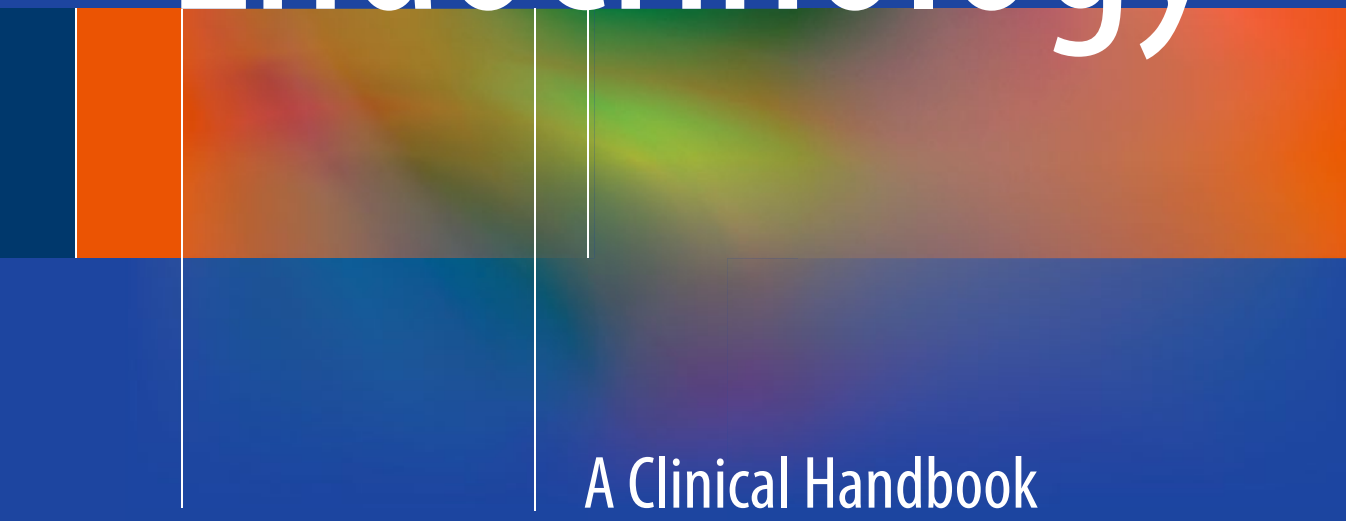
Dennis M. Styne

Pediatric Endocrinology



A Clinical Handbook

Springer

Pediatric Endocrinology

Dennis M. Styne

Pediatric Endocrinology

A Clinical Handbook

Springer

Dennis M. Styne
Pediatrics
University of California
Davis School of Medicine
Sacramento, CA, USA

ISBN 978-3-319-18370-1 ISBN 978-3-319-18371-8 (eBook)
DOI 10.1007/978-3-319-18371-8

Library of Congress Control Number: 2015940868

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

To my loving wife Donna and my amazing children Rachel, Jonathan, Juliana, and Aaron, my wonderful son-in-law Michael, and my beautiful grandchildren Cooper and Samara all of whom immeasurably enrich my life.

Preface

This book is written for practitioners ranging from students to residents, family physicians, and pediatricians puzzling over the approach to a child who seems to have an endocrine disorder in order to help readers evaluate and treat the more straightforward pediatric endocrine issues. The information in the text might prepare a provider for a meeting with parents of a child with an endocrine condition in order to improve communication or alternatively might provide the facts that will allow the practitioner to avoid an unnecessary consultation. The chapters begin with the basic physiologic processes and concepts of endocrinology before putting this knowledge into action by addressing the major signs and symptoms and the diagnosis and management of pediatric endocrine disorders. This work is provided for anyone who wishes to have a consultation with a pediatric endocrinologist in absentia still realizing that an actual person-to-person consultation sets the gold standard. There are a multitude of more complex issues within pediatric endocrinology that cannot be mastered without adequate experience; managing a baby with ambiguous genitalia is only one example of the issues that are introduced in this text to allow the reader to understand the basics, but this small volume cannot possibly cover the complexities in their entirety. This volume is not meant to replace the outstanding larger and more detailed texts, manuscripts, and websites to which I refer the reader in the "suggested reading" section at the conclusion of each chapter. The concepts covered are designed to address in varying detail the subjects in the first ten headings in the content outline of the Sub-board of Pediatric Endocrinology of The American Board of Pediatrics dealing with clinical conditions. However, there is no claim that this book will give the reader the expertise of a pediatric endocrinologist; for that a 3-year fellowship is only the first step!

Sacramento, CA, USA — Dennis M. Styne

Acknowledgements

I am indebted to my colleagues in the field of pediatric endocrinology across the world whose wisdom in print and in words I value and have tried to reflect in this book. This text grew out of my teaching and clinical experiences and I am grateful to the innumerable students, house officers, and postgraduate practitioners I have encountered in the last 45 years that I have pursued this field. Presentations to them helped me organize my thoughts and their probing questions led me to look at the issues in new ways. I am grateful to my first teachers of this field, Melvin M. Grumbach, Felix Conte, and the late Selna Kaplan, at the University of California San Francisco. They deserve much of the credit for my accomplishments as they started me in this wonderful field. I am indebted to my coworkers at the University of California Davis School of Medicine, Drs. Nicole Glaser, Lindsey Albrecht, Abigail Fruzza, and Yvonne Lee: they have daily imparted their wisdom to me. My clinical team that provide outstanding care every day, especially to our numerous patients with diabetes mellitus, include Sultanna Iden, RN, CDE; Erin Conboy-Heiser, RN, CDE; Alexander Nella, RD, CDE; Dayna Green-Burgeson, RD, CDE; Vincent Fong, LCSW; and Breanne Harris, BS Diabetes Concierge. Edna Gun Utter, our AA (administrative assistant), helped me organize and format this volume expertly. The supportive staff at Springer including Richard Lansing and Joseph Quatela gave indispensable editorial help. I acknowledge Dr. Edward Steinberg who provided initial support in my redirection into pediatric obesity and continues to provide constant wisdom. I am deeply indebted to the Yocha Dehe Wintun Nation who have endowed my faculty position and unwaveringly supported my work in pediatric endocrinology and health disparities over the last 15 years.

Contents

Introduction to Pediatric Endocrinology: The Endocrine System

1

The endocrine system regulates reproduction, growth and development, homeostasis of the organism (or maintenance of the internal environment), and the production, storage, and utilization of energy. The endocrine system was originally understood to regulate metabolism by biochemical messengers or hormones that were released from specialized organs (glands) into the general circulation so that they could act at a distance. Thus, hormones were classically defined as circulating messengers, with the location of their action far from the site of secretion, *endocrine* action. Hormone action also may be *paracrine* (acting on adjacent neighboring cells to the cell of origin of the hormone by diffusion), *autocrine* (acting on the cell of origin of the hormone itself by diffusion), or intracrine (acting on the cell of origin without actually being secreted); often agents acting in these ways are called factors rather than hormones. Indeed, these factors (e.g., growth factors) may be produced in most cells of the body rather than discrete endocrine glands (Fig. 1.1). The effects of hormones and factors may be generally considered to be directed toward the processes of cell differentiation, cell growth, and metabolism of the cell and the organism.

In the past, some of the endocrine glands appeared to be controlled by the pituitary gland, which was therefore considered to be "the master gland." The discovery of the hypophysiotropic hormones of the hypothalamus and their role in the control of pituitary secretion made it clear that a higher level of control of these functions exists. Now it is recognized that various regions of the brain regulate the hypothalamus with complex interconnections in the central nervous system. Many of the hormones of the pituitary–hypothalamic axis or molecules that share much of their structure and function are also found in the gastrointestinal tract and other tissues throughout the body, as well as the placenta. Overlap occurs between the control of the endocrine system and the nervous system; hormone secretion can be regulated by nerve cells, and endocrine agents can serve as neural messengers. Further, the endocrine system is regulated by factors important in the immune system (e.g., cytokines interact with the secretion of glucocorticoids, which then exert an influence on inflammation). An entire system of regulation, rather than the simplistic view of the endocrine system, best describes the control of metabolism.

Many hormones are regulated in a feedback loop, so that the production of a hormone is controlled by its effect; for example, the corticotropin-releasing factor (CRF) stimulates the adrenocorticotropic hormone (ACTH) to produce cortisol, which in turn feeds back to suppress CRF and ACTH production so that equilibrium is reached and serum cortisol and ACTH remain in the normal range (Fig. 1.2, Table 1.1). The set point of the equilibrium may change with development; in prepuberty, small amounts of sex steroids strongly suppress gonadotropin secretion, but during pubertal

D.M. Styne, *Pediatric Endocrinology*, DOI 10.1007/978-3-319-18371-8_1

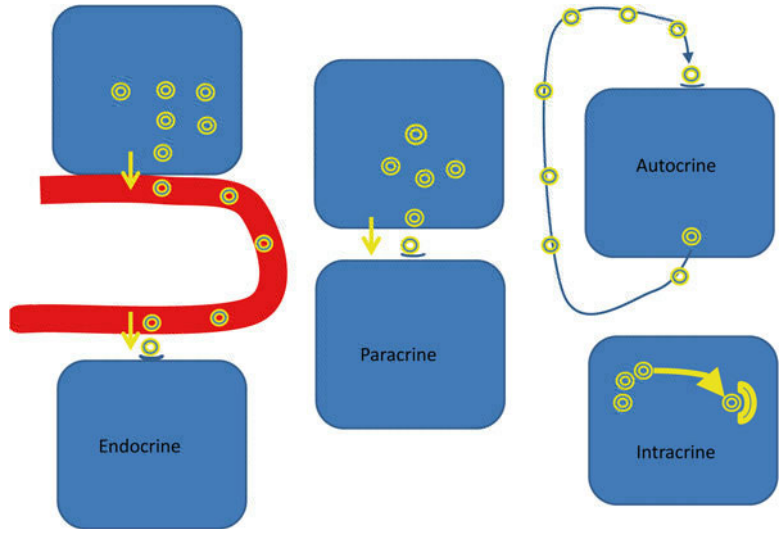


Fig. 1.1 Endocrine, paracrine, autocrine, and intracrine effects. *Endocrine* effects occur when a hormone is secreted by a cell into the bloodstream to be carried a distance until it leaves the bloodstream to interact with the cellular receptor, in this case a peptide cellular membrane receptor, to exert intracellular activity. *Paracrine* effects occur when a cell secretes a substance to cause biological effects on a neighboring cell, in this case via a peptide cellular membrane receptor, without entering the bloodstream. *Autocrine* effects occur when the cell secretes a substance to cause biological effects on the cell of origin, in this case via a peptide cellular membrane receptor, without entering the bloodstream nor necessarily affecting nearby cells. *Intracrine* effects occur when a substance acts within the cell in which it was produced without crossing the cell membrane, in this case via an intracellular receptor. Endocrine effects are measured by assays on blood samples, but paracrine and autocrine effects cannot be directly measured by assaying blood samples. In fact, the results of blood sample analyses only provide a reflection of what might be going on locally

development, the sensitivity of this feedback loop decreases. Thus increased sex steroid production that brings about the ensuing physical changes of puberty occurs because these pubertal levels of sex steroids can no longer suppress gonadotropin secretion, as would occur at a similar level of sex steroid secretion in the prepubertal state.

A clinician may deduce the level of an endocrine defect in the system by measuring the concentrations of hormones in serum or plasma at various steps of the process (e.g., a low serum cortisol and high adrenocortical-stimulating hormone (ACTH) indicates a primary defect at the level of the adrenal gland, whereas a low serum cortisol along with a low ACTH indicates a disorder of the pituitary gland or the hypothalamus (Table 1.1)). Positive feedback loops occur as well; the midcycle LH peak which triggers ovulation occurs due to positive estrogen feedback on higher CNS centers. In most cases, it is not sufficient to obtain a single hormone measurement without considering its controlling factors or the effects it exerts.

Endocrine disorders may manifest in several ways:

1. By excess hormone effect (e.g., in Cushing syndrome, an excess of glucocorticoid is present; e.g., if the excess is secondary to autonomous glucocorticoid secretion by a target organ (cortisol secretion by the adrenal gland), the trophic hormone ACTH will be suppressed).
2. By deficient hormone: e.g., in glucocorticoid deficiency, inadequate cortisol is present; if the deficiency is at the target organ (the adrenal gland), the trophic hormone (ACTH) will be elevated.
3. By an abnormal response of end organ to a hormone: e.g., in pseudohypoparathyroidism, resistance to parathyroid hormone (PTH) occurs, and so PTH is elevated, but the parathyroid hormone exerts no effects.

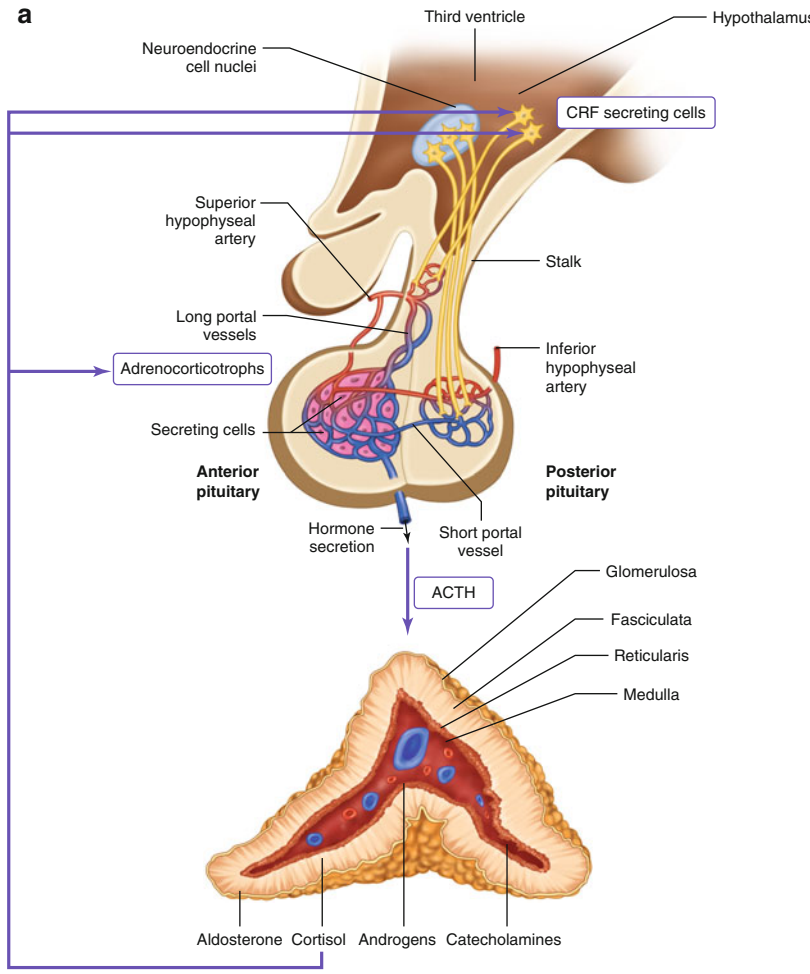


Fig. 1.2 Logic of evaluation of hypothalamic–pituitary feedback loops using the hypothalamic–pituitary–adrenal axis as an example. (**a**) The normal situation where the target gland (adrenal gland) regulates the stimulatory hormone by negative feedback inhibition. (**b**) Primary defect due to failure of the target gland and decrease in its secretion of hormone: the stimulatory hormone (ACTH) increases due to absence of negative feedback inhibition. (**c**) Decreased or "hypo" situation whereby the stimulatory hormone is absent and the target gland's hormone product falls. In the hypothalamic–pituitary–target gland axis, this would be a secondary (ACTH secretory defect illustrated here) or tertiary (CRF secretory defect not illustrated in the figure) defect

4. By gland enlargement that may cause effects as a result of size rather than function; with a large nonfunctioning pituitary adenoma, abnormal visual fields and other neurological signs and symptoms will result, and pituitary endocrine cells may cease to function, even though no hormone is produced by the tumor itself.

Tumors of other nonendocrine organs also may produce hormones as with the ectopic production of ACTH from an oat cell carcinoma of the lung in adults. Endocrine disorders may be revealed by the response of various organs to an excess or deficiency of various hormones well before the size of the endocrine tumor makes it apparent (adrenal carcinoma may cause virilization before it exerts a mass effect).

Hormones have various molecular structures. Thus there are peptide (e.g., TRF), glycoprotein (LH), monoamine (epinephrine), amino acid

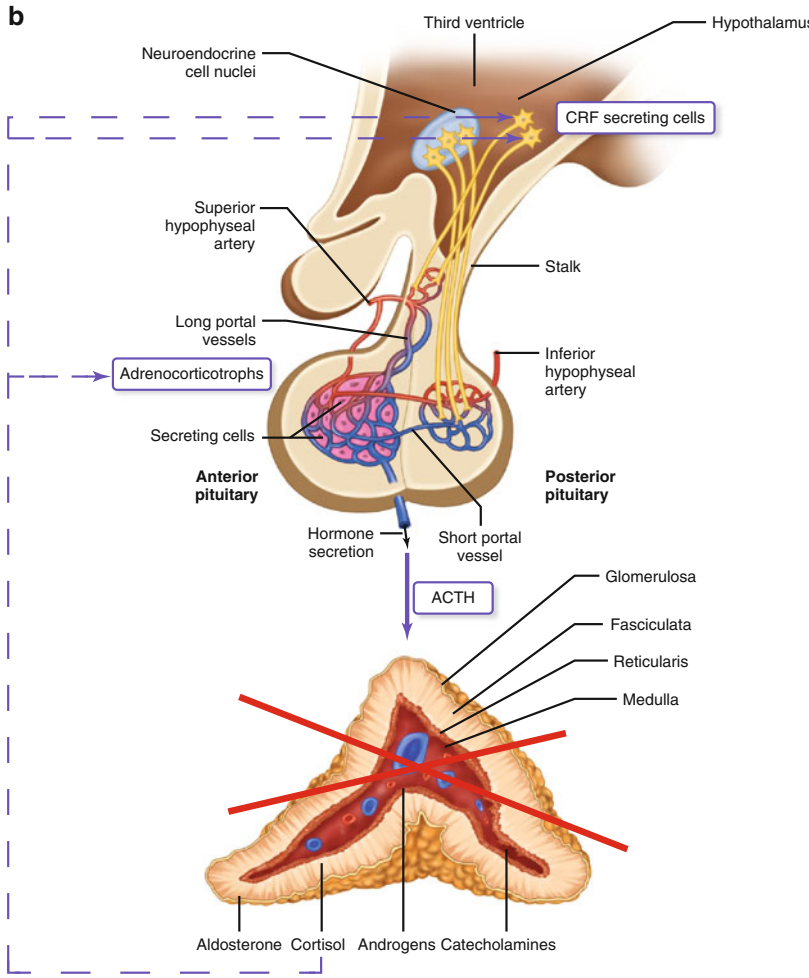


Fig. 1.2 (continued)

derivative (thyroxine), steroid (testosterone), and lipid (prostaglandin) structures of hormones. Different structures of hormones necessitate different receptors. Receptors are then linked to intracellular processes that bring about the (in normal situation) desirable effects. Some hormones exert a limited effect on a single organ (GnRH) or a few organs, and others have widespread effects (thyroxine). Some hormones are stored in their gland of origin (peptide hormones), while others have limited storage and must be synthesized to exert effects (steroids). Many hormones circulate in a protein-bound state that acts as a reservoir for future use or limits biological effect (SHBG for sex steroids or growth hormone- binding protein for growth hormone).

Peptide hormones are produced by various endocrine organs or in an ectopic manner by the cells of certain neoplasms. Peptide hormones act through specific cell membrane receptors; the receptors consist of an extracellular domain, which directly interacts with the ligand hormone, a transmembrane domain that connects actions outside the cell with the actions destined to occur within the cell, and the intracellular domain that contains the cellular constituents that cause various biological actions (Fig. 1.3). These internal cellular actions include phosphorylation of peptides or proteins and the generation of other molecules that cause a cascade of events, ultimately leading to the metabolic action expected by the presence of the hormone on the receptor (Fig. 1.3).

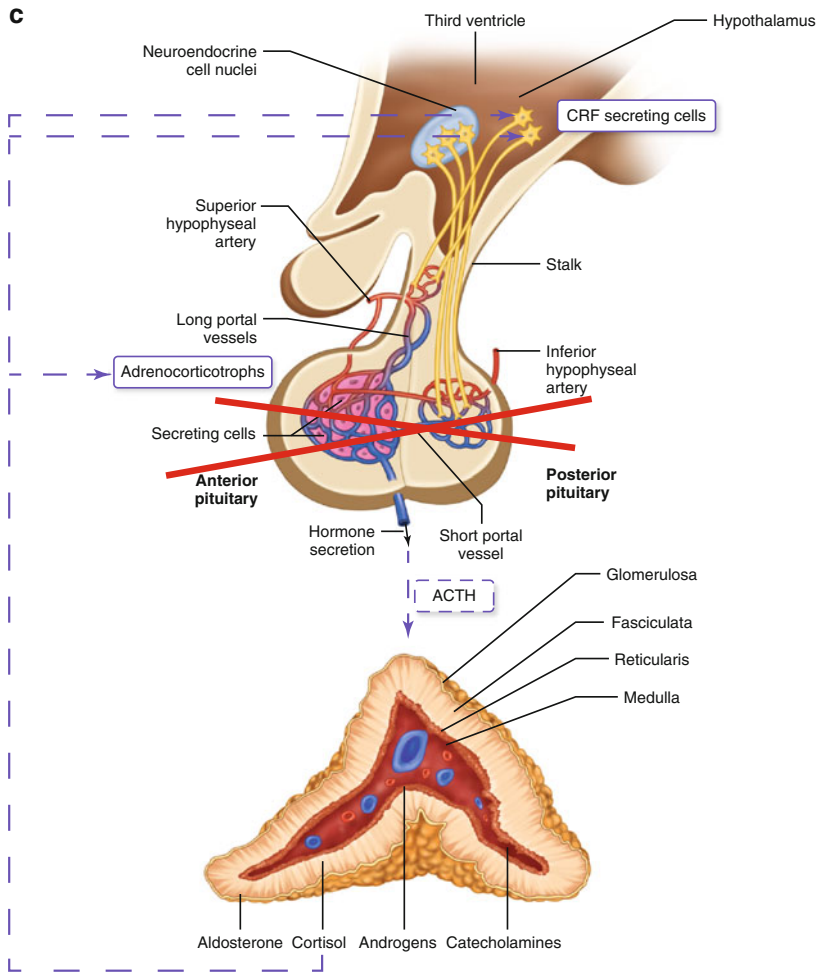


Fig. 1.2 (continued)

Table 1.1 The differential diagnosis of primary versus secondary or tertiary endocrine disease or autonomous function

Trophic hormone secretion (e.g., ACTH)	Target organ hormone secretion (e.g., adrenal gland)	Condition	Example
Normal	Normal	Normal	
Low	High	Autonomous function of target gland	Adrenal adenoma (see Fig. 10.6)
High	High	Target gland is stimulated by hypothalamic–pituitary axis	Cushing disease caused by pituitary microadenoma (see Fig. 10.5)
Low	Low	Secondary or tertiary failure of target gland	ACTH deficiency (see Fig. 1.2c)
High	Low	Primary failure of target gland	Addison's disease (see Fig. 1.2b)

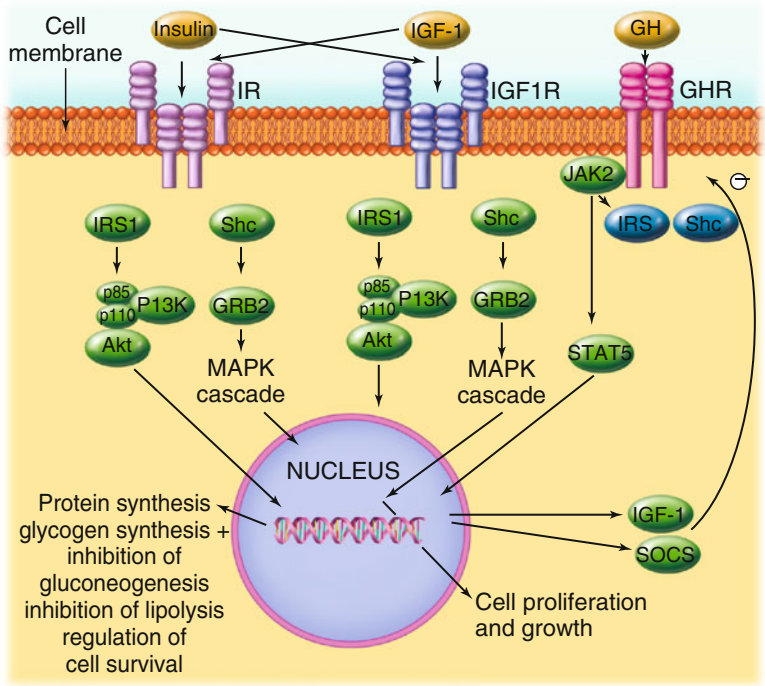


Fig. 1.3 Schematic structure of cell-surface heterodimeric insulin/insulin-like growth factor 1 (IGF-1) receptor and GH receptor (GHR) on an exemplary cell surface. The insulin receptor is a heterodimer composed of two α- and two β-subunits. The type 1 IGF receptor has a similar structure to the insulin receptor. Both have similar cellular responses to the ligand binding to the receptor, more the insulin sequence favors the IRS-1 to Akt pathway while the IGF-1 receptor proceeds through the MAPK pathway. In a situation in which there is excess insulin, such as found in the infant of a diabetic mother, insulin can cross-react with the IGF-1 receptor leading to increased growth. Conversely, IGF-1 can interact with the insulin receptor, causing insulin effects including hypoglycemia. Two independent GH receptor (GHR) molecules must interact with one molecule of GH to cause intracellular activities. This leads to the recruitment of Janus kinase 2 (JAK2), which phosphorylates the GHR, which provides a docking site for STAT (signal transducer and activator of transcription). STAT is then phosphorylated and migrates uncoupled to the nucleus, where it regulates transcription through binding elements of target genes. SOCS (suppressor of cytokine signaling) provides a localized feedback loop in which the consequences of GH binding to its receptor can be regulated. IGF-1 also provides a localized feedback loop. The amino acid sequence of the extramembrane portion of the GH receptor is cleaved from the GHR and becomes the circulating GH-binding protein (*GHBP*) which thereby reflects the abundance of GHRs. Abbreviations: IGF-1 – insulin-like growth factor 1, GH – growth hormone, IR – insulin receptor, IGF-1R – insulin-like growth factor 1 receptor, GHR – growth hormone receptor, IRS-1 – insulin receptor substrate 1, Shc – Shc protein, GRB2 – growth factor receptor-bound protein 2, PI3K – phosphatidylinositol 3-kinase, Akt – Akt protein, JAK2 – Janus kinase 2, STAT5 – signal transducer and activator of transcription 5, SOCS – suppressor of cytokine signaling (Modified from Trobec K, von Haehling S, Anker SD, Lainscak M. Growth hormone, insulin-like growth factor 1, and insulin signaling-a pharmacological target in body wasting and cachexia. J Cachexia Sarcopenia Muscle. 2011 Dec;2(4):191–200)

G protein-coupled receptors (including ACTH, vasopressin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, gonadotropin-releasing hormone (GnRH), thyroid-releasing factor (TRF), growth hormone-releasing factor (GHRH), CRF, somatotropin-releasing inhibiting factor (SRIF or SS), glucagon, PTH receptors) have seven transmembrane domains and a G protein complex that regulates the second messengers such as calcium and cyclic adenosine monophosphate (AMP). Cytokine receptors for GH, prolactin, and leptin consist of extracellular, transmembrane, and cytoplasmic domains (Fig. 1.3). The extra membrane domain may

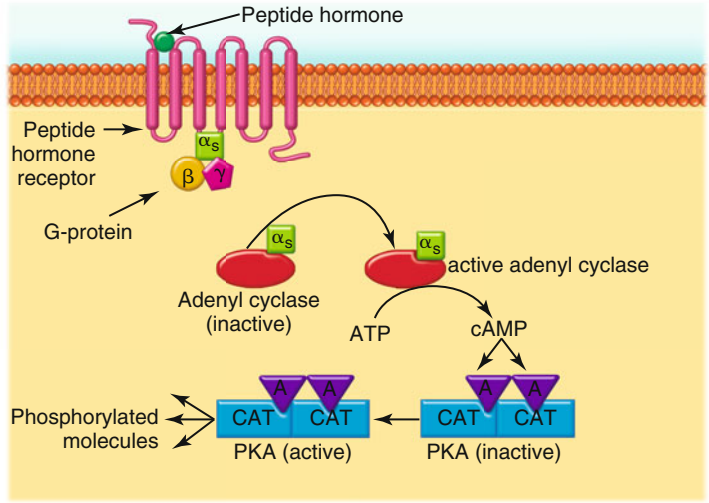


Fig. 1.4 The binding of a peptide hormone to its cell membrane receptor, triggering intracellular events which elicit a response. Note the seven-transmembrane structure of the G-protein-coupled peptide hormone receptor (GPCR) which in this case is a receptor for glucagon used as an example for the general class of membrane-bound receptors. When the ligand attaches to its receptor, the GPRC undergoes a conformational change leading to activation of the associated heterotrimeric G protein compound by exchanging its bound GDP for GTP which then associates with a specific G protein subunit, in this case, a Gs-alpha protein subunit, which converts inactive adenyl cyclase to the active form which in turn catalyzes the conversion of ATP into cyclic adenosine monophosphate (cAMP). cAMP then activates protein kinase A (PKA) by binding to the regulatory subunits of PKA (noted by an A). The regulatory subunits then dissociate from PKA and the remaining catalytic subunits in turn phosphorylate other proteins. Various effects can occur in the system based upon the G protein involved. Adapted from biochemistrypage.org, 2015

reflect the structure of circulating binding proteins; e.g., the extracellular domain of the growth hormone receptor (GHR) bears the same amino acid sequence as a circulating growth hormone-binding protein (GHBP) with which GH circulates. The cytokine receptors must dimerize (two receptor molecules must join) to trigger a metabolic effect. The intracellular domain causes phosphorylation of tyrosine molecules (JAK2 kinases), which then phosphorylate signal transducers, and activators of transcription (signal transducer and activator of transcription; STAT), which then travel to the nucleus to regulate deoxyribonucleic acid (DNA) action.

Peptide hormone receptor number and avidity may be regulated by hormones; continuous rather than episodic exposure to GnRH downregulates GnRH-receptor number as well as receptor activity on pituitary gonadotropes. This phenomenon is utilized in treatment with super-active gonadotropin-releasing hormone agonists. Mutations of receptors may cause disease by rendering the receptor inoperative, or alternatively, the receptor may be stimulated without the presence of the hormone in constitutive activation. The G protein complex may be abnormal in certain diseases; e.g., McCune–Albright syndrome is associated with constitutive activation of G stimulatory protein in affected cells. A constitutively active mutation in the seven-transmembrane domain may be present, as occurs in familial germ cell and Leydig cell maturation. Alternatively, dimerization may fail to occur in some cases of GH insensitivity.

The family of insulin receptors includes the insulin and insulin-like growth factor (IGF)-1 receptors (Fig. 1.4). These are heterodimeric, consisting of two α- and two β-chains. When the appropriate hormone binds to the extracellular domain, the conformation is altered, and phosphorylation of tyrosine occurs in the intracellular portion. Through a cascade of effects involving

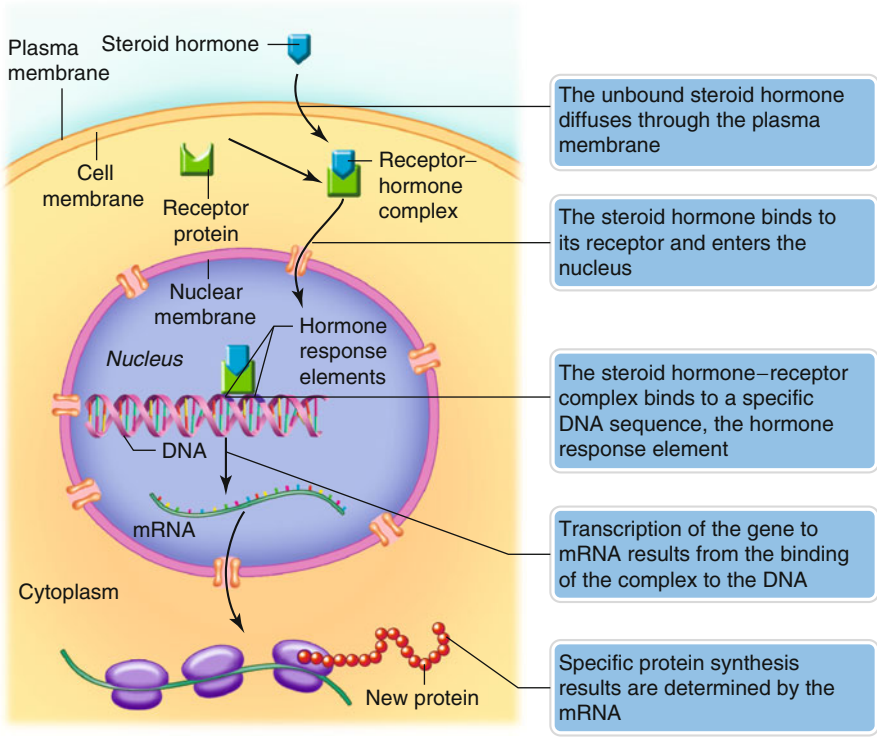


Fig. 1.5 Molecular pathway of steroid hormone action. The steroid circulates with a binding protein, from which it dissociates to pass through the cell membrane and reach the cytoplasm. The receptor is complexed with heat shock proteins (not shown), which dissociate, allowing the steroid to bind to the receptor. Once bound to the steroid, the steroid receptor is activated and is transported into the nucleus. The steroid receptor complex changes conformation, allowing it to bind to the hormone response elements (HREs), or receptor sites, of DNA causing the subsequent transcription of DNA into mRNA and translation of the mRNA into proteins which exert their subsequent effects. Similar mechanisms are employed by members of the thyroid receptor (*TR*) gene family, though most of the latter are concentrated in the nuclear compartment and are not associated with the heat shock protein (HSP) complex prior to binding with the ligand. Adapted from Studyblue.com, 2015

insulin-receptor substrates (IRSs), activation of mitogenesis and proliferation as well as effects on carbohydrate metabolism occur. Insulin and IGF-1 have differing effects on cell growth and metabolism, and while each molecule has greater effect on its own specific receptor, insulin can bind to the IGF-1 receptor, and IGF-1 can bind to the IR exerting effects characteristic of the other molecule. In states of elevated insulin such as in the infant of a diabetic mother, interaction of the insulin with a receptor similar to the insulin receptor, in this case the IGF-1 receptor, occurs stimulating growth.

Steroid hormones circulate noncovalently bound to various binding proteins. Steroid hormones exert their effects by diffusion through the cell wall into the cytoplasm. Specific cytoplasmic steroid receptors bind to the steroid molecule, and the hormone–receptor complex translocates to the nucleus (Fig. 1.5). The steroid receptor then binds to DNA hormone response elements to produce the synthesis of messenger RNA (mRNA) which leads to translation of the mRNA on ribosomes and the production of proteins or peptides predicted by the steroid hormone that result in changes in cell function.

Thyroid hormone receptors are similar to steroid receptors in structure and function and are members of the steroid hormone superfamily. The receptors are present either as monomers (TR), heterodimers with retinoid X receptor (TR/RXR), or homodimers (TR/TR). TR/RXR

heterodimers are the most transcriptionally active complex. In the absence of hormones, TR exists in a complex with corepressor proteins binding to hormone response elements (HREs) in DNA in an inactive state. Binding of thyroid hormone results in a conformational change in TR which displaces corepressors from the receptor/DNA complex while adding coactivator proteins to the complex. Once the DNA/TR/thyroid hormone/coactivator complex is formed, RNA polymerase transcribes DNA into mRNA which leads to translation of the mRNA on ribosomes and the production of proteins or peptides predicted by the hormone that result in changes in cell function.

Because of the feedback loops, interpretation of serum hormone levels must be related to their controlling factors; a given value of PTH may be normal in a eucalcemic patient, but the same value may be inadequate in a hypocalcemic patient with partial hypoparathyroidism, and this same value of parathyroid hormone may be excessive in a hypercalcemic patient who might have hyperparathyroidism. Thus a single endocrine test may be inadequate to evaluate anomalies of a feedback loop.

A diurnal rhythm of hormone secretion occurs in some systems (e.g., serum ACTH increases in the early morning hours, followed by an increase in serum cortisol and by a decrease in both during the afternoon and evening). If the rhythm is disturbed, the amount of hormone present will vary from the normal pattern, and disease might occur; if the normal decrease of cortisol does not occur in the evening, Cushing syndrome might result, simply because the p.m. cortisol values match the a.m. values and total daily cortisol secretion is excessive. Thus, although there is little increase in serum cortisol values above normal a.m. values, a great increase in cortisol effect occurs in such patients affected by Cushing disease.

Knowing the basic functions of hormones and their interactions lends logic to the evaluation of patients with endocrine diseases. This volume attempts to emphasize such a systematic evaluation of endocrine disease. The chapters are based on organ systems and begin with a brief explanation of the basic physiology at work.

Many of the conditions in this book are caused by gene mutations. If there is a genetic link for a given condition, a reference to the Online Mendelian Inheritance in Man (OMIM) is placed after the first mention of the condition. Further information can be found on the OMIM website, http://www.ncbi.nlm.nih.gov/Omim/. (OMIM can also be found under a pulldown menu tab entry on the PubMed site).

The format is as follows as described verbatim on the OMIM website:

Each OMIM entry is given a unique six-digit number as summarized below:

1----- (100000-) 2----- (200000-) Autosomal loci or phenotypes (entries created before May 15, 1994)
3----- (300000-) X-linked loci or phenotypes
4----- (400000-) Y-linked loci or phenotypes
5----- (500000-) Mitochondrial loci or phenotypes
6----- (600000-) Autosomal loci or phenotypes (entries created after May 15, 1994)

Allelic variants are designated by the MIM number of the entry, followed by a decimal point and a unique 4-digit variant number. For example, allelic variants in the factor IX gene (300746) are numbered 300746.0001 through 300746.0101.

The symbols preceding a MIM number represent:

An asterisk (*) before an entry number indicates a gene.

A number symbol (#) before an entry number indicates that it is a descriptive entry, usually of a phenotype, and does not represent a unique locus. The reason for the use of the number symbol is given in the first paragraph of the entry. Discussion of any gene(s) related to the phenotype resides in another entry(ies) as described in the first paragraph.

A plus sign (+) before an entry number indicates that the entry contains the description of a gene of known sequence and a phenotype.

A percent sign (%) before an entry number indicates that the entry describes a confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known.

No symbol before an entry number generally indicates a description of a phenotype for which the Mendelian basis, although suspected, has not been clearly established or that the separateness of this phenotype from that in another entry is unclear.

A caret (^) before an entry number means the entry no longer exists because it was removed from the database or moved to another entry as indicated.

*, The gene location is reliably matched with the clinical situation.

#, Two or more genes can cause the phenotype.

Lack of either symbol, no mode of inheritance has been *proven*.

The website often has a link to photographs demonstrating any dysmorphic characteristics of a condition. This source is frequently updated with clinical and basic information on the subjects referenced. There is a useful clinical synopsis of many conditions that are listed. The reader may benefit from frequently accessing this resource or the associated GeneTests website. It will be apparent if an entry has that many of the entries have been recently updated with new references and new information as indicated by a date noted at the bottom of the entry; other entries may still await such updates and may date from several years earlier.

It is important to remember that many of the autosomal-dominant conditions in OMIM may actually arise de novo rather than in an inherited pattern.

Two other websites are listed below for genetic information. GeneReviews is a peer-reviewed website which addresses various genetic syndromes, some of which are listed in this book. The GeneTests website lists genetic clinics and locations, and genetic tests can be obtained from research labs or commercial laboratories.

Suggested Readings

Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: http://omim.org/ https://www.genetests.org/

Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2015. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1116/

Kublaoui B, Levine MA. Chapter 3—Receptor transduction pathways mediating hormone action. In: Pediatric Endocrinology (Fourth Edition). Sperling MA editor. 2014: 34–89.

Menon RK, et al. Chapter 2—Molecular endocrinology and endocrine genetics. In: Pediatric Endocrinology (Fourth Edition). Sperling MA, editor, 2014:9–33.

Habener JF. Mechanism of action of hormones that act on nuclear receptors. In: Williams textbook of endocrinology. Kronenberg HM, Mel. Med S, Larsen PR, Polonsky KS, editors. Elsevier/Saunders 2011.

Spiegel AM, Carter-Su C, Taylor SI, Kulkarni RN. Mechanism of action of hormones that act at the cell surface. In: Williams textbook of endocrinology. Kronenberg HM, Mel. Med S, Larsen PR, Polonsky KS, editors, Elsevier/Saunders. 2011.

Gardner DG, Anderson M, Nissenson RA. Hormones and Hormone Action. In: Greenspan's Basic & Clinical Endocrinology (9th edition). Gardner DG, Shoback DM, Greenspac FS, editors. New York: McGraw-Hill Medical, 2011.

The Evaluation of a Child or Adolescent with Possible Endocrine Disease

2

As in all disciplines, the history and physical examination are crucial in determining a course of evaluation. A standard pediatric history and physical examination will serve the evaluator well, but in a few areas, increased attention is required. The type of problem under consideration may change the direction of questioning and evaluation. The following general approach is discussed in more detail in the following chapters regarding specific disorders, but this outline is meant to direct the initial evaluation.

The Medical History

In many cases, the diagnosis is apparent from the medical history (Table 2.1). In general, the parents will be the sources of information, but in most cases, it will be useful to obtain previous medical records, often from several sources because of the recent tendency of transferring care of a child if the child moves to new locations or has a mandatory change of insurance. Modern electronic medical records have menus for medical, surgical, family, and birth histories, which should be carefully filled out once and easily accessed in future visits for reference or updating.

All aspects of the pregnancy history may be of importance. This includes medical complications, nutritional status, toxic or medication exposures (smoking, infections, medications), gestational age, complications or difficulties of delivery, and Apgar scores.

Medical history must aim to uncover any possible chronic disorders that might have contributed to the disease under evaluation or might complicate the treatment. Many chronic disorders may decrease growth rate; it might be said that almost every page of a pediatric textbook has a reason for impaired growth. If no previous height measurements are available, a history of changes in shoe or clothing size can be of value to determine whether the child is growing adequately, although follow-up measurements over a period of at least 3 months (and longer if possible, as accuracy increases with the length of time of follow-up) are necessary for diagnosis. In older girls, or younger ones if the issue requires it, a menstrual history is necessary; age of menarche (onset), regularity, and amount of flow and discomfort are important. Inquire about abnormal patterns of urination or defecation.

The interview to obtain a medication history must often be specific, as many do not consider vitamins or "natural substances" as medicine, although excessive vitamins might be the very cause of a disorder (e.g., hypervitaminosis D). In addition, medications found around the house may be of importance; did the child get into the oral contraceptives or hormone replacement therapy used by another member of the family? Lotions, creams, and hair treatments may contain hormones; tea tree oil may cause feminizing effects while testosterone gel can be transferred from the intended recipient to children by touch or by the use of a common towel. Diet and nutritional

D.M. Styne, *Pediatric Endocrinology*, DOI 10.1007/978-3-319-18371-8_2

Table 2.1 Medical history for pediatric endocrinology

Chief complaint
History of present illness
Birth history and prenatal history
Gestational age
Complications of pregnancy
Toxic exposures
Maternal accidents
Medication taken including vitamins and "natural" treatments
Substances used, including cigarettes
Were ultrasounds obtained, and was the growth normal?
Was fetal motion normal?
Newborn period
Method of delivery
Complications of delivery
Orientation of delivery
Apgar scores
Birth weight % related to gestational age
Developmental assessment
Use of oxygen or other types of support or treatment
Hypoglycemia; documented by blood sugar value or inferred by activity or behavior?
Development
Age of milestones: sitting, cruising, walking; speaking words, sentences. Perform a developmental test if problems are noted
Family history
Direct questions are often necessary, as family might not volunteer information to general questions. Refer to chapters for associated conditions of importance
Note full siblings, half siblings, stepparents, or biologic parent relationships
Construct a family tree if possible
Were there any miscarriages?
Age and percentile of height and weight of siblings
Height and weight of parents; approximate weight, if obesity is noted, is important
Ethnicity of parents
Area where parents spent their childhood, especially if there is a possibility of famine, war, or refugee status in their history
Is there consanguinity?
Age of menarche in mother and sisters if old enough
Age father stopped growing or started to shave and the same information from brothers, if old enough
History of disease similar to patient or otherwise of importance in related individuals
Ask about early deaths due to heart disease or strokes specifically in all conditions under evaluation
Social: who lives at home, what is their relationship, how do they interact, and are there adequate funds for the child's benefit especially for nutrition?
Diet: is there adequate food and of a healthful quality? Is there any aversion to eating, is there lack of satiety, or is there an unusual diet? In evaluation of obesity, much more detail of diet composition and a dietician consultation are important
Surgical procedures
Allergies
Accidents, especially to the head

(continued)

Table 2.1 (continued)

Medications taken, including vitamins or "natural substances." Direct questions are often necessary, as family might not volunteer information to general questions such as, "Does the child take any medications?" Does anyone have high blood pressure may be answered negatively until you find that the individual is taking medications to make the blood pressure normal!
School history: grade level, grades obtained, any changes, interrelationships with schoolmates, teasing or bullying interactions?
Educational achievement in patient and in siblings and parents
Review of systems in general and directed specifically to the issues under consideration
Areas of concern will vary with the disease under consideration, so check the appropriate chapters to determine specific symptoms and signs of importance
In most situations today, ask about amount of television viewing or screen time per day, amount of activity, sports or other forms of exercise, and especially do so in children with obesity

patterns are of general importance but also may contribute to the etiology of a condition. Significant levels of estrogen or other substances might be found in a noncommercial source of beef.

Educational achievement, ability, and history are important. In addition, it is important to determine if of psychological problems if related to the condition the child is manifesting (e.g., severe short stature or precocious puberty)?

Family history is of great importance in the evaluation. Family history of chronic disease, including neurologic or endocrine conditions, is determined, and the construction of a family tree is helpful. In many cases, the questions must be direct, such as, "Has anyone in the family had thyroid disease?" rather than a general query since many feel that once treated, there is no disease; asking if someone in the family has hypertension may elicit "no" as an answer; asking whether some of the family members take medication for hypertension might be returned with the statement "I do but it is all under control now." Because parents of pediatric patients are young and subject to developing new medical conditions (such as type 2 diabetes, hypertension, or dyslipidemia) which are of importance in the evaluation of the child, family medical history must be obtained repeatedly at subsequent visits. Did the parents immigrate from a developing country or live an underprivileged life to account for their own history or stature, if abnormal? Was the child adopted, or should another biologic parent who is no longer in the house be included in the history? If an autosomal recessive defect is suspected, determine whether consanguinity is present. Are there relatives who died young without diagnoses? Indeed in this era of obesity, all cardiac events or strokes at a young age (various definitions are used for "young," but one suggested is the occurrence of an event before age 50 years in men and before age 60 years in women) must be noted. Even though it may be an endocrine visit, queries about dyslipidemia or hypertension are important in this age of obesity. The examiner must ask the age of menarche in the mother or of the growth spurt or age at first shaving in the father (a father will rarely recall his age of onset of puberty!).

Interfamilial interactions can be observed during the interview process to evaluate the possibility of psychosocial dwarfism or other psychosocial complications.

A history of surgery, allergies, and accidents to the central nervous system (CNS) or other important areas is pertinent.

Physical Examination

Physical examination must be complete (Table 2.2). Accurate determination and plotting of height (in centimeters) as described in Chap. 5, weight (in kilograms), and body mass index (BMI) must accompany the determination of vital signs (see Chap. 13 for details). An infant should have weight and height interpreted in terms of gestational age (by using intrauterine growth charts; see Chap. 5).

A patient who has stature below the third percentile for height according to the Centers for

Table 2.2 Physical examination for pediatric endocrinology

All vital signs will vary with the age of the child, so refer to the *Harriet Lane Manual* or other sources for standards for age
Pulse
Blood pressure (interpret in terms of blood pressure for height, and make sure there is an adequate-sized cuff; see Chap. 13)
Respiratory rate
Temperature if pertinent to disease under consideration or intercurrent illness
Infant length, measured as described in Chap. 5, performed by two adults
After age 2 years, measure height in centimeters on a stadiometer without shoes on; repeat 2 or 3 times if stature is the main complaint, and make sure measurements are consistent and repeatable within 0.3 cm
Weight in kilograms in light or no clothes
Calculated body mass index (BMI) (kg/m^2) interpreted on chart for sex and age
Upper/Lower-segment ratio as necessary (especially in boys with disorders of puberty) (see Chap. 5)
Arm span as necessary (especially in chondrodystrophies or abnormalities of puberty) (see Chap. 5)
HEENT (head, eyes, ears, nose, throat)
Look for midline defects, including cleft palate or lip
Observe for signs of syndromes
Cataracts or colobomas?
Development and status of dentition for age. Single central maxillary incisor as a midline defect that might relate to hypopituitarism?
Acne or comedones?
Beard?
Voice change?
Neck
Motion
Goiter? Measure width and height of thyroid lobes, and estimate thickness (e.g., 25 % or 50 % greater than normal) Nodules? Bruits?
Acanthosis nigricans at back of neck?
Lungs: customary pediatric examination
Heart: customary pediatric examination
Abdomen: customary pediatric examination
Axillary hair or odor; enlarging axillary sweat glands?
Breast stage in girls (see Chap. 9)
Stage of pubic hair (see Chap. 9)
Stage of genital development in boys (see Chap. 9)
Extremities: customary pediatric examination unless chondrodystrophy is suspected, and then note ratio of proximal to distal portions of extremities. Look for Madelung deformity in short stature (see Chaps. 5 and 9). Note motion of joints and back. Evaluate upper-to-lower segment ratio. Observe for contractures or subtle signs of cerebral palsy.
Scoliosis evaluation
Skin
Café-au-lait spots (number, type, shape, and size), subcutaneous calcifications, acanthosis nigricans
Neurologic: customary pediatric examination with special attention to the CNS in most cases
Cranial nerves: signs of central nervous system (CNS) disease, optic disk development, visual fields, and, in delay of puberty, sense of smell
Chvostek or Trousseau signs
Tremor
Deep tendon reflexes: customary pediatric examination but look for delayed relaxation of ankle reflexes

Disease Control (CDC) or WHO charts, who is growing at a rate less than the fifth percentile for height velocity for age, or is below the third percentile for corrected mid parental height is worthy of evaluation; a combination of two or more of these characteristics warrants increased concern. Determination of arm span and upper-to-lower segment ratio is useful in the evaluation of short stature (e.g., to indicate hypochondroplasia or achondroplasia or other abnormalities of disproportionate growth) or of delay in puberty (e.g., to look for the long arms and lower upper-to-lower segment ratio of hypogonadism known as eunuchoid proportions). The arm span is measured with the patient standing with the back to the wall with arms spread horizontally and is the distance from one outstretched middle fingertip to the other. The lower segment is measured from the top of the symphysis pubis to the floor, whereas the upper segment is calculated by subtracting the lower segment from the height of the child. The upper-to-lower segment ratio varies with age (Fig. 5.7). A decreased upper-to-lower segment ratio is found in Klinefelter syndrome, and an increased ratio is found in untreated hypothyroidism, among other possibilities.

If a problem of growth or pubertal progression is under evaluation, one must consider whether a low body weight is the source of the problem. If nutrition is suboptimal, usually the problem is not endocrine in origin, and other causes must be considered. Alternatively, if the child is starting puberty early or progressing too fast, is excess weight the cause? Every child must have a BMI calculated and interpreted on a chart. Body mass index charts are found at www.CDC.com; low BMI for age might indicate malnutrition due to chronic disease, whereas elevated BMI for age might indicate rapid growth due to obesity.

The general appearance of the child may furnish a clue as to the chronicity of the problem and its emotional effects. Levels of energy and activity are important. Suspicion of a syndrome must be clarified by the examination. The head, eyes, ears, nose, and throat (HEENT) examination may point to a midline defect, syndrome, or neurologic condition. Is there a goiter or nodule of the thyroid gland? Cardiac, pulmonary, and abdominal examinations must be thorough but do not differ appreciably from those in a general pediatric examination. Skin examination might reveal café-au-lait spots or subcutaneous calcifications. The extremities may appear to be curved or abnormal or an abnormality of gait may be noted, as an indication of rickets. Neurologic examination is essential in many disorders considered in the book. Signs of dysfunction might suggest a neoplasm or a congenital defect associated with an endocrine condition.

In almost all conditions, it is important to determine the stage of pubertal development. This must be done with care and consideration, as the patient, especially in the teenage years, may be embarrassed; if the patient refuses and the caregiver cannot achieve acquiescence, this portion of the examination may have to be omitted on this visit, as it should not be done by force. Even with cooperation, a nonrelated adult chaperone should be in the room during the examination. Determination of stage of breast and pubic hair growth is performed in girls and genitalia and pubic hair (as well as beard) in boys, according to standard rating techniques (see Chap. 9). If a child refuses the exam, pictures as in Figs. 9.1, 9.2, and 9.3 may be presented to the patient to ask which figure they think they look most like their stage of development; this is not as accurate as a detailed exam, but it may be all it is possible. In addition, the development of axillary odor or hair, the presence of comedones or acne, and the maturation of facial features are noted in all; if the child refuses genital examination, at least this other information is helpful. The appearance of abnormal distribution or amount of facial or body hair may be an indication of a problem.

Often when no other diagnosis is found in the general clinician's office, an endocrine disorder is considered and referral made. The results are often disappointing as not every obscure symptom or finding can be related to endocrinology!

Disorders of the Hypothalamic–Pituitary Axis

3

The hypothalamic–pituitary axis might be considered as a translator of the action of higher central nervous system activity into endocrine secretion. In many cases, hypopituitarism is the term used to describe a defect in the secretion of pituitary hormones, but in fact, the condition may be a hypothalamic problem; growth hormone deficiency most often is caused by the lack of growth hormone-releasing factor from the hypothalamus rather than a defect in the growth hormone-secreting cells of the pituitary gland. Thus, hypopituitarism is a vague term although it is in frequent use.

Physiology

The *hypothalamus* is located in the forebrain below the thalamus, hence the name. Under the influence of higher central nervous system centers the hypothalamus exerts endocrine effects either directly, in the production and release of vasopressin and oxytocin from the posterior pituitary, or indirectly, through the release of hypothalamic-releasing or inhibiting factors, small peptides produced in minute quantities, which reach the anterior pituitary gland from the median eminence of the hypothalamus through the hypophysiotropic, or hypothalamic–pituitary, portal vessels to regulate anterior pituitary hormone secretion (Fig. 3.1). Thus, disorders of any of these interconnected regions, the CNS, the hypothalamus, or the pituitary gland, can cause endocrine disease.

A sequence of homeodomain proteins and transcription factors cause primordial cells to develop into the characteristic cells of the anterior pituitary gland, the gonadotroph, the thyrotroph, the lactotroph, the somatotroph, and the corticotroph. Mutations in several of these, PROP 1, PIT 1, LHX3, LHX4, HESX1, and TPIT lead to hypopituitarism with a varying array of pituitary hormone defects depending on the mutation. There are commercial tests available to screen for these mutations.

The pituitary gland receives arterial blood from the superior hypophyseal artery which gives rise to the capillary bed that bathes the endocrine cells of the median eminence of the hypothalamus and into which they release their trophic hormones. These capillaries form the long hypophysiotropic, or hypothalamic–pituitary, portal system which carries the hypothalamic trophic factors to ensure that they reach the cells of the anterior pituitary gland to stimulate the secretion of their pituitary hormones. There is a second short portal system which connects the posterior and anterior pituitary glands as well. A second capillary bed drains the pituitary secretions into the venous system.

The hypothalamic factors are peptides—the shortest, TRF, composed of three amino acids—that regulate anterior pituitary function. These

(A more detailed discussion of specific hormones is found in the chapters related to their functions (e.g., growth hormone (GH) is presented in Chap. 5))

D.M. Styne, *Pediatric Endocrinology*, DOI 10.1007/978-3-319-18371-8_3

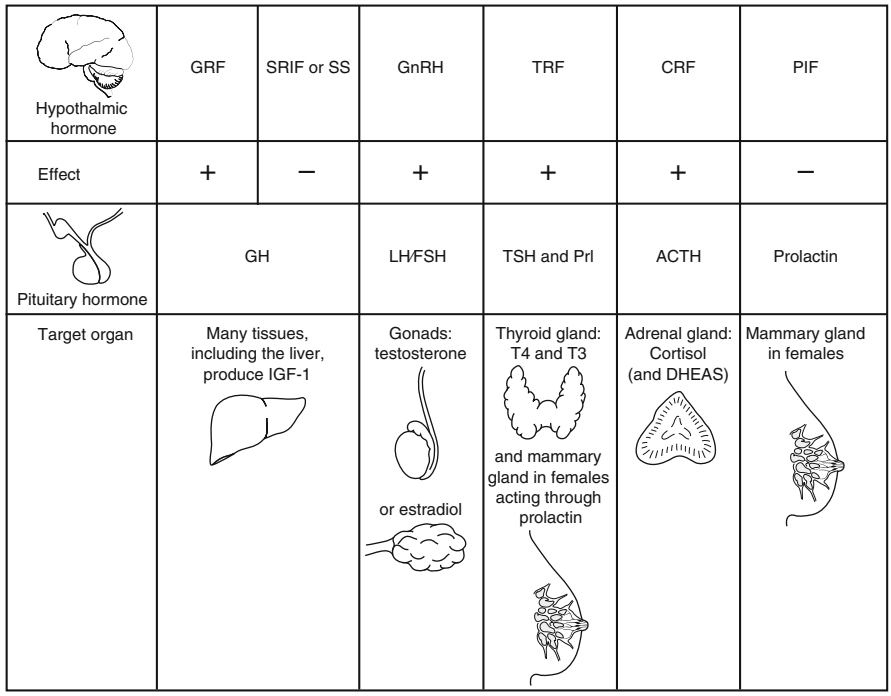


Fig. 3.1 The hypothalamic factors, the pituitary hormones that they control, and the target organs of the pituitary hormones

peptides are growth hormone-releasing factor (GRF) which stimulates the release of growth hormone (GH), gonadotropin-releasing hormone (GnRH) which stimulates the release of the gonadotropins (luteinizing hormone (LH) and follicle-stimulating hormone (FSH)), thyrotropin-releasing factor (TRF) which stimulates the release of thyrotropin (TSH), and prolactin, corticotropin-releasing factor (CRF) which stimulates the release of adrenocorticotropin (ACTH) and vasopressin, and prolactin inhibitory factor (PIF or dopamine) which suppresses the release of prolactin. Somatostatin (SRIF) has many functions throughout the body including the gastrointestinal (GI) tract, but for the purposes of this discussion, somatostatin suppresses growth hormone secretion as well as TSH and prolactin secretion. The glycoprotein hormones LH, FSH, TSH, and hCG are heterodimers composed of an alpha and a beta subunit. The alpha subunit is common for all of these hormones, but the beta subunits confers specificity on each hormone.

Prolactin and growth hormone share some structural homology to human placenta lactogen and derive from a common gene of origin. Prolactin is released in a pulsatile manner and increases during stress. Dopamine is secreted by tuberoinfundibular dopamine (TIDA) neurons of the arcuate nucleus and exerts inhibitory effect on the D2 receptors of lactotrophs, causing suppression of prolactin secretion, and also on the D2 receptors of the thyrotroph, causing suppression of TSH secretion. Estrogen exerts a stimulatory effect on prolactin secretion, and pregnancy is a period of increased prolactin secretion. Prolactin is high in the neonatal period and then reaches a plateau in childhood only to decrease during male puberty. Prolactin remains stable during female puberty. Like growth hormone, prolactin exerts its effects by binding to a cytokine-like receptor on the cell membrane. Prolactin's most notable endocrine effect relates to the production of breast milk but it exerts many other effects on the immune system, cell cycle, growth differentiating and anti-apoptosis, hematopoiesis and angiogenesis, and blood clotting.

After secretion into the peripheral circulation, the pituitary hormones exert their effects on target glands and organs specific for that pituitary hormone. Target endocrine glands in most cases

produce their own hormones that provide feedback to suppress their controlling hypothalamic and pituitary hormones in turn (e.g., cortisol from the adrenal gland provides negative feedback inhibition to the hypothalamic–pituitary system to suppress hypothalamic corticotropin-releasing hormone that stimulates pituitary adrenocorticotropin that in turn stimulates the release of adrenal cortisol). Prolactin is the only pituitary hormone that is mainly suppressed by a hypothalamic factor, prolactin inhibitory factor (dopamine) and GABA (although centrally administered GABA may also stimulate prolactin secretion), whereas all other pituitary hormones are mainly stimulated by hypothalamic factors (it is true that GH is suppressed by the somatotropin release-inhibiting factor (SRIF), but it is also stimulated by the growth hormone-releasing factor (GRF)). Thus hypothalamic disease may lead to a decrease in secretion of most pituitary hormones and an increase in prolactin secretion, whereas a pituitary gland disorder may cause a decrease in prolactin secretion as well as a decrease in other pituitary hormones, a useful diagnostic feature.

The hypothalamus contains the terminal of the axons of vasopressin-secreting neurons while also serving as a location through which other vasopressin-secreting axons pass on their way to their own axon terminal in the posterior pituitary gland. Thus hypothalamic damage will cause diabetes insipidus, whereas the result of pituitary stalk section is variable, depending on the level of lesion. If a pituitary stalk section or disorder is high on the pituitary stalk, all vasopressin-secreting neurons may be affected, and the result is diabetes insipidus, whereas if the pituitary stalk section is low, some vasopressin-secreting neurons may survive intact, and vasopressin secretion and action are still possible, so that diabetes insipidus may not develop or may only be transient (Chap. 4, Fig. 4.4).

Oxytocin is produced in the hypothalamus and transported by neurophysin 1 to and stored in the posterior pituitary. Oxytocin is released with dilation of the uterus and cervix and plays a role in normal parturition; exogenous oxytocin is invoked to promote the delivery of the baby in certain circumstances. Oxytocin plays a role in maternal bonding with a newborn baby and plays a role in lactation after stimulation of the nipples by suckling.

Pathology

Disorders of the hypothalamus or pituitary gland affect endocrine function, but disorders elsewhere in the CNS or radiation therapy to the CNS for other conditions may also cause significant endocrine effects. Although destructive lesions of the hypothalamic–pituitary axis usually decrease endocrine activity (e.g., hypogonadotropic hypogonadism), depending on location, some diseases of the hypothalamic–pituitary axis may instead cause increased function (e.g., precocious puberty). Alternatively, functioning lesions may cause endocrine effects because of their secretions rather than exerting effects due to destruction of tissue by their size or location (e.g., pinealomas secrete the human chorionic gonadotropin (hCG) and cause precocious puberty in boys, while nonfunctioning adenomas of the pituitary gland destroy cell structure and can cause decreased pituitary secretion).

Specific terminology relates to the level of the endocrine lesion. A disorder of the target gland (e.g., thyroid, adrenal gland) is considered a primary disease. A lesion of the pituitary gland is considered a secondary defect, and a lesion of the hypothalamus is a tertiary condition (see Chap. 1, Fig. 1.2).

Central Nervous System Tumors

Most CNS tumors affecting the hypothalamic–pituitary axis will cause multiple pituitary defects. A hypothalamic tumor may, for example, be detected by the presence of galactorrhea, due to increased prolactin secretion from the pituitary gland in the absence of prolactin inhibitory factor from the hypothalamus, occurring along with deficiencies of other pituitary hormones. However, in hypothalamic disease, GH is most often affected, and GH deficiency is the most common outcome. GH deficiency may at first appear to be an isolated finding until more careful endocrine evaluation reveals other pituitary defects.

Because tumors of this area are manifest well after birth, compared to congenital defects which exert effects soon after birth, late onset of

hypothalamic–pituitary deficiencies without contributing history (e.g., surgery or trauma to the area) may very well indicate the development of a CNS tumor, especially if anterior and posterior deficiencies occur together. In contrast, congenital defects of hypothalamic–pituitary hormones appear at or soon after birth, so that early onset of combined posterior and anterior deficiencies may cause significant effects but do not necessarily reflect the development of a tumor. Nonetheless, a magnetic resonance imaging (MRI) evaluation of a child with onset of hypopituitarism of any age is indicated to determine whether a definable anatomic defect is causing the condition.

Craniopharyngioma

Craniopharyngioma is a rare embryonic malformation of nonglial origin in childhood (0.5–2.0 new cases/million population/year or 1.2–4 % of pediatric intracranial tumors) but is a more common CNS neoplasm in pediatrics. It is the most common brain tumor associated with hypothalamic–pituitary dysfunction and sexual infantilism and comprises 80–90 % of neoplasms found in the pituitary and up to 15 % of all intracranial tumors in childhood. Symptoms usually arise before the age of 20 years with a peak incidence between the ages of 6 and 14 years with about 30–50 % occurring in the pediatric age range. Harvey Cushing introduced the term "craniopharyngioma" and said that they were "the most formidable of intracranial tumors."

Various theories of the embryologic origin of this nonglial intracranial tumor are current: one theory favors development from ectodermal remnants of Rathke's pouch and another development from residual embryonic epithelium of the anterior pituitary gland and of the anterior infundibulum. Craniopharyngiomas may reside within or above the sella turcica, or, more rarely, they may be found in the nasopharynx or the third ventricle.

Craniopharyngioma appears to be a monoclonal tumor, and about 50 % have genetic abnormalities such as gains in activity at 1q, 12q, and 17q. About 70 % of cases of craniopharyngioma in childhood are the adamantinomatous type with cyst formation. These types have dysregulation of the Wnt signaling pathway and a mutation in the β-catenin gene (CTNNB1) in contrast to the papillary type of craniopharyngioma which has BRAF mutations and is more often found in adult patients.

CNS signs of craniopharyngiomas develop as the tumor encroaches on surrounding structures. Symptoms of craniopharyngioma include headache, visual disturbances, short stature, diabetes insipidus, vomiting, and weakness of one or more limbs. Visual defects including bilateral temporal field deficits due to impingement on the optic chiasm), optic atrophy or papilledema, and signs of GH deficiency, delayed puberty, and hypothyroidism are features of craniopharyngiomas. Although most patients are shorter than the mean in height and have decreased height velocity at diagnosis, a long, indolent course is possible. Deficiencies of gonadotropins, GH, thyrotropin (TSH), ACTH, and arginine vasopressin are common. The serum concentration of prolactin may be decreased. The bone age reading may be delayed and is common and may point to the age of onset of tumor growth.

About 70 % of patients with a craniopharyngioma have suprasellar or intrasellar calcification (found in fewer than 1 % of normal individuals) and an abnormal sella turcica, which are sometimes found on radiographs taken for other indications, including orthodontia. CT reveals fine calcifications that are not apparent on lateral skull radiographs. MRI scan before and after gadolinium is the diagnostic procedure of choice for suspected craniopharyngioma and can determine whether the tumor is cystic or solid and indicate the presence of hydrocephalus; if necessary, a CT scan can be used to search for calcifications. The new susceptibility weighted imaging (SWI) technique allows MRIs to reveal calcifications where older techniques did not.

Smaller craniopharyngiomas, usually intrasellar, can be treated by transsphenoidal microsurgery, but larger or suprasellar masses which are more frequently found in childhood require craniotomy, and the approach must be individualized. Shunting may be required for hydrocephalus prior to surgical treatment of the tumor. The reported post surgical 5-year overall survival is 88–94 %, the 10-year overall survival is 70–92 %, and the 20-year survival is 76 %. The combination of limited tumor removal and radiation therapy leads to a satisfactory neurologic prognosis, better cognitive outcome, and better endocrine outcome compared with attempts at complete surgical extirpation. Frequent and early tumor relapse after apparently complete resection and tumor progression after incomplete resection suggest the wisdom of radiation therapy after surgery. Alternative approaches include proton beam therapy, and, in mainly cystic craniopharyngioma cases, instillation of radioisotopes or sclerosing substances such as bleomycin or interferon-alpha is being investigated. Nonetheless, the preferred manner of treatment to retain the best quality of life is not yet established, but longitudinal studies such as the randomized multinational trial KRANIOPHARYNGEOM 2007 may answer this question. It is recommended that craniopharyngioma be considered a chronic disease requiring constant monitoring.

The hypothalamic syndrome is comprised of obesity; fatigue; behavioral changes; circadian rhythm irregularities; abnormal sleep patterns; dysregulation of body temperature, heart rate, and blood pressure, as well as abnormalities in thirst and is found in approximately one-third of patients at diagnosis in childhood. After surgery, these findings may occur in 65–80 % of patients. Postoperative hyperphagia and obesity (e.g., BMI >5 SD above normal) can be striking and correlate with the magnitude of hypothalamic damage on cranial MRI. Injury to the hypothalamic ventromedial nuclei (associated with increased parasympathetic activity and hyperinsulinemia) or to the paraventricular nuclei may cause these findings, and suppression of the increased insulin secretion may be helpful with the use of octreotide. Short-term follow-up studies demonstrate the efficacy of bariatric surgery in the management of obesity in affected patients. Hypothalamic-sparing surgery decreases the risk of postoperative hyperphagia and obesity. Aberrant sleep patterns and even narcolepsy and daytime somnolence may follow surgical treatment of craniopharyngiomas, with melatonin improving sleep patterns in some. Although the endocrine complications are more manageable, the combination of antidiuretic hormone insufficiency (i.e., diabetes insipidus) and impaired sense of thirst that arises after surgery in some patients remains a complex management problem.

A Rathke-cleft cyst is often discovered as an incidental finding on MRI, but it can produce symptoms and signs indistinguishable from those of a craniopharyngioma, such as precocious or delayed puberty. Surgical drainage and excision of the cyst wall are customary approaches.

Germinomas

Germinomas (i.e., pinealomas, ectopic pinealomas, atypical teratomas, or dysgerminomas) and other germ cell tumors of the CNS are the most common extrasellar tumors that arise in the suprasellar hypothalamic region and in the pineal region that commonly cause sexual infantilism. Germinomas constitute 66 % of all intracranial germ cell tumor (GCT) which comprise 3–11 % of pediatric brain tumors. About 84 % are found in the pineal and the neurohypophyseal regions. Peak incidences occur in the second decade and during infancy. They are found more often in males. Polydipsia and polyuria are the most common symptoms, followed by visual difficulties and abnormalities of growth and puberty or movement disorders. Diagnosis is often delayed for months to years because the findings are sometimes attributed to psychiatric disorders. Deficiencies of vasopressin and GH are most common, but other anterior pituitary hormone deficiencies (including gonadotropin deficiency) and elevated serum prolactin levels are also frequent. Determination of the concentration of hCG in spinal fluid and in serum and assessment

of α-fetoprotein levels provide useful tumor markers in children and adolescents with germ cell tumors. Germ cell tumors in boys can cause isosexual GnRH-independent sexual precocity by secretion of hCG (see Chap. 9). Subependymal spread of germ cell tumors along the lining of the third ventricle is common, and seeding may involve the lower spinal cord and cauda equina. MRI with contrast enhancement is useful in the detection of isolated enlargement of the pituitary stalk, an early finding of germinomas that requires periodic MRI monitoring, especially in patients with diabetes insipidus. The size of the pituitary gland increases by 100 % between year 1 and year 15, but the pineal gland does not normally change in size after the first year of life; any later enlargement indicates a mass lesion. Pineal cysts are a rare cause of central precocious puberty.

Irradiation is the preferred treatment for pure germ cell tumors such as germinomas; surgery is rarely indicated, except for biopsy to establish a tissue diagnosis. However, attempts to decrease the long-term morbidity of radiation therapy leads to consideration of chemotherapy. Chemotherapy alone is inadequate, but the combination of chemotherapy and radiation therapy can be successful, and both treatment methods are recommended for a mixed germ cell tumor. Because testicular germ cell tumors are occasionally found years after successful therapy for CNS germ cell tumors, long-term surveillance is indicated.

Hypothalamic and optic gliomas or astrocytomas, occurring as part of neurofibromatosis (von Recklinghausen disease (*162200 NEUROFIBROMATOSIS, TYPE I; NF1, due to mutations in the neurofibromin gene)) or arising independently, can also cause sexual infantilism. Gliomas and meningiomas are the most common CNS tumors to develop in childhood cancer survivors treated with CNS radiation, often in the young adult or even late teenage years.

Pituitary Adenomas

Only 2–6 % of all surgically treated pituitary tumors occur in childhood and adolescence, with about 1 in 1,000,000 children affected. Most functional pituitary adenomas are ACTH secreting, with prolactinomas, GH secreting, or nonfunctioning adenomas occurring less commonly. Most pituitary tumors are monoclonal lesions caused by mutations of guanine nucleotide-binding protein, GNAS; a transcript of the GNAS gene, Gs-alpha, encodes the alpha subunit of the stimulatory guanine nucleotide-binding protein (G protein). Gs-alpha is expressed biallelically in nearly all tissues and plays essential roles in a multitude of physiologic processes. Adolescent onset of pituitary tumors may be the first manifestation of multiple endocrine neoplasia type I (see Chap. 10). Familial isolated pituitary adenoma (FIPA) (#102200 PITUITARY ADENOMA) is diagnosed in a family with a history of pituitary adenomas including prolactinomas. About 20 % of cases of FIPA have a germline mutation in aryl hydrocarbon receptor-interacting protein (AIP).

With more sensitive imaging techniques, the presence of a pituitary incidentaloma, a previously unsuspected pituitary lesion that is discovered on an imaging study performed for an unrelated reason, may be discovered. Evaluation of secretory activity of such a lesion, consideration of mass effects, and follow-up to monitor a change in size are important, but some lesions detected will not be related to the endocrine abnormality for which the imaging procedure was ordered.

The incidence of prolactinoma is low in childhood, but one in five presents in the 15–24-year age group. A case survey reported that 61 % of prolactinomas were macroadenomas (more often in boys; hypopituitarism and growth failure were common) and 39 % were microadenomas (more often in girls; delayed puberty was common). Delayed onset of puberty was rare, although primary amenorrhea was the presenting symptom in more than 50 % of pubertal females. Presenting symptoms included oligomenorrhea and galactorrhea in the girls and headache in the boys. Galactorrhea may be demonstrable only by manual manipulation of the nipples (blood samples for prolactin should be obtained before examination or many hours later, because manipulation of the nipples raises prolactin levels). The degree of elevation of prolactin may indicate the size of the

prolactinoma. Microadenomas may demonstrate prolactin levels over 100 ng/mL, while values over 500 ng/mL are suggestive of a macroprolactinoma. Certain medications will also raise prolactin to levels suggestive of an adenoma when in fact there is no adenoma; risperidone and metoclopramide are two examples although there are many more psychiatric medications that can raise serum prolactin values.

Dopaminergic therapy is often successful in decreasing prolactin values. The dopamine agonist bromergocriptine may decrease serum prolactin concentrations and decrease tumor size, which is a useful approach before surgery of large macroprolactinomas is undertaken and when resection of the adenoma is incomplete. Pubertal progression and normal menstrual function in girls usually follow reduction of serum prolactin levels. Caberogline is a D2 receptor agonist that can be given 2 times per week (not approved for children). Pituitary apoplexy followed caberogline treatment of a macroprolactinoma in a 16-year-old girl; this complication has been seen in adults treated with bromocriptine. Tricuspid regurgitation may occur as a cumulative effect of treatment. Transsphenoidal resection of microprolactinomas in children and adolescents is an effective treatment if medication is ineffective.

High serum levels of macroprolactin, a complex of immunoglobulin G and monomeric prolactin with little biologic activity in vivo, cross-react in commercial prolactin assays, leading to a finding of pseudohyperprolactinemia; high prolactin values should be rechecked with subfractionation after polyethylene glycol precipitation to elucidate this potential confusion. When prolactin levels are truly quite high, the molecule may complex with IgG antibodies used in certain assays causing a "hook effect" leading to artifactually low prolactin levels when values actually are quite high. In this situation, a 1–100 dilution of serum before analysis is necessary. As prolactin rises in stress, an upset child may have a falsely elevated prolactin suggesting a disorder when there is none.

It is recommended that screening for multiple endocrine neoplasia type I (MENIN gene) and FIPA (AIP gene) occur in anyone with a pituitary adenoma under 21 years of age.

Other Central Nervous System Disorders

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (604856 ICD+ LANGERHANS CELL HISTIOCYTOSIS) is a clonal proliferative disorder of Langerhans histiocytes or their precursors characterized by the infiltration of the skin, viscera, and bone with lipid-laden histiocytic cells or foam cells. The cause is not clear, but there are features of a neoplasm and features of a reactive immunologic disorder. Diabetes insipidus, caused by infiltration of the hypothalamus or the pituitary stalk, is the most common endocrine manifestation, with GH deficiency and delayed puberty as possible outcomes. The lung, liver, and spleen may be involved with this infiltration, and exophthalmos due to infiltration of the orbit is seen. Other findings include cyst-like areas in flat and long bones of the skull, the ribs, the pelvis, and the scapula and the long bones of the arms and legs and in the dorsolumbar spine. The appearance of "Floating teeth" within rarefied bone of the mandible and absent or loose teeth are found. Mastoid or temporal bone involvement may lead to chronic otitis media. Treatment with glucocorticoids, antineoplastic agents, and radiation therapy is promising in terms of survival, but more than 50 % of patients have late sequelae or disease progression. The natural waxing and waning course of this rare disease makes evaluation of therapy difficult and highlights the importance of national treatment protocols. Letterer–Siwe disease (%246400 ICD+LETTERER-SIWE DISEASE) has similarities to Langerhans' cell histiocytosis but may occur in an autosomal recessive pattern.

Postinfectious Inflammatory Lesions of the Central Nervous System, Vascular Abnormalities, and Head Trauma

Postinfectious or other inflammatory lesions of the CNS, granulomatous disease of the area and vascular abnormalities, and head trauma may

cause abnormal hypothalamic–pituitary function. Tuberculous or sarcoid granulomas of the CNS are associated with delayed puberty. The original case of adiposogenital dystrophy, or Fröhlich's syndrome characterized by decreased growth and delayed puberty with obesity, is thought to have been caused by tuberculosis infection rather than a neoplasm.

Hydrocephalus may cause hypopituitarism, but precocious puberty also is a possible result, depending on the amount of pressure exerted on various central nervous system locations. Clinical findings will include signs of increased intracranial pressure. When hydrocephalus or subarachnoid cysts, which can cause similar effects, are decompressed, pituitary abnormalities may improve.

Irradiation of the Central Nervous System

Radiation of the head for treatment of CNS tumors, leukemia, or neoplasms of the head and the face, in which the radiation field involves the hypothalamus or pituitary field, may result in the gradual onset of hypothalamic–pituitary failure over a period of months to a few years. This occurs mainly due to hypothalamic rather than pituitary damage by the radiation and is dose-dependent. This etiology comprises an growing group of patients with hypopituitarism because of the increasing success in radiation treatment of such neoplasms. GH deficiency is the most common hormone disorder resulting from radiation of the CNS, but gonadotropin deficiency, hypothyroidism, and decreased bone density also occur. Self-reported fertility was reported to be lower in women who received CNS radiotherapy for acute lymphoblastic leukemia at about the time of menarche, although the average age of women in a long-term study was in the early 20s, and longer follow-up of fertility may change the results. Conversely, early or central precocious puberty may occur after radiation therapy for CNS lesions. The combination of GH deficiency and precocious puberty is a possible outcome of central nervous system radiation for a brain tumor and may be difficult to detect clinically, as the growth rate of the child is greater than that found in patients with GH deficiency alone, because the sex steroid secretion increases growth rate during pubertal development (see Chaps. 5 and 9). Irradiation of the CNS in early life predisposes the patient to later onset of secondary CNS tumors sometimes in just a few years after treatment of the first tumor. Such patient must be monitored to determine what pituitary defects have developed so that it may be treated appropriately.

Developmental Defects of the Midline

Congenital defects of pituitary secretion also may result from anatomic malformations of the hypothalamus, from pituitary hypoplasia or aplasia, or from more subtle defects of hormone secretion. Congenital defects of the midline associated with hypopituitarism range from holoprosencephaly (cyclopia, cebocephaly, orbital hypotelorism) to single maxillary incisor and even to cleft palate (4 % of cases of cleft lip and/or palate are associated with GH deficiency, so that all growth failure in cleft palate should not necessarily be attributed to poor feeding or nutrition alone). Individuals with myelomeningocele (myelodysplasia) have an increased frequency of endocrine abnormalities, including hypothalamic hypothyroidism, hyperprolactinemia, and decreased gonadotropin concentrations, whereas some patients demonstrate central precocious puberty.

Septo-Optic and Optic Dysplasia

Septo-optic dysplasia (optic nerve hypoplasia, absent septum pellucidum, or variations of both caused by abnormal development of the prosencephalon) (# 182230. SEPTOOPTIC DYSPLASIA due to a mutation at 3p21.2-p21.1). The HESX1 homeobox gene or SOX2 (see below), SOX3, and OTX2 may be associated with

significant visual impairment which often leads to pendular nystagmus (to-and-fro nystagmus due to inability to focus on a target). Small, pale optic disks occur, but not the appearance of optic atrophy, which would suggest previous development of the optic nerves with subsequent deterioration due to acquired pathology.

A midline hypothalamic defect may lead to the combination of GH deficiency and diabetes insipidus and may be associated with deficient ACTH, TSH, and gonadotropin secretion as well. Short stature and delayed puberty may be the most obvious results, although true precocious puberty is an alternative outcome in rare cases of this midline defect. The septum pellucidum is absent in about 50 % of cases of optic hypoplasia or dysplasia, and this defect is readily demonstrable by CNS imaging techniques, most frequently by MRI.

The MRI findings of congenital hypopituitarism may include an ectopic posterior pituitary gland "hot spot" and the appearance of what appears to be a "pituitary stalk transection" and a hypoplastic pituitary gland due to the lack of hypothalamic stimulatory factors. In some patients, the neurohypophysis may appear absent because of a missing hot spot although physiologic changes in hydration may affect the hot spot, which represents vasopressin content, with no true anatomic defect. Abnormalities of the corpus callosum and cerebellum are common on MRI. Four groups are described: those with normal MRI results, those with abnormalities of the septum pellucidum and with a normal hypothalamic–pituitary area, those with abnormalities of the hypothalamic–pituitary area and a normal septum pellucidum, and those with abnormalities in both areas. No endocrine abnormalities were described in the first group, but the others had progressively more endocrine abnormalities, with precocious puberty most common in the second group. Early diagnosis is important because of the risk of sudden death associated with adrenal insufficiency if ACTH is inadequate.

Delayed puberty is rarely described in duplication of the hypophysis.

The Solitary Median Maxillary Incisor Syndrome

(#147250 SOLITARY MEDIAN MAXILLARY CENTRAL INCISOR; SMMCI) Solitary median maxillary incisor is associated with the eponymous midline defect and with a prominent midpalatal ridge (torus palatinus) and hypopituitarism. The defect in this autosomal dominant condition is in the sonic hedgehog gene (SHH) at gene map locus 7q3.

Idiopathic Hypopituitary Dwarfism

In addition to HESX1 homeobox mutations, autosomal recessive mutations in homeobox genes encoding transcription factors involved in the early aspects of pituitary development lead to hypogonadotropic hypogonadism and other pituitary hormone deficiencies (Table 3.1). PROP1 mutations (#262600 PITUITARY HORMONE DEFICIENCY, COMBINED, 2; CPHD2) at gene map locus 5q35.3 cause GH and TSH deficiency and produce delayed puberty or late onset of secondary hypogonadism in adulthood and more rarely may also cause ACTH deficiency. In one study of 73 patients with idiopathic multiple pituitary hormone deficiencies, 35 had a mutation in PROP1. Homozygous Arg73Cys mutation of PROP1 allowed spontaneous puberty in 2 of 10 affected family members. ACTH deficiency may develop later and is more rarely a feature of PROP1 deficiency; patients must be monitored for this serious complication.

Mutations of POU1F1 (PIT *173110 POU DOMAIN, CLASS 1, TRANSCRIPTION FACTOR 1; POU1F1 at 3p11) cause deficiency in GH, TSH, and prolactin.

Homozygous mutations occur in the LHX3 gene (#221750 PITUITARY HORMONE DEFICIENCY, COMBINED, 3; CPHD3) at gene map locus 9q34.3. The LHX3 gene encodes a member of the LIM class of homeodomain proteins, which are associated with multiple pituitary hormone deficiencies, including LH and FSH, and often with severe restriction of head rotation. LH4 (#262700

Table 3.1 Genetic forms of multiple pituitary/hypothalamic hormone deficiencies

Defect	Hormones deficient	Inheritance	Mutations	Other features
POU1F1	GH, Prl, TSH	Auto-recessive and autosomal dominant	Missense, nonsense, frameshift, splicing	Severe impairment of postnatal growth, variable pituitary hypoplasia
PROP1	GH, Prl, TSH, LH, FSH, and ACTH developing later in some	Auto-recessive	Nonsense, frameshift, splicing	Transient pituitary hyperplasia in some
HEX1	Any or all, including vasopressin	Auto-recessive and autosomal dominant	Missense, frameshift	Septo-optic dysplasia or hypoplasia
LIM HOMEO BOX GENE 3; LIM3 LHX3	GH, Prl, TSH, LH, FSH, and ACTH in some	Auto-recessive	Missense, nonsense, frameshift, splicing	Limited neck rotation, short cervical spine, sensorineural deafness
LIM HOMEO BOX GENE 4; LIM4 LHX4	GH, Prl, TSH, LH, FSH, and ACTH	Autosomal dominant	Missense, frameshift	Cerebellar abnormalities, very small sella turcica in some, abnormal petrous bone
SOX2	LH,FSH, variable GH	Autosomal dominant	Missense, nonsense, frameshift	Anophthalmia/microphthalmia, esophageal atresia, genital tract abnormalities, hypothalamic hamartoma, sensorineural hearing loss, diplegia
GLI2	GH, Prl, TSH, LH, FSH, and ACTH	Haploinsufficiency	Missense, frameshift	Holoprosencephaly, craniofacial abnormalities, polydactyly, partial agenesis of the corpus callosum
FGF8	LH, FSH, and vasopressin	Auto-recessive and autosomal dominant	Missense, chromosome deletion	Anosmia, holoprosencephaly, Moebius syndrome, septo-optic dysplasia
SOX3	Isolated GHD or GH, Prl, TSH, LH, FSH, and ACTH	X-linked	Variations in polyalanine tract length, chromosome duplication	Mental retardation, infundibular hypoplasia, ectopic posterior pituitary, midline abnormalities
OTX2	Isolated GHD or GH, Prl, TSH, LH, FSH, and ACTH	Autosomal dominant	Missense, nonsense, microdeletion	Anophthalmia/microphthalmia, coloboma, developmental delay
TBX19	ACTH	Autosomal recessive	Missense, nonsense, frameshift, splicing	Neonatal hypoglycemia, neonatal cholestatic jaundice

GH growth hormone, *Prl* prolactin, *TSH* thyroid-stimulating hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *ACTH* adrenocorticotropic hormone