronoma, bilateral adrenal hyperplasia, and glucocorticoid remediable aldosteronism.

c. Other

(1) Bartter and Gitelman syndromes

(a) Clinical implications

Know the clinical presentation and laboratory findings in Bartter syndrome.

Understand the therapy of Bartter Syndrome.

(2) Apparent mineralocorticoid excess

(a) Pathophysiology

Know that licorice ingestion can cause hypertension by inhibiting 11-beta-hydroxysteroid dehydrogenase enzymatic activity.

Understand the molecular biology of apparent mineralocorticoid excess.

(b) Clinical implications

Understand the treatment of apparent mineralocorticoid excess.

Understand that familial early onset, severe hypertension deserves a thorough evaluation for endocrine disorders.
E. Catecholamines

1. Physiology

   a. Ontogeny/embryology

      Know the maturational pattern of the sympathoadrenal system

      Know that glucocorticoids are important for the development and function of the adrenal medulla

   b. Synthesis/processing/storage

      Know the biosynthetic and metabolic pathways of the catecholamines

      Know the sites of synthesis and storage of the catecholamines

   c. Secretion

      Understand the stimuli for catecholamine release

      Understand the reuptake and metabolism of catecholamines

   d. Transport

      Know that the catecholamines circulate either free or protein bound

      Understand the measurement of circulating catecholamines and their urinary metabolites

      Know the preferred assays for serum/plasma catecholamines

   e. Receptor/action

      Know the physiologic effects of catecholamines

      Know the different forms of the adrenergic receptor system and their mechanism of function

      Know the role of G-proteins and second messengers in catecholamine response

      Understand that physiologic catecholamine effects are rapid in onset and quickly terminated

      Understand the interrelationship between catecholamines and other hormones such as insulin, glucagon, renin, parathyroid, calcitonin, thyroxine, cortisol, and aldosterone
2. Pathology

a. Catecholamine deficiency

(1). Pathophysiology

Know that epinephrine secretion can be attenuated in diabetes mellitus

Know that cortisol deficiency can result in epinephrine deficiency

b. Catecholamine excess

(1). Pathophysiology

Know the syndromes and genetic disorders underlying excessive production of catecholamines and catecholamine metabolites

(2). Clinical implications

Know the clinical presentation of disorders associated with excessive production of catecholamines

Know the outcome of treatment of lesions associated with excessive production of catecholamines

Know the treatment of disorders associated with excessive production of catecholamines

Know the diagnostic evaluation of disorders associated with excessive production of catecholamines

c. Other

(1). Pathophysiology

(2). Clinical implications

V. Pituitary/Hypothalamus

A. Physiology

1. Ontogeny/Embryology

Know maturational patterns of individual hypothalamic/pituitary-target gland axes in the fetus

Know the embryologic derivation of all sections of the pituitary gland

Know the role of transcription factors in hypothalamic-pituitary development
2. **Synthesis/processing/storage**

Understand that LH, FSH, TSH, and hCG are heterodimers composed of a common alpha subunit and a hormone-specific beta subunit.

Know the general structure of pituitary and hypothalamic hormones including which are short peptides, which are proteins, and which are glycoproteins.

Understand the processing involved in transport to, storage of, and secretion of pituitary hormones from secretory vesicles.

3. **Secretion**

Understand the characteristics of diurnal neuroendocrine rhythm.

Understand the clinical and physiologic importance of pulsatile secretion of pituitary hormones.

Know the development pattern of circadian neuroendocrine rhythms.

Know the effects of insulin-induced hypoglycemia on anterior pituitary hormone secretion.

Understand the function of the hypothalamic-pituitary portal circulation in the regulation of pituitary hormones.

B. **Pathology**

1. **Hormone deficiencies**

   a. **Pathophysiology**

   Recognize association of hypopituitarism with midline facial defects and presence of a single central incisor.

   Recognize that CNS infections such as meningitis and encephalitis may be associated with temporary or permanent hypothalamic/pituitary dysfunction.

   Recognize the causes of acquired hypopituitarism.

   Understand the time- and dose-dependent effects of ionizing radiation on the function of the hypothalamus and pituitary.

   Recognize that autoimmune disorders may cause hypopituitarism.
Recognize possibility of progressive loss of or decrease in function of anterior pituitary

Know patterns of inheritance associated with multiple anterior pituitary hormone deficiencies

Understand the role of pituitary developmental genes in the genesis of multi-tropic pituitary hormone deficiencies

Understand the spectrum of anterior and posterior hormone deficiencies associated with holoprosencephaly

Understand the classification, histology, and etiology of different types of craniopharyngioma

b. **Clinical implications**

Recognize the physical signs associated with neonatal hypopituitarism

Recognize the metabolic abnormalities associated with neonatal hypopituitarism

Recognize clinical characteristics of patients with septo-optic dysplasia/optic nerve hypoplasia and the likelihood of resulting hypothalamic/pituitary dysfunction

Know the clinical features of patients who have various forms of Langerhans cell histiocytosis

Know appropriate therapeutic approaches to patients with Langerhans cell histiocytosis affecting the hypothalamus and the pituitary

Know types of CNS and pituitary neoplasms associated with hypopituitarism

Recognize characteristic behavioral patterns of children with either maternal deprivation or psychosocial dwarfism

Differentiate psychosocial dwarfism from other causes of short stature or failure to thrive

Differentiate hypothalamic from pituitary causes of sporadic multiple pituitary hormone deficiencies

Plan appropriate diagnostic studies and replacement therapies for sporadic multiple pituitary deficiencies dependent on age

Know the clinical signs, symptoms, and laboratory findings of children and adolescents with craniopharyngiomas

Recognize the endocrine signs and symptoms of obstructive hydro-
cephalus

Know the appropriate pre-, peri-, and postoperative endocrine management of patients with tumors of the pituitary and/or hypothalamic areas

Know the clinical characteristics and appropriate management of patients with an optic glioma

Know the common endocrine disorders associated with neurofibromatosis

Know the differential diagnoses of midline tumors in the hypothalamic/pituitary area such as germinomas and pineal tumors

Know how to manage the endocrine requirements of hypopituitary patients before, during, and after undergoing minor or major surgical procedures

Know how to manage the endocrine requirements of hypopituitary patients during minor and severe medical illnesses

Know the management and prognosis of children with hormone deficiencies secondary to hypopituitarism that can present with hypoinsulinemic hypoglycemia

Know the value of combined dynamic hormone testing in evaluating pituitary hormone deficiency

Know the value of neuroradiologic (MRI, CAT scan) imaging in evaluating pituitary hormone deficiency

2. Other

   a. Pathophysiology

      Know the physiologic basis for the regulation of thirst

      Understand the mechanisms of the regulation of urine osmolality

      Know the conditions responsible for pathologic loss of thirst

   b. Clinical implications (See also V.B.1.b.)

      Understand the typical neuroendocrine alterations in patients with anorexia nervosa at low body weight

      Know the usual neuroendocrine alterations in patients with psychosocial deprivation (dwarfism)

      Know the common endocrine side effects of drugs used
to treat major affective disorders

Know the typical neuroendocrine alterations in patients with severe weight loss

Know the value of combined dynamic hormone testing in evaluating pituitary hormone excess

Know the value of neuroradiologic (MRI, CAT scan, inferior petrosal sampling) imaging in evaluating pituitary hormone excess

C. Hormones

1. Growth hormone (GH)

   a. Physiology

      (1). Ontogeny/embryology (See V.A.1)

      (2). Synthesis/processing/storage (See also V.C.5.a.(2))

      Know number, function, and chromosomal proximity of GH genes

      (3). Secretion (See also V.A.3.)

      Know the effects of synthetic GHRH on GH secretion

      Know the effects of somatostatin and its analogues on the secretion of GH

      Understand the feedback effects of IGF-I on GH secretion

      Know the effects of stress on GH secretion

      Understand the physiologic effects of metabolic signals such as serum glucose on GH secretion

      Understand the physiologic effects of metabolic signals such as free fatty acids on GH secretion

      Understand the physiologic effects of metabolic signals such as selective amino acids on GH secretion

      Understand the pulsatile nature of GH secretion

      Understand the effects of sleep stages on GH secretion

      Know the effects of insulin-induced hypoglycemia on GH secretion

      Understand the clinical and physiologic importance of pulsatile secretion of GH
Know how neurotransmitters contribute to the regulation of GH

Know how neuromodulators contribute to the regulation of GH

Understand the mode of action of growth hormone-releasing peptides (GHRPs)

Recognize the differences in action of synthetic GHRH and GH-releasing peptides on GH release

Know the effects of GH administration on GH secretion

Understand the actions of galanin in the regulation of GH

Understand the actions of ghrelin in the regulation of GH

Understand that ghrelin is the natural ligand for receptors that recognize synthetic GH-releasing peptides

Know the effects of sex steroids on GH secretion

Understand how serum GH concentrations change with age

(4). Receptor/action

(a). Tissue/organ specific (See also V.A.5.a.)

Understand the structure and function of the GH receptor

Understand GH signal transduction mechanisms

Know the relationship between plasma GH binding protein concentrations and GH insensitivity syndrome

Understand the physiologic mechanisms involved in abnormalities of GH receptor structure, abundance, and function

Understand that deficiencies in nutrition and chronic illness can cause functional GH resistance

Understand that GH receptors belong to a large family of cytokine receptors and that there is cross-talk in their signaling

(b). Integrated hormone effects on metabolism

Know the effects of GH on immunologic and inflammatory responsiveness

Know the interactive effects of GH and sex steroids on linear growth rate
Understand the species- specificity of GH action

Know the metabolic actions of GH on carbohydrate and lipid metabolism

Know that GH actions on growth are mediated at least in part by the generation of IGF-I, both endocrine and paracrine

Know the direct and the indirect physiologic effects of GH

b. Pathology

(1). Hormone deficiencies (see VI.C.2.a.(3))

(a). Clinical implications

Know the mechanism of action of insulin-induced hypoglycemia during testing for GH secretory capacity

Know the effects and mechanism of action of 1-DOPA, clonidine, glucagon, propranolol, arginine hydrochloride during testing for GH secretory capacity

(2). Hormone excess (see VI.C.2.b.(1).(f))

(3). Other

(a). Pathophysiology

Know the chemical nature of GHRH and normal and pathologic sites of formation/secretion

(b). Clinical implications

2. Thyrotropin (TSH)

a. Physiology

(1). Ontogeny/embryology (See V.A.1.)

(2). Synthesis/processing/storage

(3). Secretion (See also V.A.3.)

Know the effects of thyrotropin-releasing hormone on the secretion of thyroid-stimulating hormone

Understand the relative roles of T4 and T3 in the regulation of thyroid-stimulating hormone secretion

Understand the physiologic and pathologic importance of T4 to T3 conversion by the anterior pituitary
Know the effects of somatostatin and somatostatin analogues on TSH secretion

Know how neurotransmitters contribute to the regulation of TSH

Understand the clinical and physiologic importance of pulsatile secretion of TSH

(4). Transport

(5). Receptor/action (See also V.A.5.a.)

(a). Tissue/organ specific (See also V.A.5.a.)

Know the physiologic effects of TSH

(b). Integrated hormone effects on metabolism

b. Pathology

3. Corticotropin (ACTH)

a. Physiology

(1). Ontogeny/embryology (See V.A.1.)

(2). Synthesis/processing/storage

Know the pathophysiology of Nelson syndrome

Understand the physiology of ACTH production and its relationship to other polypeptides encoded by the proopiomelanocortin gene

(3). Secretion (See also V.A.3.)

Know the effects of synthetic CRH on ACTH and cortisol secretion

Know the effects of glucocorticoids on CRH secretion

Know the effects of glucocorticoids on proopiomelanocortin synthesis and subsequent cleavage into ACTH, beta-lipotropin, endorphins, and related peptides

Know how neurotransmitters and neuromodulators contribute to the regulation of ACTH

Understand the clinical and physiologic importance of pulsatile secretion of ACTH

Know the effects of stress on the function of the hypothalamic-pituitary
adrenal axis

Understand the effects of vasopressin on ACTH secretion

(4). Transport

(5). Receptor/action

(a). Tissue/organ specific (See also V.A.5.a.)

Know that ACTH binds to a G-protein-coupled membrane receptor which results in the activation of adenylate cyclase and increased synthesis of cyclic AMP

Know the role of ACTH in the regulation of cortisol synthesis

Know the physiologic effects of ACTH

Know that the ACTH receptor belongs to the melanocortin receptor family

(b). Integrated hormone effects on metabolism

Understand the response of the hypothalamic-pituitary adrenal axis to physical stress

Understand the response of the hypothalamic-pituitary adrenal axis to psychologic stress

Know the effects of glucocorticoids and ACTH on immune responsiveness

b. Pathology

(1). Hormone deficiencies

(a). Pathophysiology

(b). Clinical implication

Know the effects of thyroid hormone replacement on therapeutic replacement requirements for cortisol and vasopressin

4. Gonadotropins (FSH/LH)

a. Physiology

(1). Ontogeny/embryology (See also V.A.1.)

Know the relative roles of pituitary and placental gonadotropins in sexual differentiation
Know sex differences in fetal maturational patterns of hypothalamic-pituitary-gonadal axes

Understand the biphasic nature of the maturational pattern of the reproductive system

Know the age-dependent effects of synthetic GnRH on LH and FSH secretion

Know the serum gonadotropin responses to GnRH in normal children and children with disorders of puberty

Know the embryology of the hypothalamic GnRH nuclei as it relates to the migration from the olfactory plate

Know the genetic regulation of the GnRH neuronal migration

(2). Synthesis/processing/storage

Understand the effects of sex steroids on gonadotropin synthesis

Understand the effects of the inhibins/activins on gonadotropin synthesis and secretion

(3). Secretion (See also V.A.3.)

Know the effects of stress on the function of the reproductive system

Know the effects of sex steroids on pituitary responsiveness to synthetic GnRH

Understand the effects of changes in GnRH pulse amplitude and frequency on LH and FSH secretion

Know the feedback effects of the major sex steroids on gonadotropin secretion

Know how neurotransmitters contribute to the regulation of gonadotropins

Know how neuromodulators contribute to the regulation of gonadotropins

Know the developmental pattern of circadian rhythms of gonadotropins in early puberty

Understand the importance of the pulsatile nature of gonadotropin secretion

Understand the effect of follistatin on gonadotropin secretion
4. Transport

5. Receptor/action

(a). Tissue/organ specific (See also V.A.5.a. and VII.B.4.a.)

Understand the structure and function of the gonadotropin receptors.

Understand the signal transduction mechanism through which gonadotropins act.

Know the physiologic effects of gonadotropins.

(b). Integrated hormone effects on metabolism

b. Pathology (see VII.B.5)

(1). Hormone excess (See also VII.B.5.b.(2))

(2). Other

(a). Clinical implications (See VII.B.5.b.(2)(a))

5. Prolactin

a. Physiology

(1). Ontogeny/embryology (See V.A.1)

(2). Synthesis/processing/storage

Understand the chemical structure of PRL.

Know the structural homology among GH, human placental lactogen, and PRL.

Recognize that prolactin is produced in other tissues beside the pituitary.

(3). Secretion (See also V.A.3.)

Know the effects of thyrotropin-releasing hormone on the secretion of PRL.

Know the effects of somatostatin and its analogues on the secretion of PRL.

Know the effects of stress on PRL secretion.

Know the site(s) of action and effects of dopamine on PRL and TSH secretion.

Know the effects of synthetic TRH on PRL secretion.
Know the effects of sex steroids, especially estradiol, on PRL secretion

Know the effects of pregnancy on PRL secretion

Know how neuromodulators contribute to the regulation of prolactin

Understand the clinical and physiologic importance of prolactin

Know the changes of serum prolactin with age and pubertal development

(4). Transport

(5). Receptor/action

(a). Tissue/organ specific (See also V.A.5.a.)

Understand the structure and function of the prolactin receptor

Understand the prolactin signal transduction mechanism

Know the physiologic effects of prolactin

(b). Integrated hormone effects on metabolism

b. Pathology

(1). Hormone deficiencies

(a). Pathophysiology

(b). Clinical implications

(2). Hormone excess

(a). Pathophysiology

Know the association of a prolactinoma with other tumors in patients with MEN I

Know that serum prolactin concentrations may increase moderately with pituitary stalk interruption

(b). Clinical implications

Know the effects and clinical indications for therapy with bromocriptine

Recognize hyperprolactinemia as a possible cause of primary or secondary amenorrhea
Know the effects of severe primary hypothyroidism on PRL secretion

Know appropriate therapy for patients with a prolactinoma

Know the mechanism by which hyperprolactinemia causes gonadotropin deficiency

Understand the use of bromocriptine in the treatment of hyperprolactinemia

Know the effects of dopamine agonists and antagonists and other drugs on PRL secretion

Know the differences between prolactin-secreting tumors and increased prolactin from other causes

Know the role of surgery in the treatment of hyperprolactinemia

Know that hyperprolactinemia can cause delayed puberty

Know the possible treatments of hyperprolactinemia and their potential results

(3). Other

(a). Pathophysiology

(b). Clinical implications

Know the drugs and other substances that can cause galactorrhea

6. Vasopressin (antidiuretic hormone)

a. Physiology

(1). Ontogeny/embryology (See V.A.1.)

(2). Synthesis/processing/storage

Know the site(s) and mechanisms of synthesis of neurophysin I and II

Know the stimuli for the secretion of neurophysin I and II

Know the genetic and functional relationships between neurophysin II and vasopressin

(3). Secretion

Know the relative roles of blood volume and osmolality in the regulation of vasopressin secretion

Know the location and function of the carotid pressure and atrial volume sensors in vasopressin physiology
Know the regulation of vasopressin secretion

Know the drugs that stimulate and inhibit vasopressin secretion

(4). Transport

(5). Receptor/action

(a). Tissue/organ specific

Know the site and mechanism of action of arginine vasopressin

Know of the existence and function of V1 and V2 receptors

Know the differences between the structure and effects of synthetic analogues and vasopressin

Know the actions of aquaporin II in mediating vasopressin activity

(b). Integrated hormone effects on metabolism

b. Pathology

(1). Hormone deficiencies

(a). Pathophysiology

(b). Clinical implications (See also V.C.3.b.(1)(b))

Know the clinical usefulness of "water deprivation testing" and hypertonic saline administration in the evaluation of vasopressin secretion

Recognize signs and symptoms of vasopressin deficiency

Know inheritance patterns of vasopressin deficiency and vasopressin unresponsiveness

Know characteristic phases of posterior pituitary dysfunction after surgical manipulation of or trauma to the median eminence area or pituitary stalk

Understand appropriate diagnostic approach to patients with "idiopathic" acquired diabetes insipidus

Know consequences of under- or over treatment of diabetes insipidus

Know the effects of glucocorticoid replacement therapy on therapeutic replacement requirements for ADH deficiency

Understand that the diagnosis of diabetes insipidus can often be made based on serum and
urine osmolality without the need for a water deprivation test

Understand the treatment of vasopressin deficiency and vasopressin unresponsiveness

Understand that vasopressin deficiency can be associated with absent thirst mechanism

(2). **Hormone excess**

(a). **Pathophysiology**

(b). **Clinical implications**

Recognize clinical syndrome of inappropriate vasopressin secretion

Differentiate SIADH from other conditions that cause decreased serum osmolality

Understand appropriate therapeutic approaches to patients with SIADH

Understand appropriate fluid therapy for patients suspected of having SIADH

Recognize characteristic clinical and laboratory findings in patients with SIADH

Recognize clinical disorders associated with SIADH

Know appropriate treatment of SIADH

Be aware of drugs which may produce SIADH

Know the features of cerebral salt wasting

(3). **Other**

(a). **Pathophysiology**

(b). **Clinical implications**

Recognize signs and symptoms of unresponsiveness to vasopressin

Know how to distinguish diabetes insipidus, nephrogenic diabetes insipidus, and compulsive water drinking

Know the clinical characteristics of ADH unresponsiveness syndromes

Recognize drugs which may induce resistance to vasopressin

7. **Oxytocin**

Know physiologic effects of oxytocin

Understand role of oxytocin in lactation
VI. Growth

A. Auxology

1. Standards

   Know the origin of commonly used growth charts and their limitations

   Know the relationship of age to upper/lower segment ratio and to arm span

2. Measurements

   Know proper technique and variances of linear measurements

   Know proper techniques and variances of body composition

   Know the normal regional distribution of body fat with age

3. Normal patterns of growth

   Know the endocrine basis for the adolescent growth spurt

   Know that genetic tall stature and familial early maturation are physiological causes of tall stature in childhood

   Know the criteria used to distinguish physiological variants of tall stature from pathologic tall stature in childhood

   Know the normal growth rates during fetal life, infancy, childhood, and adolescence

   Know that physical factors such as twinning and maternal size are important factors controlling fetal growth

   Know the ages at which growth ceases in boys and girls

   Know how to utilize longitudinal growth data to distinguish between physiological and pathological patterns of growth

   Know the criteria used to distinguish normal variants of short stature from pathologic short stature in childhood

   Know how to calculate target adult height

   Know the effects of maternal illness and smoking on fetal growth

4. Skeletal age

   Understand the concept of skeletal age and the nutritional, hormonal and genetic factors that influence it
Know the procedures and limitations of adult height prediction

Know the effect of under- and over-nutrition on skeletal age

Know the effect of sex steroid hormones on skeletal age

Understand the concept of skeletal age and how it relates to physical maturation and adult height

Know the different methods utilized to determine skeletal age

5. **Dental development**

Know the factors that influence the timing of dental eruption

Know the normal sequence and ages of dental eruption and loss

B. **Determinants and regulation of normal growth**

1. **Genetic influences**

Describe familial influences on prenatal and postnatal growth patterns

2. **Nutritional influences**

Know how variations in nutritional practices affect growth

Know that overfeeding accelerates linear growth in infancy and childhood

3. **Classic hormones**

   a. **GH (see V.C.1.a(3))**

   b. **Thyroid hormones**

   Know linear and weight growth patterns that are suggestive of hypothyroidism or hyperthyroidism

   c. **Sex steroids**

   Know the hormonal factors controlling pubertal growth and the relationship between peak growth velocity and the stages of pubertal development

   Know the effects of sex steroids on linear growth, body composition, and bone maturation

   Know the clinical manifestations of estrogen deficiency with respect to growth in adolescent girls
d. Insulin

Know the effects of excessive serum insulin concentrations on fetal growth

4. Growth factors

Understand the structural homologies among peptide growth factors

Be familiar with the principal growth factor superfamilies and their members

a. Insulin-like growth factors and binding proteins

(1). Somatomedin hypothesis

(2). Structure, regulation, and function

Know that IGF-I is the name given to the 70-amino acid, single chain, basic peptide

Know that the production of IGF-I is under the control of GH as well as other factors such as nutrition, sex steroids, chronic disease

Know that IGF-I possesses insulin-like properties and that it stimulates sulfate uptake, DNA synthesis, RNA synthesis and protein synthesis

Know that IGF-I is produced in multiple tissues and stimulates tissue growth by endocrine, paracrine, and autocrine modes of action

Understand the role of growth factors IGF-I and IGF-II in normal growth

Know the structure of receptors for IGF-I and IGF-II

Know that IGF-I exerts anti-apoptotic effects

Know that there is positive correlation between serum IGF-I levels and certain malignancies

(3). Factors affecting serum concentrations and their measurement

Understand the clinical usefulness and limitations of total serum IGF-I determinations

Know the age-dependent changes in the serum concentrations of IGF-I and IGF-II

Know the effects of GH on IGF-II

Know that cord IGF-I concentrations (although low) correlate with birth weight

Know that girls have a higher and earlier mid-pubertal peak in plasma IGF-I concentrations than boys

Recognize that fasting and/or malnutrition will decrease plasma IGF-I concentrations
Recognize that hypothyroidism will lower plasma IGF-I concentrations

Recognize the dose and route dependency of estrogen administration on IGF –I concentrations

Understand the relationship between levels of IGF-I and peak height velocity

Know the effects of obesity on GH and insulin-like growth factors

(4). **Binding proteins**

Recognize that serum IGF-I and IGF-II are associated with carrier proteins

Know that the large molecular weight circulating complex of IGF-I is GH dependent

Know that IGF-I concentrations are relatively stable throughout a 24-hour period

Know that the major normal circulating form of IGF-I and IGF-II is a three subunit 150 kD complex of IGF peptide, IGFBP-3, and an acid labile subunit

Understand the functional characteristics of the IGFBPs

Know the factors that regulate IGFBP -1, -2, -3, -4, -5, and -6, physiologically

Know the structural and functional relationship of the IGFBP and related binding proteins to the IGFBP family

Know that IGFBPs have IGF-independent effects

**b. Other growth factors**

Know that epidermal growth factor is a potent mitogen for ectodermal and mesodermal cells and tissues

(1). **Fibroblast growth factor**

Know the disorders due to fibroblast growth factor receptor mutations

Know the effects of inflammation on IL-1, IL-6, and TNF-alpha

(2). **Erythropoietin**

Recognize that erythropoietin production is stimulated by hypoxia, androgens, GH

(3). **Oncogenes**

Know the relationship of oncogenes to growth factors and growth factor receptors

Understand the basic mechanisms that underlie neoplastic transformation
Know that oncogenes have roles in both normal and pathologic states

C. Disorders of growth

1. Fetal

Know the causes and clinical features of intrauterine growth retardation

Know the proportion of small for gestational age children that remain short

Know the relationship between first year growth rate and subsequent stature in patients with intrauterine growth retardation

Know the risks associated with intrauterine growth restriction, such as type 2 diabetes in later life

Know the effect of deficiencies of IGF secretion or action on fetal growth

Understand the role of IGF-II action in disorders of fetal growth

Differentiate the fetal alcohol syndrome from other causes of IUGR

Know the association of intrauterine growth retardation and premature pubarche

Know the association of intrauterine growth retardation and metabolic syndrome (insulin resistance syndrome)

Know the genes responsible for pancreatic ontogenesis

a. Russell-Silver syndrome

Know the clinical features of Russell-Silver syndrome

Know the causes of Russell-Silver syndrome

b. Perinatal insulin deficiency

Know the intrauterine and postnatal growth pattern of infants with congenital diabetes

2. Postnatal

a. Growth failure

Know the genetic abnormalities and clinical features of in Noonan syndrome

(1). Intrinsic defects of growing tissues

(a). Skeletal dysplasias and chondrodystrophies

Know how to recognize and diagnose the skeletal dysplasias
(b). Genetic syndromes (Turner syndrome, Prader-Willi syndrome)

Know the expected growth pattern of untreated Turner syndrome

Know the relationship of karyotype to clinical features in Turner syndrome

Know the clinical features of Prader-Willi syndrome

Know the inheritance of Prader-Willi syndrome and the appropriate tests that establish the diagnosis

Know that short stature in Turner syndrome is due, at least in part, to SHOX haploinsufficiency

Be able to recognize the somatic phenotype of pseudo hypoparathyroidism

Recognize the physical findings characteristic of Turner syndrome

Know the clinical features and causes of dyschondrosteosis (Leri-Weill syndrome)

Know the effects and adverse events of GH therapy in Prader Willi syndrome

(2). Abnormalities in environment of growing tissues

Know the effects of general metabolic abnormalities (eg, hypoxia, acidosis) on growth

Know the effect of specific metabolic disorders (eg, cystinosis) on growth

Know the effect of chronic renal insufficiency on metabolism, including growth

Know the effects of various medications on linear growth in children (eg, inhaled corticosteroids, stimulants, etc)

Know the effects of chronic systemic illness and their therapies on linear growth and body composition

(a). Nutrient insufficiency

Know the impact of suboptimal nutrition on growth

Know the effects of protein/calorie malnutrition on the GH-IGF-IGFBP axis

Be able to recognize and diagnose the gastroenterologic/nutritional disorders that may present as growth failure

(3). Disease of endocrine system

(a). GH deficiency
Know the side effects of 1-DOPA, clonidine, glucagon, propranolol, arginine hydrochloride, and synthetic GHRH during testing for GH secretory capacity

Know the clinical characteristics and growth patterns of children with isolated GH deficiency and multiple pituitary hormone deficiencies

Recognize possible hormonal causes for a poor response to appropriate GH replacement therapy

Know that the single central incisor and cleft lip and palate are associated with GH deficiency

Know the laboratory tests used to diagnose GH deficiency and their limitations

Know the conditions, diseases, and treatments that produce GH deficiency

Understand the appropriate use of GH in treatment for GH deficiency

(b). **Hypercortisolism**

Be able to recognize growth failure due to hypercortisolism

Understand the mechanism of growth suppression by glucocorticoid excess

(c). **GH-resistant syndromes (See also V.C.1.b.(3)(b))**

Know the clinical characteristics and inheritance patterns of GH unresponsiveness syndromes

Know that the lack of functional GH receptors in Laron syndrome (GH insensitivity syndrome) is often but not always reflected in a decrease in GH binding protein

Know the clinical features and molecular basis of growth hormone insensitivity syndrome

Know that IGF-I can be used to treat children with GH insensitivity and GH gene defects

b. **Overgrowth**

(1). **Syndromes/metabolic disease/hormonal**

(a). **Klinefelter syndrome**

Know that disproportionately long legs (but not long arms) may be present prior to puberty in Klinefelter syndrome

Know the clinical features of Klinefelter syndrome

(b). **Marfan syndrome**

Know the clinical features of Marfan syndrome
Know the methods used to diagnose Marfan syndrome

Know the pros and cons of using sex hormones and somatostatin analogues to prevent excessive tall stature

Know the prognosis of Marfan syndrome

Know that the fibrillin gene is defective in Marfan syndrome

** (c). Homocystinuria

Recognize that homocystinuria can be distinguished from Marfan syndrome by the presence of homocystinuria due to cystathionine synthase deficiency, mental retardation (present in 50% of patients), fine sparse hair and thromboembolic phenomena

Know that tall stature, arachnodactyly, and ectopia lentis are features of Marfan syndrome and homocystinuria

** (d). Cerebral gigantism (Sotos syndrome)

Know the clinical features of Sotos syndrome

Know that serum GH and IGF-I concentrations are normal in Sotos syndrome

Recognize the genetic factors in Sotos syndrome

** (e). Weaver syndrome

Know that tall stature occurs in Weaver syndrome

** (f). Acromegaly/gigantism

Recognize clinical disorders which result from excessive secretion of GHRH

Understand the clinical usefulness of long acting analogues of somatostatin

Differentiate pituitary gigantism from cerebral gigantism (Sotos syndrome)

Know appropriate diagnostic and therapeutic approach to patients with suspected gigantism

Recognize hypothalamic and pituitary causes of GH oversecretion

Know that IGF-I and IGFBP-3 are increased in acromegaly/gigantism

Differentiate acromegaly from other overgrowth syndromes

Know that GH excess can be associated with McCune-Albright syndrome

Recognize the metabolic effects of GH excess
Know the side effects of the therapies for GH excess

Know the therapeutic modalities used to treat GH excess (surgery, irradiation, somatostatin analogs, GH antagonists)

Know the methods that are useful in assessing the response to therapy for GH excess

Understand the process to diagnose GH excess

3. Evaluation and diagnosis

a. Clinical evaluation

Know the criteria which identify the child with short stature due to intrinsic or genetic factors

Know the criteria which identify the child with constitutional growth delay

Know the criteria which distinguish the child with pathologic growth failure from physiological variants of growth

Know the significance of previous growth measurements, and how to use growth velocity charts, mid-parental height, and target vs. predicted heights

Know how to obtain and evaluate a dietary history for qualitative and/or quantitative nutritional deficiencies

Know when it is appropriate to observe (rather than treat) children with short stature

b. Laboratory evaluation

Know that a low plasma IGF-I level in a growth retarded child is consistent with but not diagnostic of GH deficiency

Be able to select appropriate diagnostic studies to identify the cause of short stature

Know the effects of GH deficiency on IGF-I, IGF-II, and specific binding proteins

Understand the role of magnetic resonance imaging in the evaluation of possible pituitary hormone deficiencies

D. Therapies to alter growth and stature

Understand the need for reassurance in the child with intrinsic short stature or constitutional delay in growth

Know the appropriate therapy for the short child with psychosocial stress

Know the appropriate therapy for the short child with vitamin-mineral abnormalities

1. GH
Understand the appropriate use of GH in the treatment of disorders including short stature, such as Turner syndrome, Prader-Willi syndrome, SGA, and renal failure

Understand the issues surrounding use of GH in treatment in children with idiopathic short stature

Know the adverse effects of GH therapy (early and late)

2. **Sex steroid manipulations**

   a. **Androgens**

      Know the pros and cons of using hormonal therapy in a child with constitutional delay in growth

      Know the forms and appropriate dosages of androgens for treatment of constitutional delay of growth

   b. **Low dose estrogens**

      Know the effects of low dose estrogen on growth, bone maturation, feminization, and lipid carbohydrate metabolism in girls with CDGP and Turner syndrome

   c. **Delaying puberty**

      Know the effects of pubertal delay on growth, adult height, and skeletal maturation

      Understand the use of GnRH analogs and aromatase inhibitors to delay puberty

   d. **Estrogen/androgen therapy for tall stature**

      Know the appropriate therapy and indications for hormonal treatment for familial tall stature

      Understand the controversy regarding the use of estrogen therapy in girls with tall stature

E. **Obesity**

Know that successful therapy depends on behavior modification leading to diminished food intake and increased activity

Be familiar with inherited patterns of obesity

Be familiar with the factors thought to be involved in the development of exogenous obesity such as the role of decreased activity level

Know the characteristic growth pattern and body composition of obese children

Know the efficacy of drugs used to treat obesity
Know the side-effect profiles and hazards of drug treatment of obesity

Know when drug treatment of obesity is indicated for children

Be familiar with the single gene causes of obesity

Know the efficacy of diet and exercise to treat obesity in children and adolescents

Know the indications for the surgical treatment of obesity in children and adolescents

1. Specific obesity syndromes
   a. Due to endocrine disease
      Know the endocrine disorders that lead to obesity
      Know the clinical and laboratory methods used to distinguish exogenous from endocrine obesity
   b. Due to hypothalamic disease
      Know the nuclei and areas of the hypothalamus involved with appetite control
      Know the growth pattern in obesity caused by hypothalamic tumors and their treatment
   c. Syndromes
      Be familiar with syndromes of which obesity is part such as Prader-Willi and Bardet-Biedel
      Know the genetics of Prader-Willi syndrome and its relationship to Angelman syndrome
      Know the karyotypic abnormalities found in Prader-Willi syndrome

2. Consequences of obesity
   Know the effect of obesity on the timing of puberty
   Know the effect of obesity on cortisol secretion and measures to assess adrenocortical status
   Know that obesity increases the risk for the development of hypertension
   Know the risk of patients with obesity for the development of diabetes mellitus
   Know the risk of patients with obesity for the development of sleep apnea and pulmonary hypertension
   Be able to recognize the symptoms and signs of pulmonary complications in an obese adolescent
Know that obesity in children is a risk factor for metabolic-insulin resistance syndrome

Know that obesity increases the risk of Blount disease and of slipped capital femoral epiphyses

Know that obesity increases the risk of pseudotumor cerebri

Know that obesity increases the risk of cholelithiasis

Know that adolescent obesity increases the risk of adult obesity

Know that childhood obesity increases the risk of premature death in adulthood

Know that obesity increases the risk of non-alcoholic steatohepatitis (non-alcoholic fatty liver disease)

### 3. Central nervous system regulators of appetite and metabolism

#### a. Leptin

Know the physiologic effects of leptin

Know that leptin suppresses appetite

Know the principle sites of leptin synthesis

Understand the role of leptin in the control of pubertal onset in boys and girls

Understand the role of the regional distribution of body fat on serum leptin concentration

#### b. Other hormones

##### (1). Neuropeptide Y

Know the physiologic function of neuropeptide Y (NPY)

Know that neuropeptide Y is produced in the pancreatic islets

Know that neuropeptide Y inhibits glucose-stimulated insulin secretion

Know that neuropeptide Y is strongly orexigenic

##### (2). Ghrelin

Know the physiologic function of ghrelin

Know that ghrelin is produced in the CNS, stomach, colon, and small intestine

Know that ghrelin is orexigenic

Know that ghrelin stimulates the hypothalamus to direct an increase in energy production
Know that ghrelin levels are several fold higher in children with Prader-Willi syndrome than in other children with similar BMIs.

(3).  Melanocortin

Know the roles of melanocortin and its receptors in appetite control.

Know the role of melanocortin receptor mutations in the pathogenesis of severe obesity.

F.  Eating disorders

1.  Anorexia nervosa

Recognize that anorexia nervosa is considered to be primarily a psychiatric disease with serious endocrine and metabolic consequences and approximately 15% mortality.

Know the primary clinical features of anorexia nervosa.

Know the endocrine changes caused by anorexia nervosa.

Know the sequence of endocrine changes that result from weight regain in anorexia nervosa.

Know that treatment of anorexia nervosa is primarily psychologic counseling and behavioral modification coupled with nutritional rehabilitation.

Know the appropriate initial therapy of anorexia nervosa.

Know the appropriate therapy of the decreased bone mineral concentration associated with anorexia nervosa.

Know that anorexia nervosa occurs in males.

Know that ballet dancers, wrestlers, and long distance runners are at increased risk for eating disorders.

Know the components, diagnostic criteria, and treatment of the female athlete triad.

2.  Bulimia Nervosa

Be familiar with the pathophysiology of bulimia and the effects of laxatives and diuretics in these patients.

Know that bulimia nervosa is commonly associated with impaired growth and undermineralization of bone in adolescents.

VII.  Reproductive Endocrine System

A.  Hypothalamus-pituitary
1. Ontogeny/embryology
   a. General (See V.C.4.a.(1))
   b. Hormonal (See V.A.1. and V.C.4.a.(1))
2. Gonadotropin synthesis/biochemistry (See V.A.2. and V.C.4.a.(2))
3. Gonadotropin secretion (See V.A.3. and V.C.4.a.(3))
4. Gonadotropin action (See V.C.4.a.(5)(a))

B. Gonadal function and disorders

1. Development and differentiation of the reproductive system
   a. General
      
      Know the events associated with development of an embryo, including the contribution of the three germ layers
      
      Understand the mechanism and genetic regulation of the differentiation and growth of external genitalia in the fetus including the tissues of origin
      
      Understand the relative functions and time of action of LH and hCG in fetal sexual differentiation
      
      Know that the yolk sac endoderm is the source of primordial germ cells
      
      Know the role(s) of key genes on the X and Y chromosomes for gonadal differentiation
      
      Know the gene maps of the X and Y chromosomes and relationships between genes on the respective chromosome
      
      Understand X chromosome inactivation
      
      Understand that germ cells migrate to the urogenital ridge to form the undifferentiated gonad
   b. Gonads
      
      Know the common derivation of the cell types of the testes and ovaries

   (1). Ovaries
      
      Know the relationship of egg meiotic phases to ovulation and the developmental stages at which the phases are reached
      
      Know that two X-chromosomes are necessary for maintenance of primordial follicle
Know the changes in the number, size, and composition of ovarian follicles with age

Know the hormonal determinants of antral follicle formation and follicular growth

Know the cell types in the ovary and the hormones they secrete

Know the hormonal determinants of ovulation

(2). Testes

Know the determinants of spermatogenesis and the developmental stages at which various phases are reached

Know the cell types in the testes and the hormones they secrete

Know the hormonal regulation of Leydig cell steroidogenesis and the rate limiting steps

Know the steps of testicular differentiation and the developmental ages at which they are reached

(a). Cryptorchidism

Know the various etiologic factors in cryptorchidism

Know the incidence of cryptorchidism at different ages and related conditions

Know the pros and cons of chorionic gonadotropin or gonadotropin analog treatment of cryptorchidism and the age at which it may be indicated

Know the pros and cons of surgical treatment of cryptorchidism and the age at which it is indicated

Know the roles of testosterone and INSL3 in the process of testicular descent

Know the role of measuring testicular products in the diagnosis of cryptorchidism versus anorchia

Know that the contralateral testis in a patient with an undescended testis might itself be abnormal

Recognize how compensatory hypertrophy in a testis relates to the function of the other testis

Know that fertility may be affected in unilateral cryptorchidism

Know that cryptorchidism may lead to testicular carcinoma, the relative incidence of such carcinoma, and recommend monitoring

c. Genital tract: differentiation and development
(1). Müllerian ducts

(a). Embryonic differentiation

Know that anti-Müllerian hormone is a member of the TGF-beta superfamily and that it is secreted by sertoli cells

Know that the Müllerian duct differentiates to the uterus, fallopian tubes, and upper vagina

Understand the paracrine actions of anti-Müllerian hormone during male reproductive development and the time at which it occurs

(2). Wolffian ducts

(a). Embryonic differentiation

Know the paracrine role of testosterone in normal and abnormal Wolffian duct differentiation

Know that the Wolffian ducts differentiate into the rete testis, efferent ducts, epididymis, vas deferens, and seminal vesicle

(b). Pubertal development

Know the role of testosterone and dihydrotestosterone in pubertal development of the Wolffian derivatives

d. External genitalia

Know the embryonic precursors of the male and female external genitalia and the mechanism and timing of their differentiation

Know the role of dihydrotestosterone in the differentiation of male external genitalia

e. Secondary sexual organs

(1). Breasts

(a). Embryonic differentiation

(b). Pubertal development

Know the role of hormones in the development of breasts and in lactation

(2). Pilosebaceous unit

Know the effects of androgens on the pilosebaceous unit on the scalp versus in the pubic and axillary area
2. Gonadal hormone synthesis, secretion, transport, metabolism, action

a. Steroid hormones

(1). Biosynthesis

Understand the physiologic and clinical importance of free (unbound) sex steroid hormone concentrations

Know the genes and biosynthetic pathways contributing to testosterone and DHT production

Know the genes and biosynthetic pathways contributing to estrogen production

(2). Specific steroids

(a). Testosterone (See also V.C.4.a.(3))

Know the organs that produce testosterone in men and women and the relative proportion secreted by each organ

Know the relative roles of secretion and peripheral metabolism in the production of testosterone in men and women

Know the relative bioavailability of the plasma free, albumin-bound, and SHBG-bound fractions of plasma testosterone

Know the factors regulating SHBG synthesis and serum concentration

Know the metabolic fates of testosterone

Know the intracellular signaling pathway of androgens within target cells

Know the characteristics of anti-androgens and their potential uses

Know the structure and function of the androgen receptor and the steroids to which they respond

Know patterns of fetal concentrations of estrogens, progestins, androgens, and gonadotropins

(b). Estradiol (See also V.C.4.a.(3))

Understand the sex steroid profile of the normal menstrual cycle

Know the organs that secrete estradiol in males and females and the relative proportion secreted by each organ
Know the role of secretion relative to peripheral metabolism in production of estradiol in men and women

Know the relative bioavailability of the plasma free, albumin-bound, and SHBG-bound fraction of plasma estradiol

Know the metabolic fate of estradiol

Know the intracellular signaling pathway of estrogen action within target cells

Know the characteristics of anti-estrogens and their potential uses

Know the characteristics and potential uses of SERMs

**Progestins (See also V.C.4.a.(3))**

Know the relationship of progesterone secretion to granulosa cell luteinization

Understand the mechanism of action of progesterone in target cells

Know the cells of origin of progesterone in testes and ovaries

Understand the synthesis of progesterone

Recognize the effects of progestins on fluid and electrolyte balance

Know the relative androgenicity of the synthetic progestins used in oral contraceptives

**Androstenedione**

Know the secretion of androstenedione relative to testosterone by the interstitial cells of ovaries and testes

Know the relative contribution of the peripheral metabolism of androstenedione to the synthesis of testosterone and estrone

**17-hydroxyprogesterone**

Know the cells of origin of 17-hydroxyprogesterone in testes and ovaries

**Peptide hormones**

**Anti-Mullerian hormone**
Know the cells that synthesize anti-Mullerian hormone

Know the control of anti-Mullerian hormone and changes in concentration throughout development

Know the actions of anti-Mullerian hormone

(2). Inhibin/activin

Know the cells of origin of inhibin/activin

Know the control of inhibin/activin secretion and changes in concentration throughout development

Know the actions of inhibin/activin on the pituitary and gonads

Know the cell of origin of follistatin

Know the control of follistatin secretion

Know the actions of follistatin on the pituitary

(3). Testis determining gene

Know the locus of the SRY gene and its role in testis determination

Know that the SRY gene might be deleted or translocated to another chromosome and the results of such changes

Know that SRY is a high mobility group gene and how it functions

3. Abnormalities of sexual differentiation and development

a. Gonadal dysgenetic abnormalities

(1). Turner syndrome

(a). Incidence

Know the incidence of Turner syndrome in conceptuses and in live born children

(b). Chromosomal etiology

Know that genetic determinants for stature and ovarian development on the X-chromosome

Compare the genetic etiology of Turner syndrome to that of Noonan syndrome
Know the different karyotypes that can lead to Turner syndrome and the resulting clinical features

Know the risk of malignant degeneration of gonads in patients with gonadal dysgenesis and Y chromosomal material and the methods of identifying Y material

Know the pattern of gonadotropin secretion in gonadal dysgenesis as a function of age in girls and the reason that it differs from a normal girl

(c). Phenotypic features

Know the time course of changes in ovarian morphology in the development of ovarian failure, including the decline in ovum at various stages

Know the typical linear growth pattern of children with Turner syndrome in the fetus and after birth

Know the congenital cardiovascular abnormalities of girls with Turner syndrome and contrast them with Noonan syndrome

Know the increased incidence of autoimmune thyroiditis, celiac disease, and type 1 diabetes in children with Turner syndrome

Recognize the changes in the skeleton, including limb and vertebral abnormalities, in Turner syndrome that can be observed on x-ray studies

Know that Madelung deformity of the wrist occurs in some individuals with Turner syndrome

Know the alterations in bone density of girls who have Turner syndrome

Recognize the cytogenetic findings that are associated with cognitive impairment in girls with Turner syndrome

Understand the behavior and psychologic problems that can be present in girls with Turner syndrome

(d). Differential diagnosis

Distinguish other similar syndromes from Turner syndrome including XX gonadal dysgenesis, noting particular features

(e). Management

Know the pros and cons of estrogen therapy with different estrogen preparations in Turner syndrome including relative dosage and
age of initiation of therapy

Know the outcome of growth hormone, estrogen and androgen therapy for Turner syndrome on metabolic changes and physical development

(2). **Klinefelter syndrome**

Know the incidence of Klinefelter syndrome is about 1:600 males

Know the chromosomal etiology of Klinefelter syndrome

Know the associated physical anomalies in Klinefelter syndrome

Know the differential diagnosis of Klinefelter syndrome

Know the pros and cons of treatment of Klinefelter syndrome with testosterone, including relative dosage and age of initiation of therapy

Know the behavioral abnormalities found in males with Klinefelter syndrome

Know the clinical distinction among males with the XXY, XYY, XXYY, and XXXXY karyotypes

Know that individuals with Klinefelter syndrome are at increased risk for germ cell tumors, what types, and where they are located

Know the effects on cognitive and language function of Klinefelter syndrome

Know the relative risk of breast cancer is increased in individuals with Klinefelter syndrome

b. **Genital tract inappropriate development**

(1). **Disorders of Sex Development**

Know the principles underlying sex assignment in individuals with genital ambiguity

Recognize the relative risks for malignancy in different disorders of gonadal development

Know the general classification and nomenclature for DSD

(a). **Ovotesticular DSD**

Know the definition and frequency of ovotesticular DSD

Know the clinical features and the genetic mechanisms of ovotesticular DSD
Plan appropriate management for a patient with ovotesticular DSD

(b) **Sex Chromosome DSD**

(c) **Turner syndrome and variants (see above)**

(d) **Klinefelter syndrome and variants (see above)**

(e) **Mixed gonadal dysgenesis**

Know the karyotype in mixed gonadal dysgenesis

Know the clinical features of mixed gonadal dysgenesis

Know the clinical management of mixed gonadal dysgenesis

Know the risk of malignant degeneration of the gonad in mixed gonadal dysgenesis.

(f) **46,XY DSD (See also V.C.4.b.(3)(a))**

Recognize clinical presentations of patients with 46,XY DSD

Understand the correlation between the genital phenotype and the timing of inadequate androgen secretion or action during sex differentiation

Know the different syndromes resulting from embryonic or fetal testicular dysgenesis at various times between 8 to 40 weeks gestation

Know the differences between partial gonadal dysgenesis and XY gonadal dysgenesis

Understand how to recognize and diagnose the genetic defects in testosterone and dihydrotestosterone synthesis

Differentiate the clinical features of androgen receptor defects from 5 alpha-reductase deficiency

Know the phenotypic variability in patients with androgen insensitivity (CAIS and PAIS), their presentation at different ages, and appropriate management

Know the pathogenesis and clinical features of LH receptor defects

Know the heredity of testicular enzyme defects, androgen insensitivity, and 5 alpha-reductase deficiency

Know the risks of malignancies in dysgenetic testes and in 46,XY DSD
Understand the effects of untreated testosterone biosynthetic
defects, androgen insensitivity syndromes, and 5 alpha-reductase
deficiency on pubertal sexual development

(c). 46,XX DSD

Know the definition of 46,XX DSD and its frequency

Know the causes, clinical features, and management of testicular 46,XX DSD (SRY translocation, SOX9 duplication, etc), gonadal dysgenesis, and 46,XX ovotesticular DSD

Know how to distinguish virilizing congenital adrenal hyperplasia as a cause of virilization from placental aromatase deficiency and maternal causes (luteoma, exogenous androgens)

Know how to distinguish among the causes of 46,XX DSD

Know the types of hormones and medications ingested by the mother that might cause fetal virilization

(2). Other genital deformations and malformations

(a). General

Be aware of disorders of embryonic development that result in genital abnormalities

(b). Penile aplasia

Know the etiology of penile aplasia

Know the characteristics of genital dysmorphology that indicate a non-endocrine cause of penile aplasia

Know the factors important in gender assignment in patients with penile aplasia

(c). Müllerian aplasia

Know the role of diethylstilbestrol in abnormal Müllerian epithelium development in subsequent generations

Know the etiology of Müllerian aplasia

Distinguish Müllerian aplasia from complete androgen insensitivity syndrome

(3). Micropenis

(a). Etiology
Know that micropenis may result from hypopituitarism or primary defects in testosterone secretion or action

Recognize that micropenis may be associated with other hormonal deficiencies resulting in hypoglycemia and nystagmus

Know the definition of micropenis for term and preterm infants

Recognize that micropenis may be the only phenotypic feature of pituitary dysfunction

(b). Differential diagnosis

Know the conditions that might mistakenly be diagnosed as micropenis

(c). Management

Know the effect of various types of androgen treatment in infancy on micropenis later in life

4. Normal sexual maturation

a. General

Know normal age ranges for acquisition of secondary sexual characteristics in the USA

Recognize that the timing and sequence of pubertal changes may differ among different ethnic groups and in different countries

b. Physical stages

(1). Tanner stages

(a). Breasts

Know the criteria for Tanner stages 1-5 breast development

Know the approximate ages for Tanner stages 2-5 of breast development and the average duration of each stage

Know the relationship between Tanner stages of breast development and menarche

(b). Pubic hair

Know that adrenarche is characterized by increases in adrenal androgens, the type of androgens, and the appearance of androgenic effects

Know the criteria for Tanner stages 1-5 pubic hair growth
Know the approximate ages for Tanner stages 2-5 of pubic hair development and the expected relationship to breast development

(c). Male genital development

Know the criteria for Tanner genital stages 1-5

Know the approximate age and duration of progression from Tanner stages 2-5

Know the lower limit of normal phallic length at each stage of pubertal development

Recognize the features of fragile X syndrome and how to diagnose the syndrome

Recognize that enlarged testes of patients with untreated CAH or Cushing syndrome may be due to adrenal rests

(2). Menarche/spermarche

Know the average chronologic and bone ages for menarche and the relationship to early and late puberty

Know the average chronologic and bone ages for spermarche and the relationship to early and late puberty

Know the hormonal correlates of spermarche in the adolescent male

(3). Relation to pubertal peak height velocity (see VI.A.3.c)

c. Hormonal levels underlying pubertal stages

Know the age and Tanner stage-associated changes in ovarian and testicular steroid and pituitary hormone secretion

Understand the use of ultrasensitive gonadotropin assays in the diagnosis of abnormalities of puberty

(1). Prepubertal children

(a). Infancy

Know the normal hormone changes and timing of the "minipuberty" of male and female infants

Know how to differentiate abnormal hormone changes from those of the normal "minipuberty" of male and female infants

Know the concentrations of sex steroids and gonadotropins in
the newborn (full-term and preterm) and the changes in concentrations during the first days after birth

(b). Midchildhood

Know how midchildhood hormone levels during the juvenile pause compare to those of younger children

Know how midchildhood hormone levels during the juvenile pause compare to those of older children

(2). Pubertal children

Know how the sex hormone profile differs by gender, age, and stage of pubertal development

Know the sequence of hormonal events which normally occurs before puberty becomes clinically evident

d. Hypothalamic-pituitary-gonadal axis

(1). Changes in activity (See V.A.1. and V.C.4.a.(1))

e. Normal menstrual cycle (See also V.C.4.a.(3))

(1). Relation of hormones to menses and ovulation

Relate the normal female cyclic hormone values to the changes in ovarian follicular maturation during the menstrual cycle

Know the relationships of the patterns of estradiol and progesterone to one another during the normal female menstrual cycle relative to menstruation and ovulation

Know the relationships of the patterns of progesterone and androgens during the normal female menstrual cycle relative to menstruation and ovulation

Know the relationships of the patterns of LH and FSH during the normal female menstrual cycle relative to menstruation and ovulation

Know the relationship between the duration of adolescent anovulation and the prognosis for normal fertility including the possibility of polycystic ovarian syndrome

(2). Uterine endometrial cycle

Know the hormonal determinants of the endometrial cycle and the changes in the endometrium that occur

(3). Breast cycle
Know the hormonal determinants of breast growth and lactation

f. Pregnancy

Know the endocrine functions of the human placenta in terms of steroid and peptide production

Know the hormones and synthetic pathways of the placenta and the fetal-placental unit including all anatomical components

Know the effects on the fetus of glucocorticoids administered to the pregnant woman

Know the effects on the fetus of androgens administered to the pregnant woman

5. Disorders of puberty

a. Constitutional delay in growth and sexual development

(1). Differential diagnosis/normal variants

Know that constitutional delay (in growth and sexual development) is a normal variation of the timing and tempo of maturation

Distinguish constitutional pubertal delay from gonadotropin deficiency and the delay resulting from chronic disease or malnutrition

Know the differential diagnosis of primary amenorrhea

Recognize the causes of primary amenorrhea with sexual infantilism and primary amenorrhea with other signs of secondary sexual maturation

Recognize the differences in diagnosis of primary versus secondary amenorrhea

(2). Nutritional disorders

(a). Simple weight loss

Know that weight loss to 80% of normal weight can cause amenorrhea and that low body weight can delay pubertal onset

(b). Anorexia nervosa

Know the similarities between amenorrhea induced by anorexia nervosa and by exercise

Know about the psychologic causes of amenorrhea
Understand the course of resumption of periods in women with anorexia nervosa in relationship to weight gain

(c). Obesity

Know the effects of obesity on the reproductive endocrine system of males and females

(3). Hypogonadotropic hypogonadism

(a). Hypothalamic dysfunction (See V.C.4.b.(1))

Know clinical characteristics of patients with GnRH deficiency

Know that defects causing hypogonadotropic hypogonadotropism are usually located in the anterior hypothalamus

(b). Pituitary dysfunction

Differentiate isolated gonadotropin deficiency from constitutionally delayed adolescence

Know clinical features and MRI findings in Kallmann syndrome

Know patterns of inheritance associated with isolated gonadotropin deficiency

Know that autoimmune hypophysitis may cause pituitary gonadotropin deficiency

Know the causes of pituitary gonadotropin deficiency

Know the gene defects that can cause gonadotropin deficiency

Know that a defect in the GnRH receptor can cause gonadotropin deficiency

Know the pathophysiology of Kallman syndrome

Know the monogenic disorders that cause hypogonadotropic hypogonadism

(4). Hypergonadotropic hypogonadism

Know the clinical characteristics and inheritance patterns of LH/FSH receptor defects causing gonadotropin unresponsiveness syndromes

Recognize the circulating gonadotropin pattern in the gonadectomized patient
Know that x-ray therapy, including preparation for bone marrow transplant, may have toxic effects on gonads

Know the effects of chemotherapy on gonadal function

Know that galactosemia may cause primary ovarian failure

Recognize the patient with oophoritis/orchitis and the etiologies that may cause this

Know which steroidogenic defects cause deficiency of estrogen and androgens

Know the factors that cause increased serum gonadotropin concentrations in a gonadectomized patient

(5). Management of hypogonadism

Know the diagnostic features which distinguish primary from secondary hypogonadism

Know the limitations of GnRH testing in the management of hypogonadism

Know the reasons for and against the initiation of puberty with low-dose testosterone/estrogen at various ages

Know the various routes of administration of gonadal steroids and their advantages and disadvantages

Plan appropriate management for an adolescent with constitutional delay of growth and sexual development

(6). Hyper/hypoprolactinemia (See V.C.5.b.(2)(b))

b. Premature puberty

(1). Normal variants

(a). Differential diagnosis of idiopathic premature thelarche

Distinguish idiopathic premature thelarche from sexual precocity

Know the natural history of premature thelarche

(b). Differential diagnosis of idiopathic premature adrenarche
Differentiate idiopathic premature adrenarche from normal adrenarche and virilizing syndromes

Know the natural history of premature adrenarche

(2). Central precocious puberty

(a). Etiology

Recognize the possibility of central precocious puberty despite deficiency of other anterior pituitary hormones such as GH

Know central nervous system lesions, congenital and acquired, such as trauma, craniopharyngioma, and septooptic dysplasia, associated with central precocious puberty

Know that the central nervous system lesions associated with central precocious puberty are usually located in the posterior hypothalamus

Know that hypothalamic tumors may increase gonadotropin secretion

Know that sex steroid exposure can cause central precocious puberty

Know that birth trauma and cerebral palsy are associated with central precocious puberty

(b). Differential diagnosis

Differentiate central precocious puberty from other causes of isosexual precocity

Recognize syndromes associated with central precocious puberty

Know the diagnostic and therapeutic usefulness of hormonal measurements such as beta-HCG and third-generation gonadotropins

Know the differential diagnosis of central precocious puberty and how this differs in males and females

Understand the clinical features of central precocious puberty in a young child, particularly relationships of gonadarche and pubarche

Know the utility of testing with GnRH and its analogues in diagnosis of central precocious puberty

(c). Management (See also V.C.4.b.(2)(b))

Plan appropriate therapy for patients with central precocious puberty
Recognize psychosocial consequences of precocious sexual development

Recognize effects of precocious exposure to sex steroids on skeletal maturation

Know the effects of GnRH agonist and other forms of therapy on central precocious puberty

(3). Pseudoprecocity

(a). Gonadal disorders (tumors and hypersecretion states)

Know that the serum concentrations of gonadotropins and sex steroids usually distinguish virilizing gonadal tumors from adrenal tumors and central precocious puberty

Distinguish familial gonadotropin-independent sexual precocity from central precocious puberty

Know the response to GnRH and its analogues in a patient with an ovarian tumor

Know the clinical features and prognosis of Leydig cell tumor

Know the clinical and laboratory findings in virilizing ovarian lesions

Understand the pathophysiology of precocity associated with hepatoma

Be aware of the effect of ketoconazole on steroid hormone synthesis

Know the management of a boy with familial gonadotropin-independent sexual precocity at various stages of pubertal development

Know that familial gonadotropin-independent sexual precocity is caused by LH receptor mutations leading to its constitutive activation

c. Hyperandrogenism/polycystic ovary syndrome

Know that an increased LH/FSH ratio and elevated circulating androgens are not found in all patients with polycystic ovary syndrome

Know the metabolic consequences of insulin resistance syndrome (metabolic syndrome) and its relationship to polycystic ovary syndrome
Know that anovulation may present as oligomenorrhea or menometrorrhagia

Know that the skin manifestations of hyperandrogenemia are variable: hirsutism, acne, both, or neither, and that age and ethnicity are important determinants of their severity

Know that not all polycystic ovary syndrome patients are obese

Know the biochemical profile of a patient with an ovarian tumor and with an adrenal tumor

Know that ovarian histology may be normal in some females with hyperandrogenism

Know the differential diagnosis of hyperandrogenism in adolescent and adult females

Know that intrauterine growth restriction may lead to metabolic syndrome and/or polycystic ovarian syndrome

Know that there is an overlap between adrenal and ovarian androgen production in some women with PCOS

Know how to differentiate PCOS from late onset congenital adrenal hyperplasia

Know that PCOS can represent as primary amenorrhea

Plan the appropriate management for a patient with PCOS

d. **Gynecomastia**

(1). **Pathophysiology**

Know the pathophysiology of gynecomastia

(2). **Incidence**

Know the incidence and natural history of gynecomastia in pubertal boys

(3). **Differential diagnosis**

Know the differential diagnosis of gynecomastia in prepubertal and pubertal boys

(4). **Management**

Know how to manage gynecomastia depending upon etiology and duration
(5). Resolution

Know that most pubertal gynecomastia spontaneously recedes within two years

VIII. Other Hormones

A. Somatostatin

1. Physiology

a. Ontogeny/embryology

b. Synthesis/processing/storage

Know the structure and function of somatostatin

Know that there are multiple sites of somatostatin production

Know the cell type responsible for somatostatin production in the islets of Langerhans

c. Secretion

Know the effects of somatostatin analogues on pancreatic endocrine functions

d. Transport

e. Receptor/action

(1). Tissue/organ specific (receptor/post receptor)

Understand the tissue specific differences in somatostatin receptor subtype expression and implications for diagnosis and therapy

(2). Integrated hormone effects on metabolism

Know the biologic effects of somatostatin

2. Pathology

a. Hormone deficiencies

(1). Pathophysiology

(2). Clinical implications

b. Hormone excess
(1). Pathophysiology

(2). Clinical implications

Recognize clinical disorders which result from excessive secretion of somatostatin

Know the clinical manifestations of somatostatin excess

c. Other

Know the therapeutic uses of somatostatin analogues

Know the diagnostic usefulness of somatostatin receptor scans

B. Vasoactive intestinal peptide (VIP)

1. Physiology

   a. Ontogeny/embryology

   b. Synthesis/processing/storage

      Know the function of vasoactive polypeptide

   c. Secretion

   d. Transport

   e. Receptor/action

      (1). Tissue/organ specific (receptor/post receptor)

      (2). Integrated hormone effects on metabolism

2. Pathology

   a. Hormone deficiencies

      (1). Pathophysiology

      (2). Clinical implications

   b. Hormone excess

      (1). Pathophysiology

      (2). Clinical implications

      Know the clinical features seen in patients with a tumor secreting
an excess of vasoactive intestinal polypeptide (VIP) and the syndrome in which it may occur

Know the clinical similarities and differences between syndromes involving excess VIP and excess serotonin

Plan the laboratory evaluation of a patient with a suspected VIPoma

c. Other

C. Serotonin

1. Physiology

a. Ontogeny/embryology

b. Synthesis/processing/storage

Know the structure and actions of serotonin

c. Secretion

d. Transport

e. Receptor/action

(1). Tissue/organ specific (receptor/post receptor)

(2). Pathophysiology

2. Pathology

a. Hormone deficiencies

(1). Pathophysiology

(2). Clinical implications

b. Hormone excess

(1). Clinical implications

Know the clinical features of carcinoid syndrome

Know the association of carcinoid syndrome in patients with MEN 1

c. Other

D. Gastrin

1. Physiology
a. Ontogeny/embryology

b. Synthesis/processing/storage

Know the function of gastrin

c. Secretion

Know the physiologic stimuli for gastrin secretion

d. Transport

e. Receptor/action

(1). Tissue/organ specific (receptor/post receptor)

(2). Integrated hormone effects on metabolism

2. Pathology

a. Hormone deficiencies

(1). Pathophysiology

(2). Clinical implications

b. Hormone excess

Know the clinical manifestations of excess gastrin secretion

(1). Pathophysiology

(2). Clinical implications

Know that gastrinomas are the most common pancreatic tumors in MEN, type I

Know the clinical features, evaluation, and treatment of a patient with a gastrinoma

c. Other

E. Natriuretic peptides

1. Physiology

a. Ontogeny/embryology

b. Synthesis/processing/storage
c. **Secretion**

Understand the regulation of atrial natriuretic peptide secretion

d. **Transport**
e. **Receptor/action**

(1). **Tissue/organ specific (receptor/post receptor)**

(2). **Integrated hormone effects on metabolism**

Know the physiologic functions of atrial natriuretic peptide

Know the effects of atrial natriuretic peptide on the renin-aldosterone system

2. **Pathology**

a. **Hormone deficiencies**

   (1). **Pathophysiology**

   (2). **Clinical implications**

b. **Hormone excess**

   (1). **Pathophysiology**

   (2). **Clinical implications**

Know in which disorders abnormal function of atrial natriuretic peptide may play a role such as in cerebral salt wasting

Know the clinical and laboratory findings that occur with excess secretion of atrial natriuretic peptide

c. **Other**

**F. Glucagon-like peptide**

1. **Physiology**

   a. **Ontogeny/embryology**

   b. **Synthesis/processing/storage**

   Understand that glucagons and glucagon-like peptide are encoded by the same gene

   Understand the major sites of production of glucagon and glucagon-like...
peptide

c. Secretion
d. Transport
e. Receptor/action

(1). Tissue/organ specific (receptor/post receptor)

(2). Integrated hormone effects on metabolism

2. Pathology

a. Hormone deficiencies

(1). Pathophysiology

(2). Clinical implications

b. Hormone excess

(1). Pathophysiology

(2). Clinical implications

c. Other

Know the physiologic function of glucagon-like peptide hormone

Know that glucagon-like peptide increases insulin secretion and decreases glucagon secretion

Know that glucagon-like peptide is released by intestinal cells and neurons in response to increased glucose and to gastric acid secretion

Know the potential therapeutic usefulness of glucagon-like peptide analogs in patients with diabetes mellitus

G. Gastric inhibitory polypeptide

1. Physiology

Be familiar with syndromes in which there is excessive production of gastrointestinal hormones

Know the structure and function of gastric inhibitory peptide

Know that gastric inhibitory polypeptide is produced in the K cells of the duodenum and proximal jejunum
Know that gastric inhibitory polypeptide increases insulin release

H. Pancreatic polypeptide

1. Physiology

Understand the connections between eating, pancreatic polypeptide, and appetite

2. Pathology

a. Hormone deficiencies

b. Hormone excess

Know that pancreatic polypeptide is commonly secreted by and is useful as a marker for enteropancreatic neuroendocrine tumors in MEN 1

I. Chromogranin A

1. Physiology

2. Pathology

a. Hormone deficiencies

b. Hormone excess

(1). Pathophysiology

(2). Clinical implications

Know conditions associated with chromogranin A

J. Amylin

1. Physiology

Know that amylin is co-secreted with insulin in response to oral intake of nutrients

Know that excessive amylin deposition is a pathogenic feature of some patients with type 2 diabetes

Know the rationale for the use of amylin analogs in the treatment of diabetes

IX. Lipoproteins and Lipids
A. Structure and synthesis

Recognize that cholesterol and triglyceride are the principal plasma lipids measured for clinical purposes.

Know that each lipoprotein consists of non-polar cholesterol esters and triglyceride in an inner core which is surrounded by polar lipids (free cholesterol and phospholipids) in combination with the apoproteins.


Know that chylomicrons, VLDL, LDL and HDL are the major varieties of lipoprotein in plasma.

Know that the enzyme HMG-CoA reductase is the major regulator of cholesterol synthesis.

Recognize that the metabolism of lipoproteins involves lipoprotein lipase, hepatic lipase, and lecithin-cholesterol acyl transferase.

Know the effect of diet on blood lipid and lipoprotein concentrations.

Understand the role of the LDL receptor and LDL metabolism and the specific proteins that interact with the LDL receptor.

B. Physiology

1. Chylomicrons

Know that chylomicrons originate from the intestine and consist mainly of triglycerides.

2. VLDL

Know that VLDL is synthesized in the liver.

Know that LDL is derived from metabolism of VLDL.

3. LDL

Know that LDL and LP(a) are the most atherogenic lipoproteins.

Understand the regulation of production of low-density lipoprotein.

Know that serum apoprotein B concentrations and apoprotein B/apoprotein A ratio predict the risk of cardiovascular disease.

Know that apoprotein B transports the atherogenic lipoproteins (LDL, VLDL, and IDL).
4. **HDL**

Recognize that HDL is considered to be protective or anti-atherogenic on the basis of epidemiologic studies

Know the influence of drugs, alcohol, and hormones on HDL cholesterol

**C. Pathology**

1. **Hyperlipidemias**

Know the most common genetic disorders that lead to hyperlipidemias

Know the causes of secondary hyperlipidemias

Know the drug therapies for hyperlipidemias, including indications and side effects

Know the dietary and lifestyle treatments for hyperlipidemias

2. **Lipoprotein lipase deficiency**

Know that lipoprotein lipase deficiency leads to impaired clearance of triglyceride containing lipoproteins from the circulation (chylomicrons and VLDL)

Know that lipoprotein lipase deficiency is a rare autosomal recessive disorder

Know that patients with lipoprotein lipase deficiency present with hypertriglyceridemia, pancreatitis and xanthomas (eruptive)

Know the treatment of lipoprotein lipase deficiency

3. **Familial hypercholesterolemia**

Know that familial hypercholesterolemia is due to an abnormal receptor for LDL which leads to defective catabolism of LDL and increased cellular cholesterol synthesis

Recognize that familial hypercholesterolemia is inherited by an autosomal dominant mechanism

Know that heterozygous familial hypercholesterolemia is present in 1 in 500 individuals

Know that tendinous xanthomas are a feature of hypercholesterolemia
Know that the homozygous form of familial hypercholesterolemia is associated with coronary artery disease in the first two decades of life and high mortality

Know the treatment of children with familial hypercholesterolemia

4. **Familial combined hyperlipidemia**

Recognize that familial combined hyperlipidemia is caused by overproduction of VLDL and LDL by the liver

Recognize that familial combined hyperlipidemia is an autosomal dominant disorder

Recognize that familial combined hyperlipidemia occurs in 1 in 100 individuals

Recognize that patients with familial combined hyperlipidemia present with either elevated cholesterol, elevated triglyceride or combined elevations of cholesterol and triglyceride in a single pedigree

Recognize that familial combined hyperlipidemia is associated with premature atherosclerosis

Recognize that the phenotype of combined hyperlipidemia is associated with poorly controlled type 1 and type 2 diabetes

Know the treatment of children with combined hyperlipidemia

Know that type 2 diabetes is associated with large numbers of small, dense LDL

5. **Hypertriglyceridemia**

Know that patients with hypertriglyceridemia are at risk for pancreatitis

Know the dietary treatment of hypertriglyceridemia

Know that fish oil decreases serum triglyceride levels

Know the classes of drugs that are most effective in decreasing triglycerides

Know that obesity and insulin resistance are associated with hypertriglyceridemia and low HDL-cholesterol levels

6. **Lipoprotein deficiency**

X. **Multiple endocrine neoplasia and polyglandular autoimmune disease**
A. Excess hormonal activity

1. Multiple endocrine neoplasia (MEN)

Know the inheritance patterns of MEN syndromes

Understand the clinical role of mutation detection in MEN syndromes

Understand the role of genetic testing for MEN in families with endocrine tumors specifically recognizing why screening for RET oncogen mutations is easier than screening for MEN1 mutations

a. MEN 1

Know that inactivating mutations in the MEN 1 gene can cause MEN 1

Know the endocrine and nonendocrine features of MEN1

Know the appropriate screening tests for a patient with MEN1 to identify additional manifestations

b. MEN 2

Recognize the typical phenotype of MEN 2A and B, including medullary thyroid carcinoma and pheochromocytoma in both types and hyperparathyroidism in MEN 2A

Know that activating mutations in the RET oncogene can cause MEN 2A, MEN 2B, and familial medullary thyroid carcinoma, while inactivating RET mutations are associated with familial Hirschsprung disease

Know that DNA-based diagnosis of hereditary medullary thyroid carcinoma risk should prompt total thyroidectomy by 5 years of age in MEN 2A and in familial medullary thyroid carcinoma

Know that total thyroidectomy should be performed in infancy in MEN 2B

2. McCune-Albright syndrome

Recognize that diffuse or multi-nodular goiter with hyperthyroidism is a manifestation of McCune-Albright syndrome and results from activating mutations of the alpha-subunit of the stimulatory G-protein

Know the endocrine and nonendocrine manifestations of McCune-Albright syndrome

Know the management of a girl with fibrous dysplasia and sexual precocity (McCune-Albright syndrome) at various stages of development
Know that there is constitutive activation of adenylyl cyclase in McCune-Albright syndrome due to a somatic mutation in the stimulatory G protein

Know that Cushing syndrome may result from bilateral adrenocortical nodular hyperplasia in McCune-Albright syndrome

3. **Li-Fraumeni syndrome**

4. **Von Hippel-Lindau disease**

Know the occurrence of pheochromocytoma in Von Hippel-Lindau disease

5. **Carney complex**

Know that Cushing syndrome may result from primary pigmented micronodular adrenocortical disease and know its association with Carney complex

**B. Diminished hormonal activity**

Know the relation of HLA haplotypes to specific autoimmune diseases

1. **Polyglandular autoimmune conditions**

   a. **Autoimmune polyendocrine syndrome, type I**

Know the genetic cause of autoimmune polyendocrine syndrome, type I (Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED))

Be familiar with the endocrine abnormalities that occur in autoimmune polyendocrine syndrome, type I

Be familiar with nonendocrine manifestations of autoimmune polyendocrine syndrome, type I

Know which screening tests should be performed periodically in patients with autoimmune polyendocrine syndrome, type I, to detect new manifestations of the disease

Know that autoimmune polyendocrine syndrome, type I, is inherited in an autosomal recessive fashion

   b. **Autoimmune polyendocrine syndrome, type II**

Be familiar with the clinical manifestations of autoimmune polyendocrine syndrome type II
XI. Methods and Biological Principles

A. Molecular biology

1. DNA

a. Structure

Be able to define cDNA

b. Function

Be familiar with the processes of transcription and translation

Be able to define intron, exon, codon, and promoter regions of genes

Understand the mechanisms that lead to non-Mendelian inheritance patterns such as imprinting and mitochondrial gene inheritance

Know the meaning of stop codon, nonsense mutation, missense mutation, polymorphism, including single nucleotide polymorphism, frame-shift mutation, and gene deletion, and describe how different types of mutations might produce differing effects

Understand the following functional categories of mutations: loss-of-function (inactivating) mutations, gain-of-function (activating) mutations, null mutations

Know linkage disequilibrium and describe how haplotype mapping aids identification of disease-causing genes

c. Analytic methods

Be familiar with the types of enzymes used in molecular biology such as DNA polymerases, RNA polymerases, restriction endonucleases and their properties

Know the techniques used to identify and isolate genetic abnormalities, including Northern blot analysis, Southern blot analysis, FISH, PCR amplification, RFLP analysis, DNA methylation, sequencing, and array comparative genomic hybridization

Know the use of methods to analyze gene function, and mechanisms of transcription such as DNAse footprinting, promoter analysis, chromatin
immunoprecipitation, etc.

Be able to describe chromosome abnormalities such as aneuploidy, small deletions, duplications, translocations, etc.

Describe different applications of DNA (or cDNA) microarrays

Understand the inability of standard DNA sequencing assays to detect heterozygous deletion mutations

2. RNA
   a. Structure
      Be able to describe the mechanism of alternative splicing and how it leads to different mRNA species
   b. Function
      Know the functional differences between messenger, micro (miRNA), ribosomal, and transfer RNAs
   c. Analytic methods
      Be able to describe the methods used for detection and quantitation of mRNA
      Understand methods to use RNAs to analyze gene function, such as small interfering RNAs

3. Protein synthesis
   a. Protein chemistry
      Understand the concept of a dominant negative mutation and the mechanisms involved
   b. Protein synthetic mechanisms
      (1). Transcription
      Know the general mechanism of action of transcription factors
      (2). Translation
      (3). Post-translational modification
      Know the meaning of post-translational modification
      (4). Analysis
4. **Manipulation of gene expression**

   a. **Experimental**

      Know the fundamentals of altering gene expression in experimental animals

   b. **Therapeutic**

      Be familiar with methods being developed for gene transfer in humans

      Be familiar with endocrine conditions that might be amenable to gene therapy

B. **Cell biology**

1. **Growth and metabolism at the cellular level**

   Be able to describe basic methodologies used to examine mechanisms of growth control at the cellular level, such as regulation of replication and apoptosis

C. **Hormone action**

1. **Receptors**

   Know the principles of methods used for determining binding capacity and affinity of receptors

   Know the general structure of receptors for hormones

   Be familiar with clinical syndromes due to hormone receptor disorders

   Understand that liganded cell-surface receptors often aggregate, are internalized into endosomes, and then can be recycled to the cell surface

   Know the principles involved and interpretation of results in radioreceptor assays

2. **Signal transduction**

   Know that phosphorylation of proteins by various classes of kinases plays important functions in signal transduction

   Know the function of receptor-linked G proteins
Understand that some receptors (eg, insulin and IGFs) act as tyrosine kinases to transduce a signal

Understand the roles of adenylate cyclase and phospholipase C in signal transduction

Understand that intracellular receptors in the steroid hormone receptor superfamily bind to hormone response elements in promoters and alter transcription of target genes

Understand that some receptor signal transduction (eg, for GH, steroid hormones, insulin) involves dimerization and understand how the requirement for dimerization allows for dominant negative mutation

D. Hormone measurement

1. General principles

Understand the principles of chemiluminescent ELISA, IRMA, and RIA procedures

Know how to calculate coefficient of variation for an assay

Understand the meaning of detection limit as it pertains to hormone assays

Recognize the value of and techniques for measuring free and protein-bound concentrations of certain hormones

Understand that the lower and upper limit of diagnostic test range is defined by the 2nd and 98th percentiles, respectively, and thus that slightly abnormal measurements are unlikely to be clinically significant

Understand the value of procedures such as extraction and chromatography to increase assay specificity

Recognize the potential effect of heterophilic/anti-animal antibodies on immunoassays and know that antibody effects may differ depending on whether the immunoassay is competitive or immunometric

2. Bioassays

Know the methods used to measure in vitro bioactivity of LH, FSH, TSH, and bioactive immunoglobulins

3. Immunoassays

a. Ligand displacement
Know that radioimmunoassays are based on competitive inhibition of the binding of labeled hormone to antibody by unlabeled hormone contained in standards and unknown samples and the methods involved.

Recognize that a valid RIA requires that standards and unknown samples be immunochemically identical.

Know that confirmation of validity in an RIA is obtained if the dilution curve of the unknown sample can be superimposed on the dilution curve of the standards.

Recognize that RIAs depend upon the availability of specific antibody and labeled antigen (ligand) as well as a method of separating antibody bound ligand from free ligand.

Recognize that RIA procedures are subject to nonspecific factors such as pH, ionic environment, temperature, incubation time, presence or absence of anticoagulants, and degradation of antibody or labeled antigen.

Know that validity of RIA procedures is influenced by cross-reacting hormones (eg, LH with hCG), by heterogeneous forms of peptide hormones in plasma (eg, GH), and by interference from hormone fragments (eg, C-terminal end of PTH).

b. **ELISA**

c. **IRMA/ICMA**

Know that immunoradiometric assays involve two antibodies directed against the standard or unknown; the unlabeled antibody captures; and labeled antibody "signals" or quantitates the standard or unknown.

d. **Mass spectrometry**

Know the basic steps involved in a high performance liquid chromatography/tandem mass spectrometry assay of a steroid molecule.

E. **Pharmacology of drugs and hormones**

Understand basic pharmacological parameters such as clearance, volume of distribution, half-life.

F. **Epidemiologic studies**

Understand the difference between disease prevalence and incidence.

Understand why epidemiological association does not imply causality, and recognize the need for randomized controlled studies to confirm.
possible associations

XII. Core Knowledge in Scholarly Activities

A. Principles of Use of Biostatistics in Research

1. Types of variables

Distinguish types of variables (eg, continuous, categorical, ordinal, nominal)

Understand how the type of variable (eg, continuous, categorical, nominal) affects the choice of statistical test

2. Distribution of data

Understand how distribution of data affects the choice of statistical test

Differentiate normal from skewed distribution of data

Understand the appropriate use of the mean, median, and mode

Understand the appropriate use of standard deviation

Understand the appropriate use of standard error

3. Hypothesis testing

Distinguish the null hypothesis from an alternative hypothesis

Interpret the results of hypothesis testing

4. Statistical tests

Understand the appropriate use of the chi-square test versus a t-test

Understand the appropriate use of analysis of variance (ANOVA)

Understand the appropriate use of parametric (eg, t-test, ANOVA) versus non-parametric (eg, Mann-Whitney U, Wilcoxon) statistical tests

Interpret the results of chi-square tests

Interpret the results of t-tests

Understand the appropriate use of a paired and non-paired t-test

Determine the appropriate use of a 1- versus 2-tailed test of significance
Interpret a p-value
Interpret a p-value when multiple comparisons have been made
Interpret a confidence interval
Identify a type I error
Identify a type II error

5. **Measurement of association**

Differentiate relative risk reduction from absolute risk reduction

Calculate and interpret a relative risk

Calculate and interpret an odds ratio

Interpret a hazard ratio

Understand the uses and limitations of a correlation coefficient

6. **Regression**

Identify when to apply regression analysis (eg, linear, logistic)

Interpret a regression analysis (eg, linear, logistic)

Identify when to apply survival analysis (eg, Kaplan-Meier)

Interpret a survival analysis (eg, Kaplan-Meier)

7. **Diagnostic tests**

Recognize the importance of an independent "gold standard" in evaluating a diagnostic test

Calculate and interpret sensitivity and specificity

Calculate and interpret positive and negative predictive values

Understand how disease prevalence affects the positive and negative predictive value of a test

Calculate and interpret likelihood ratios

Interpret a receiver operator characteristic curve

Interpret and apply a clinical prediction rule
8. Systemic reviews and meta-analysis

Understand the purpose of a systematic review

Understand the advantages of adding a meta-analysis to a systematic review

Interpret the results of a meta-analysis

Identify the limitations of a systematic review

Identify the limitations of a meta-analysis

B. Principles of Epidemiology and Clinical Research Design

1. Study types

Distinguish between Phase I, II, III, and IV clinical trials

Recognize a retrospective study

Understand the strengths and limitations of retrospective studies

Recognize a case series

Understand the strengths and limitations of case series

Recognize a cross-sectional study

Understand the strengths and limitations of cross-sectional studies

Recognize a case-control study

Understand the strengths and limitations of case-control studies

Recognize a longitudinal study

Understand the strengths and limitations of longitudinal studies

Recognize a cohort study

Understand the strengths and limitations of cohort studies

Recognize a randomized-controlled study

Understand the strengths and limitations of randomized-controlled studies

Recognize a before-after study

Understand the strengths and limitations of before-after studies
Recognize a crossover study
Understand the strengths and limitations of crossover studies
Recognize an open-label study
Understand the strengths and limitations of open-label studies
Recognize a post-hoc analysis
Understand the strengths and limitations of post-hoc analyses
Recognize a subgroup analysis
Understand the strengths and limitations of subgroup analyses

2. **Bias and confounding**

Understand how bias affects the validity of results
Understand how confounding affects the validity of results
Identify common strategies in study design to avoid or reduce bias
Identify common strategies in study design to avoid or reduce confounding
Understand how study results may differ between distinct sub-populations (effect modification)

3. **Causation**

Understand the difference between association and causation
Identify factors that strengthen causal inference in observational studies (eg, temporal sequence, dose response, repetition in a different population, consistency with other studies, biologic plausibility)

4. **Incidence and prevalence**

Distinguish disease incidence from disease prevalence

5. **Screening**

Understand factors that affect the rationale for screening for a condition or disease (eg, prevalence, test accuracy, risk-benefit, disease burden, presence of a presymptomatic state)

6. **Decision analysis**
Understand the strengths and limitations of decision analyses

Interpret a decision analysis

7. Cost-benefit, cost-effectiveness, and outcomes

Differentiate cost-benefit from cost-effectiveness analysis

Understand how quality-adjusted life years are used in cost analyses

Understand the multiple perspectives (e.g., of an individual, payor, society) that influence interpretation of cost-benefit and cost-effectiveness analyses

8. Sensitivity analysis

Understand the strengths and limitations of sensitivity analysis

Interpret the results of sensitivity analysis

9. Measurement

Understand the types of validity that relate to measurement (e.g., face, construct, criterion, predictive, content)

Distinguish validity from reliability

Distinguish internal from external validity

Distinguish accuracy from precision

Understand and interpret measurements of interobserver reliability (e.g., kappa)

Understand and interpret Cronbach's alpha

C. Applying Research to Clinical Practice

1. Assessment of study design, performance & analysis (internal validity)

Recognize when appropriate control groups have been selected for a case-control study

Recognize when appropriate control groups have been selected for a cohort study

Recognize the use and limitations of surrogate endpoints
Understand the use of intent-to-treat analysis

Understand how sample size affects the power of a study

Understand how sample size may limit the ability to detect adverse events

Understand how to calculate an adequate sample size for a controlled trial (e.g., clinically meaningful difference, variability in measurement, choice of alpha and beta)

2. Assessment of generalizability (external validity)

Identify factors that contribute to or jeopardize generalizability

Understand how non-representative samples can bias results

Assess how the data source (e.g., diaries, billing data, discharge diagnostic code) may affect study results

3. Application of information for patient care

Estimate the post-test probability of a disease, given the pretest probability of the disease and the likelihood ratio for the test

Calculate absolute risk reduction

Calculate and interpret the number-needed-to-treat

Distinguish statistical significance from clinical importance

4. Using the medical literature

Given the need for specific clinical information, identify a clear, structured, searchable clinical question

Identify the study design most likely to yield valid information about the accuracy of a diagnostic test

Identify the study design most likely to yield valid information about the benefits and/or harms of an intervention

Identify the study design most likely to yield valid information about the prognosis of a condition

D. Principles of Teaching and Learning

1. Educational theory

Understand the basic principles of adult learning theory (e.g., adult
learners are self-directed, goal-oriented, practical; need to feel respected, build on life experiences; learn best when learning is based on an existing framework)

Understand the attributes of an effective learning environment

Understand the importance of "reflective practice" in teaching and learning

Identify strategies that motivate learners

Recognize the impact of the "hidden curriculum" on learning

2. Feedback and evaluation

Identify components of effective feedback

Distinguish between formative and summative feedback

Distinguish between evaluation and feedback

Understand the strengths and weaknesses of various methods to evaluate learners

3. Teaching methods

Understand the strengths and weaknesses of various teaching methods (eg, lecture, small group discussion, bedside teaching, simulation)

Understand that individuals may learn more effectively with certain teaching methods (eg, reading, hearing, doing) than with others

4. Educational planning

Understand the role of needs assessment in educational planning

Distinguish between goals and learning objectives

Identify components of well-formulated learning objectives

Recognize the strengths and weaknesses of various educational outcome measures (eg, participant satisfaction, acquisition of knowledge and skills, behavioral change, patient outcomes)

E. Ethics in Research

1. Conflicts of interest and commitment

Evaluate whether an investigator has a conflict of interest during the course of a study
Understand ways to manage a conflict of interest

Understand what constitutes a conflict of commitment

2. **Professionalism and misconduct in research**
   Identify forms of research misconduct (e.g., plagiarism, fabrication, falsification)

   Differentiate honest error and differences of opinion from research misconduct

   Understand the criteria for authorship of clinical research publications

3. **Principles of research with human subjects**
   Understand and apply the three main principles of research ethics articulated in the Belmont Report (e.g., respect for persons, beneficence, and justice)

   Understand the role of analysis of risks and benefits in the ethical conduct of research

   Understand the federal regulatory definitions regarding which activities are considered research

   Understand the federal regulatory definitions regarding when research includes the use of human subjects

   Understand the federal regulatory definition of minimal risk

   Understand the functions of an Institutional Review Board

   Understand when an exemption from review by the Institutional Review Board is permissible

   Understand the functions of a Data Safety Monitoring Board

   Understand the importance of clinical equipoise in research with human subjects

   Understand the impact of "therapeutic fallacy" on clinical research with human subjects

   Understand the ethical considerations of study design (e.g., placebo, harm of intervention, deception, flawed design)

   Understand the privacy rules regarding recruitment and participation of subjects in a research study and reporting the results of that study
4. **Principles of consent and assent**

Understand what constitutes informed consent in research

Understand how undue influence can affect obtaining consent for research

Understand how coercion can affect obtaining consent for research

Understand the special ethical considerations related to research utilizing children because of their inability to give informed consent

Distinguish among consent, assent, and permission in research involving children

5. **Vulnerable populations**

Recognize that the definition of "children" is related to the underlying clinical intervention in the jurisdiction in which the child is located rather than a fixed nationwide notion of age

Recognize the types of protections that might be accorded to vulnerable populations (eg, incarcerated individuals, pregnant women, fetuses, children, mentally disabled individuals, educationally or economically disadvantaged individuals)

Understand the concept of minimal risk as it applies to research involving children

Understand the circumstances under which research that involves children and that entails greater than minimal risk may be permissible

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