Objectives

After reading this chapter, you should be able to:

- Describe the roles, actions and regulation of growth hormone and IGFs
- Name other factors affecting growth
- Name four peptide growth factors, the tissues that secrete them, and where they affect
- Understand how to determine height and mean parental height
- Understand the principal diagnosis and management of growth disorders
- Describe the main changes that occur in the body during puberty.

Growth hormone (GH) is a pituitary hormone that can act directly on tissues throughout the body; however, its main effects are mediated by insulin-like growth factors (IGFs). These are secreted from the liver in response to GH. In this way, growth follows the conventional pattern of starting in the hypothalamus (described in Chapter 2).

Growth is a process that takes place at many levels. It can be defined as an increase in:

- Anabolism (e.g. protein synthesis)
- Cell size and number
- Cell mutation and maintenance
- Organ size
- Body size or weight.

Acting through IGFs, GH stimulates all the processes listed above. By promoting anabolic processes, the cell increases in size. This promotes cell division and maturation, causing the organ to grow. The cellular actions of GH begin at birth and continue throughout life, though the level of action varies. The fastest rate of growth is in the fetus and neonate; however, a growth spurt also occurs during puberty.

The growth of the body is limited by the epiphyses (growth plates) at the ends of the long bones. GH stimulates these plates to grow, causing bones to lengthen and body height to increase. It also stimulates fusion of these growth plates preventing further growth.

Important words:

- **Anabolism**: the process of building large molecules from smaller ones
- **Epiphysis**: the end of a long bone (plural epiphyses)
- **Epiphyseal growth plate**: an area of cartilage between the epiphysis and shaft of the bone that proliferates during childhood, resulting in elongation of the bone

**DIRECT CONTROL OF GROWTH**

**Growth hormone (GH)**

GH (also called somatotrophin) is a polypeptide that is secreted by the somatotroph cells in the anterior pituitary gland. Like many pituitary hormones, it is synthesized as a precursor molecule (pre-progrowth hormone). Two cleavages release the active hormone. For more information about the anterior pituitary, see Chapter 2.

**Regulation of secretion**

GH secretion is regulated by two hypothalamus releasing factors:

- Growth-hormone releasing hormone (GHRH)
- Somatostatin (also called growth-hormone inhibiting hormone or GHIH).

GHRH is released in a pulsatile manner, especially during deep sleep or hypoglycaemia, and GH release follows this pattern. Secretion of GH from the anterior pituitary gland is also regulated by the negative feedback of IGF-1 and other growth factors (Fig. 9.1).

**Effects**

GH promotes the growth and maintenance of most cells. It exerts most of its effects by:

- Stimulating the uptake of amino acids
- Stimulating the synthesis of proteins.
GH exerts most of its effects via IGFs. GH promotes their synthesis, mainly in the liver but also in other tissues. GH is transported in the blood bound to GH-binding protein. It acts via G-protein and Janus kinase (JAK) receptors on the cell surface of the target cells.

Insulin-like growth factors

Insulin-like growth factors (IGFs or somatomedins) are polypeptide hormones that exist in two forms: IGF-1 and IGF-2. They resemble insulin in structure and they act via similar receptors. IGF-1 is more important as a stimulator of growth. It is transported in the blood by a number of IGF-binding proteins.

Metabolic actions

Both IGF hormones have some insulin-like actions, e.g. increasing amino acid uptake and protein synthesis. However, they also oppose the actions of insulin on glucose by preventing glucose uptake and causing glycogen breakdown to raise blood glucose.

Growth actions

The increase in protein synthesis caused by the metabolic effects of IGF hormones causes cells to grow. This stimulates cell division and maturation, causing organs and soft tissues to enlarge.

The growth of the long bones depends on the state of the epiphyseal growth plate. This is a layer of chondrocytes (cartilage cells) located between the end (epiphysis) and shaft (diaphysis) of the bone (Fig. 9.2). Before puberty, IGFs stimulate these chondrocytes to grow, divide and mature into osteocytes (bone cells), allowing the bone to lengthen whilst maintaining a population of chondrocytes in the plate for further growth. During puberty, IGFs and sex steroids stimulate the chondrocytes within the plate to mature into osteocytes so that the epiphysis and diaphysis become fused together. The bone is no longer able to lengthen with further IGF stimulation so final adult height is reached.

Other growth factors

Growth in specific tissues is also stimulated by a number of growth factors, many of which are small peptides that act in a paracrine (local) manner. Their relationship to GH is not known. The actions and secretion of several such peptides are described in Fig. 9.3.

INDIRECT CONTROL OF HORMONES

Many factors apart from GH control growth, including:

- Genetics – tall parents often have tall children
- Adequate nutrition – however, excess nutrition does not increase height
- Health – chronic disease affects height
- Other hormones.
Other hormones

Growth problems can be caused by the abnormal secretion of a number of hormones, including:

- Insulin
- Antidiuretic hormone (ADH)
- Parathyroid hormone and vitamin D
- Cortisol
- Sex steroids.

Thyroid hormones

Thyroid hormones, described in Chapter 3, stimulate cell metabolism, promoting cell growth and division, especially in the skeleton and developing central nervous system (CNS). Thyroid hormones also stimulate GH secretion from the pituitary.

Cortisol is described in Chapter 4; it inhibits pituitary GH secretion, so chronic ill health or stress can suppress growth.

Normal growth can only occur if both the hormone milieu and the nutritional supply of proteins are suitable.

Fetal growth

In the fetus, a hormone called placental lactogen is secreted from the placenta. It stimulates fetal cartilage development and acts in a similar manner to prolactin on the maternal mammary glands.

Thyroid hormones are essential for the development of the skeleton and CNS. A deficiency in the fetus or neonate results in cretinism.

Puberty

Sexual maturation and the pubertal growth spurt are described later in this chapter.

DETERMINATION OF HEIGHT

A person’s final height is determined simply by the rate and duration of growth.

During puberty, the epiphyseal growing plates at the end of the long bones begin to fuse. This fusion prevents further growth and, therefore, further height gain.
Complete fusion occurs between 18 and 20 years of age in males, and earlier in females.

Fusion of the epiphyseal plates is stimulated primarily by GH and sex steroids; however, thyroid hormone also promotes this effect. A simple increase in GH during puberty is not sufficient to increase final height since bones simply mature faster and stop growing.

Only the bones that grow in this manner are prevented from responding to further GH. The jaw and skull can continue to grow past puberty; this effect is seen in GH excess. Ultimately, height is determined by multiple genetic factors.

Short stature, defined as a height less than the third centile, is associated with poor academic achievement and anxiety. Growth rates less than the 25th centile will result in a child dropping down centiles on a growth chart. Short stature can be primary, secondary or idiopathic. Primary disorders reflect an intrinsic bone defect and include achondroplasia and some causes of intrauterine growth retardation. Secondary disorders occur in the presence of other factors that limit bone growth. Malnutrition, chronic disease and endocrine disorders, such as Cushing’s, can also be secondary causes. Idiopathic short stature is the most common cause of short stature and is a variant of normal.

**Disorders of Growth**

**Excess of growth hormone**

Excess GH prior to epiphyseal fusion causes gigantism, proportional abnormal growth. Since the epiphyses also fuse at an earlier age, the child may have an unremarkable height in adulthood. Diabetes is very common in this group because of the opposing actions of insulin and GH on blood glucose.

An excess of GH is slightly more common in adults, where it manifests as acromegaly (prevalence approximately 60 per million). The signs and symptoms are shown in Fig. 9.4. The long bones can no longer lengthen, so there is no increase in height. However, the soft tissues and other bones can still grow, causing the distinctive features of this condition (Fig. 9.5). Acromegaly is a serious condition, associated with an increase in mortality from cardiovascular disease, respiratory disease and malignancy. A therapeutic reduction in plasma GH is effective in reducing this excess mortality.

GH-secretion pituitary adenomas are the most common cause of acromegaly. These adenomas can cause other symptoms by compressing surrounding structures (e.g. pituitary stalk compression). Assessment of acromegaly should therefore include demonstration of excess GH, localization of the tumour, global assessment of anterior pituitary function and assessment of metabolic and structural complications.

**Diagnosis**

Excess GH can be diagnosed by high IGF-1 levels, but the best test is to measure GH levels following an oral glucose tolerance test. GH levels should fall with the rise in glucose. Computed tomography (CT) or magnetic resonance imaging (MRI) scans can be used to confirm the presence of a functional pituitary adenoma.

**Treatment**

The mainstay of treatment is surgical removal of the tumour. At 3 months post-op, a day curve of GH levels is measured (4–5 samples, aiming for a mean GH >5 mU/L) or a repeat oral glucose tolerance test (OGTT), measure IGF-1, and do pituitary function tests to rule out hypopituitarism.

Additional treatments may be needed if surgery is unsuccessful. These include somatostatin/GHIH analogues, recombinant GH analogue (acts as a GH receptor antagonist) and radiotherapy.

**Deficiency of growth hormone**

The deficiency of GH in children is called dwarfism. It is detected by short stature along with either:

- Dropping between growth chart centiles (i.e. not following the expected course)
- Being significantly shorter than mean parental height (MPH).

The most common cause of dwarfism is a deficiency of GHRH from the hypothalamus; craniopharyngiomas can also be responsible. See Chapter 2 for more details.

**Diagnosis and treatment**

GH deficiency is diagnosed using a stimulation test. Impaired GH rise is seen after sleep, hypoglycaemia induced by IV insulin (used less often because of risks) or an arginine stimulation test. The treatment for GH deficiency is subcutaneous injections of recombinant human growth hormone (rhGH) before sleep each night.

**Genetic short stature**

Children can be short as a consequence of genetics without pathological correlates. These children have short parents and they start growing below the 5th centile but at a normal rate with a normal age of pubertal onset. Mean parental height (MPH) is the average of the parents’ heights plus 7 cm in males or
minus 7 cm in females. Constitutional delay in growth and maturation involves delayed puberty and a delayed pubertal growth spurt, but the normal adult height is attained.

**PUBERTY**

Puberty is when the sexually immature child becomes a sexually fertile adult. Prepuberty girls and boys develop pubic and axillary hair. This prepubertal phase is the result of adrenarche (Chapter 3). Puberty starts with the reactivation of gonadotrophin (LH and FSH) release after the dormancy of childhood. The age of pubertal onset varies widely between individuals (females 8–13 years; males 9–14 years). Puberty is characterized by a number of processes:

- Pubertal growth spurt
- Development of secondary sexual characteristics
- Achievement of fertility
- Psychological and social development

### Gonadarche and the initiation of puberty

From an endocrine perspective, puberty is marked by the onset of pulsatile gonadotrophin release from the anterior pituitary gland during the night.
Gonadotrophins stimulate the production of sex steroids (i.e. testosterone and oestrogen) from the gonads; the activation of the gonads is gonadarche. The onset of puberty is not fully understood; however, the CNS integrates a number of signals. According to the gonadostat hypothesis, a reduction in hypothalamic sensitivity to the negative feedback of the sex steroids causes the hypothalamus to secrete higher levels of gonadotrophin-releasing hormone (GnRH) in a pulsatile manner. Secretion of growth hormone (GH), thyroid-stimulating hormone (TSH) and adrenocorticotrophic hormone (ACTH) is also increased. Other evidence favours the central maturation of the CNS and its common final communication pathways between the hypothalamus GnRH neurons and the pituitary.

**Body weight and puberty**

In the last few decades the onset of puberty has occurred at an increasingly young age. This change is often attributed to improved nutrition and rising body weight of 47 kg is a better predictor of the start of periods than age.

In recent years, a possible mechanism for this effect has been found. The hormone leptin is secreted by the adipose tissue, and is a hormonal indicator of body fat: higher levels of leptin are present with increasing body fat. Leptin may be the trigger for GnRH activation. Puberty cannot begin without leptin, but evidence suggests that it is only one of a number of factors. The exact details of the causal relationship between a critical metabolic mass derived from lean body weight, body fat and total body water and the onset of puberty remains unclear.

**The pubertal growth spurt**

The earliest developmental event in puberty is an increase in growth velocity called the growth spurt. It occurs about 2 years earlier in females, giving a temporary height advantage. The initial rise in growth velocity is slight, so growth of the breasts or testes is usually noticed first.
The increase in growth is caused by increased GH and sex steroid secretion. Sex steroids also cause bone maturation. As the bones mature, the growing plates (epiphyses) fuse, preventing further growth. This fusion occurs 2 years earlier in females, giving males an extra 2 years of growth. This largely accounts for the increased height of adult males.

**Puberty in the male**

Puberty usually occurs between 9 and 14 years of age in boys; however, it is considered normal if it occurs between 9 and 16 years of age. Once the testes have developed, male pubertal changes are brought about by the secretion of androgens such as DHT and testosterone.

**Testes development and early puberty**

Growth of the testes from $<2\text{ mL}$ to $>4\text{ mL}$ is often the first sign of puberty noticed in boys around 12 years. The increase is mainly due to proliferation of the seminiferous tubules under the influence of FSH. LH stimulates the interstitial Leydig cells to secrete testosterone. The scrotum becomes larger, thicker and pigmented; pubic hair growth follows.

Spermatogenesis begins once the testes have enlarged and matured and is associated with a rise in serum inhibin B. Nocturnal emissions and daytime ejaculations are often around 13–14 years of age at stage 3 of Tanner’s male genital staging, with fertile ejaculations around 15 years.

**Penile development and late puberty**

The penis begins to enlarge after the testes about the same time the growth spurt is noticed. The penis doubles in size during puberty to reach an average size of 9.5 cm flaccid or 13.2 cm erect.

Klinefelter’s syndrome (XXY) is associated with small testicles, abnormal spermatogenesis and infertility. The syndrome is also associated with delayed motor learning. Treatment is with testosterone. Women with Turner’s syndrome lack part of the X chromosome (or a whole X chromosome) needed for normal ovarian development and acquisition of normal secondary sexual characteristics. These women are often amenorrheic, infertile and have abnormal breast and pubic hair development. Treatment is with oestrogen to promote sexual development and growth hormone to encourage growth.

Facial and axillary hair growth usually starts at about 15 years of age. The sebaceous glands in the skin are also activated, often causing acne. The breaking of the voice is also a late feature. The larynx, cricothyroid cartilage and laryngeal muscles enlarge to give an Adam’s apple.

**HINTS AND TIPS**

Clinically, male puberty has begun when the testes reach 4 mL. This is measured with an orchidometer.

**Puberty in the female**

Puberty in females usually occurs between 8 and 13 years of age in girls; however, it is considered normal between 8 and 15 years of age. The changes caused by oestrogens and progesterone are shown in Fig. 9.6.

**Breast development and early puberty**

The development of breast buds is often the first sign of puberty noticed in girls. The breast then continues to grow under the influence of oestrogen while the ductal system develops; the number of lobules remains the same from infancy (Fig. 9.6). Pubic hair begins to grow about 6 months later.

**HINTS AND TIPS**

Tanner’s staging is used to assess puberty milestones and compare individuals. The stages are based on testis, scrotum and penile growth and pubic hair in males:

- **Stage 1:** height increases 5 cm per year, no pigmented pubic hair, testes volume $<4\text{ mL}$, no penis growth.
- **Stage 2:** height increases 5 cm per year, small amount of pigmented pubic hair, testes volume 4–6 mL, increased penis dimensions. Stage 3: height increases 7.5 cm per year, darker pubic hair, testes volume 8–10 mL, increased penis dimensions. Stage 4: height increases 10 cm per year, testes volume 14–16 mL, increased penis dimensions, adult pubic hair quality. Stage 5: adult pubic hair distribution, testes volume 18–25 mL, maximum height reached, mature penis size reached.

Additional changes: axillary hair, increased muscle mass, voice breaks.
Menarche and late puberty
The uterus begins to enlarge after the development of pubic hair. The onset of menstruation (periods) is called menarche. The mean age of menarche is 13 years, making it a late feature of puberty. In the ovary, follicular development begins and the first ovulation occurs 10 months after the first menarche, on average, i.e. the early menstrual cycle are often anovulatory and infertile.

Tanner’s stages and the female
In the female, the stages are based on breast and pubic hair development.

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<thead>
<tr>
<th>Oestrogen-mediated changes</th>
<th>Progesterone-mediated changes</th>
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<tr>
<td>Fat deposition and proliferation of the ductal system in the breasts, causing growth</td>
<td>Proliferation of the secretory lobules and acini in the breast</td>
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<tr>
<td>Growth of the vagina and maturation of the epithelium</td>
<td>Contribution to vaginal and uterine growth</td>
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<tr>
<td>Growth of the clitoris</td>
<td>Initiation of cyclical changes in endometrium and ovary</td>
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Breast development
Stage 1: preadolescent, only papillae are elevated. Stage 2: breast bud develops with papillae and breasts elevated. Stage 3: juvenile smooth stage with further growth of breasts and areolae. Stage 4: areolae and papillae project above the breasts. Stage 5: adult pattern with areolae on the same level as the rest of the breasts.

Pubic hair development
Stage 1: preadolescent, no pubic hair. Stage 2: sparse hair on labia majora. Stage 3: darker, coarser and curlier hair, spreads over pubis. Stage 4: adult-type pattern but covers smaller area. Stage 5: adult pattern.