Physiology for Medical Students
Endocrine 3

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Growth Hormone

Growth Hormone

- Growth hormone, in contrast to other hormones, does not function through a target gland but exerts its effects directly on all or almost all tissues of the body.
- It causes growth of almost all tissues of the body that are capable of growing.

Growth Hormone

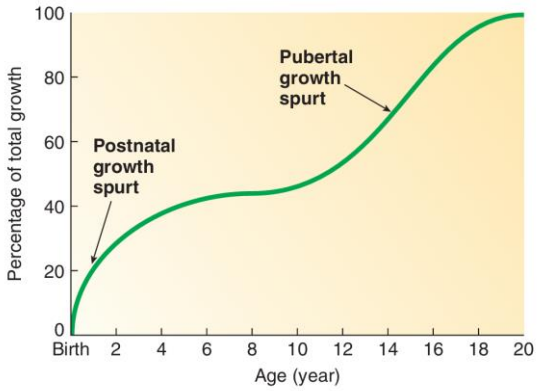
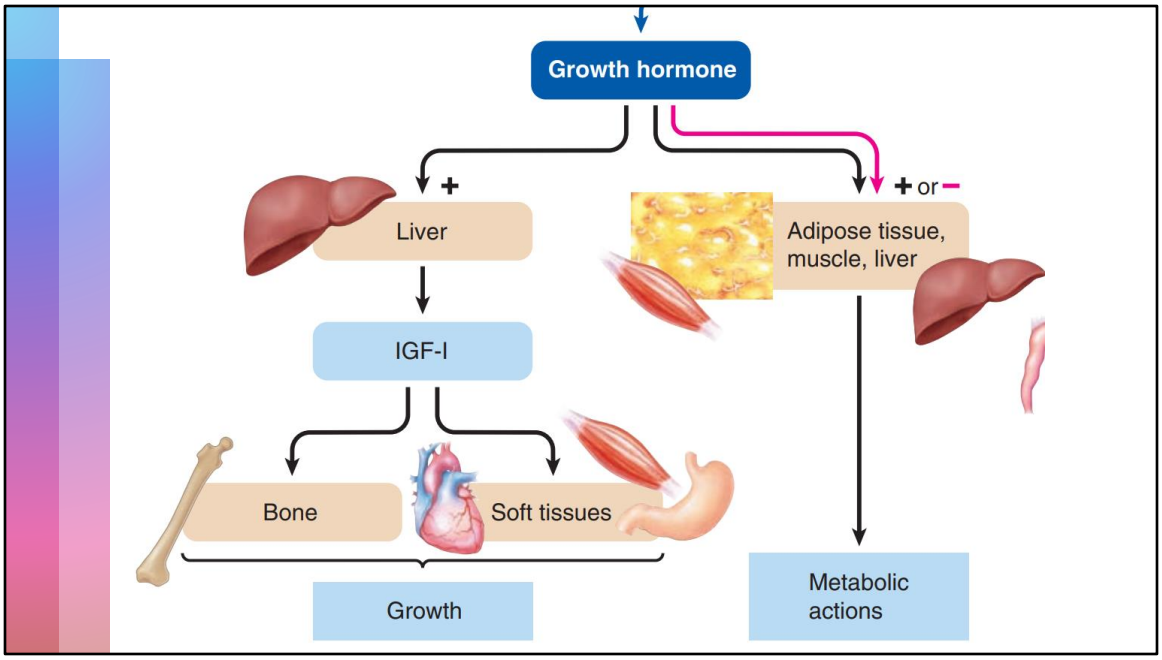


Figure 18-8 Normal growth curve.

** ** In **growing children**, continuous **net protein synthesis** occurs under the influence of growth hormone (GH) as the body steadily gets larger.
** **Weight gain alone is not synonymous with growth** because weight gain may occur from retaining excess water or storing fat without true structural growth of tissues. ** Growth requires net synthesis of proteins and includes **lengthening of the long bones** (the bones of the extremities) and **increases in the size and number of cells in the soft tissues.**

**** Although, as the name implies, growth hormone is essential for growth, it is not wholly responsible for determining the rate and final magnitude of growth in a given individual, genetic, diet, diseases, other hormones.



** GH is the **most abundant hormone produced by the anterior pituitary**, even in **adults in whom growth has already ceased**, although GH secretion typically starts to decline after middle age. The continued high secretion of GH beyond the growing period implies that this **hormone has important influences beyond its influence on growth, such as metabolic effects.**

Growth Hormone metabolic effect (protein)

- **Enhancement of Amino Acid Transport Through the Cell Membranes**
- **Enhancement of RNA Translation to Cause Protein Synthesis by the Ribosomes**
- **Increased Nuclear Transcription of DNA to Form RNA**
- **Decreased Catabolism of Protein and Amino Acids**

GH Promotes Protein Deposition in Tissues

** GH decreases breakdown of cell protein, probable reason for this decrease is that GH also mobilizes large quantities of free fatty acids from the adipose tissue, and these are used to supply most of the energy for the body's cells, thus acting as a potent "protein sparer."

Growth Hormone metabolic effect (Fat)

- Growth hormones increases mobilization of fatty acids from adipose tissue.
- GH increases free fatty acids in the blood.
- GH increases use of fatty acids for energy.

The ability of GH to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass.

Growth Hormone metabolic effect (carbs)

(1) **Decreased glucose uptake in tissues such as skeletal muscle and fat.**

(2) **Increased glucose production by the liver.**

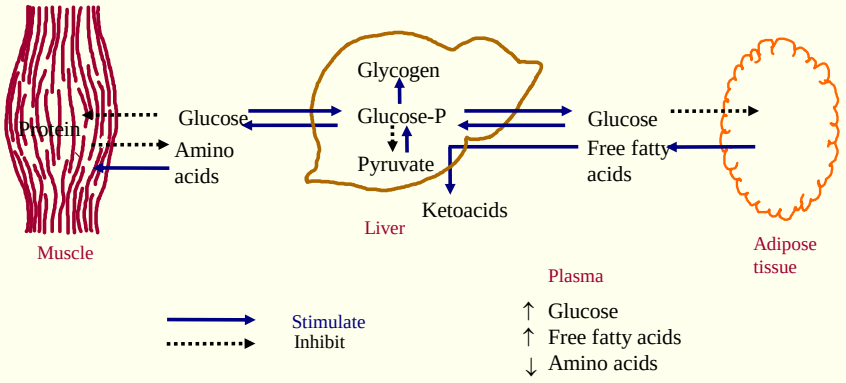
(3) **Increased insulin secretion (compensatory).**

Insulin Resistance

GH Decreases Carbohydrate Utilization

Each of these changes results from growth hormone–induced "insulin resistance," which attenuates insulin's actions to stimulate the uptake and utilization of glucose in skeletal muscle and adipose tissue and to inhibit gluconeogenesis (glucose production) by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone's effects are called *diabetogenic,* and excess secretion of growth hormone can produce metabolic disturbances similar to those found in patients with type II (non-insulin-dependent) diabetes, who are also resistant to the metabolic effects of insulin.
We do not know the precise mechanism by which growth hormone causes insulin resistance and decreased glucose utilization by the cells. However, growth hormone–induced increases in blood concentrations of fatty acids likely contribute to impairment of insulin's actions on tissue glucose utilization. Experimental studies indicate that raising blood levels of fatty acids above normal rapidly decreases the sensitivity of the liver and skeletal muscle to insulin's effects on carbohydrate metabolism

Metabolic Effects of Growth Hormone



** To exert its metabolic effects, **GH binds directly** with its target organs, namely, **adipose tissue, skeletal muscles, and liver**.

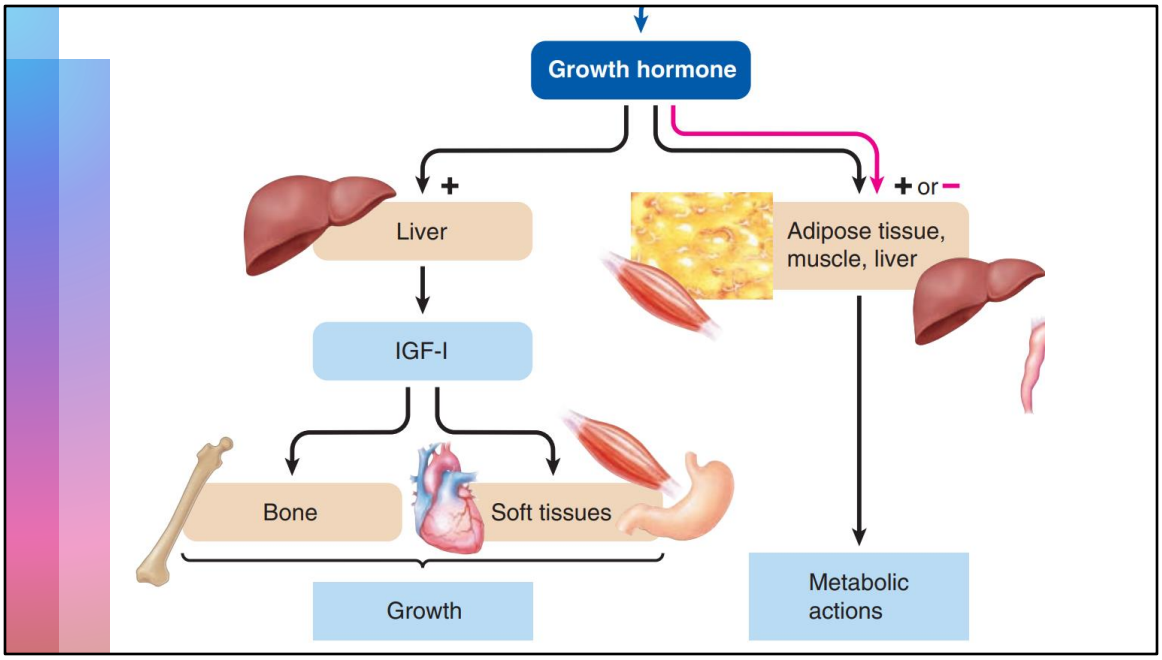
** Thus, the overall metabolic effect of GH is to mobilize fat stores as a major energy source while **sparing glucose for glucosedependent tissues such as the brain**. The brain can use only glucose as its metabolic fuel, yet nervous tissue cannot store glycogen (stored glucose) to any extent. **This metabolic pattern induced by GH is suitable for maintaining the body during prolonged fasting or other situations when the body's energy needs exceed available glucose stores.**

Growth Hormone Has Several Metabolic Effects

1) **Protein**: **Increased** rate of protein **synthesis** in most cells of the body.
2) **Fat**: Increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and **increased use of fatty acids for energy.**
3) **Carbs**: **Decreased** rate of **glucose utilization** throughout the body.

Regulation of Growth Hormone Secretion (metabolic)

Glucose decrease	Stimulation
Glucose increase	Inhibition
Free fatty acid decrease	Stimulation
Free fatty acid increase	Inhibition
Amino acid increase (arginine)	Stimulation
Fasting	Stimulation
Prolonged caloric deprivation	Stimulation
Stress	Stimulation
Exercise	Stimulation



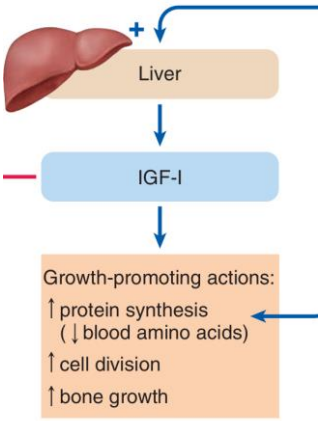
** growth-promoting effects: GH stimulates growth of both the soft tissues and the skeleton.

** GH promotes growth of soft tissues by (1) increasing the size of cells (hypertrophy) and (2) increasing the number of cells (hyperplasia).

** GH increases the size of cells by favoring synthesis of proteins.

Growth Hormone Exerts Much of Its Effect Through Intermediate

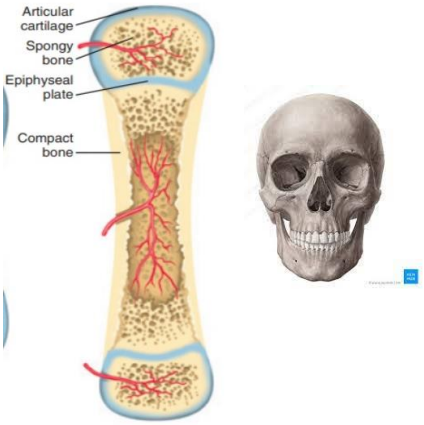
- Called “Somatomedins” “Insulin-Like Growth Factors”.
- Synthesized by liver (and other tissues locally) in response to growth hormone.
- Potent effect of increasing all aspects of bone growth.
- Most common somatomedin C or IGF-I.



** GH mostly exerts its growth-promoting effects **indirectly** by stimulating insulin-like growth factors.
** The major source of circulating IGF-I is the liver, which releases this peptide product into the blood in response to GH stimulation. IGF-I is also produced by most other tissues, although they do not release it into the blood to any extent.
** insulin-like growth factors (IGFs), which directly act on the target cells to cause growth of both soft tissues and bones. IGFs are produced in many tissues and have endocrine, paracrine, and autocrine actions. Originally called somatomedins, they are called insulin-like growth factors because they are structurally and functionally similar to insulin.
**It has been postulated that most, if not all, of the growth effects of growth hormone result from somatomedin C and other somatomedins, rather than from direct effects of growth hormone on the bones and other peripheral tissues.

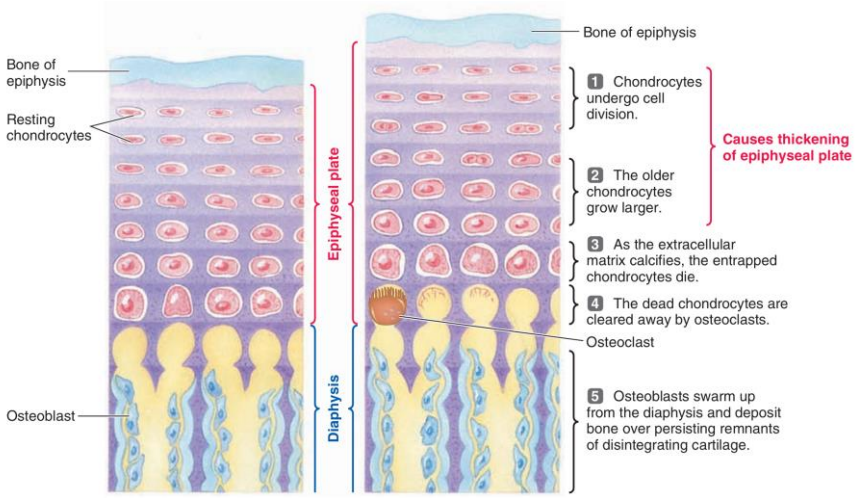
Bone grows in thickness and in length, both stimulated by GH.

- Growth in thickness: Osteoblast > Osteoclast
- Growth in length: chondrocyte proliferation at the epiphyseal plate, ossification.



osteoblasts in the bone periosteum and in some bone cavities deposit new bone on the surfaces of older bone. Simultaneously, *osteoclasts* in the bone remove old bone. When the rate of deposition is greater than that of resorption, the thickness of the bone increases. ***Growth hormone strongly stimulates osteoblasts***. Therefore, the bones can continue to become thicker throughout life under the influence of growth hormone; this is especially true **for the membranous bones**. **For instance, the jaw bones can be stimulated to grow even after adolescence, causing forward protrusion of the chin and lower teeth. Likewise, the bones of the skull can grow in thickness and give rise to bony protrusions over the eyes.**

Bone grows in thickness and in length, both stimulated by GH.



This growth first causes **deposition of new cartilage, followed by its **conversion into new bone**, thus elongating the shaft and pushing the epiphyses farther and farther apart. At the same time, the epiphyseal cartilage itself is progressively used up, so by late adolescence, no additional epiphyseal cartilage remains to provide for further long bone growth. At this time, bony fusion occurs between the shaft and the epiphysis at each end, so no further lengthening of the long bone can occur.

**GH Control of bone Growth GH causes bones to grow both in length and in thickness via IGF-I, which has profound effects on cartilage and bone. IGF-I stimulates proliferation of epiphyseal cartilage, thereby making space for more bone formation, and stimulates osteoblast activity. GH/IGF-I can promote lengthening of long bones as long as the epiphyseal plate remains cartilaginous, or is “open.” At the end of adolescence, sex steroids completely ossify, or “close” the epiphyseal plates so that the bones cannot lengthen any further despite the presence of GH and IGF-I. Thus, after the plates are closed, the individual does not grow any taller

African pygmies

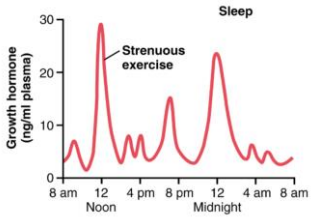
- The rate of growth hormone secretion is normal or high,
- but there is a hereditary inability to form somatomedin C (IGF-I.)

Regulation of Growth Hormone Secretion

Regulation of Growth Hormone Secretion

As one ages, the average plasma concentration of growth hormone in an otherwise normal person changes approximately as follows:

Age (years)	ng/ml
5 to 20	6
20 to 40	3
40 to 70	1.6



** Growth hormone is secreted in a pulsatile pattern.

** After adolescence, GH secretion decreases slowly with aging, finally falling to about 25% of the adolescent level in very old age.

** The aged appearance seems to result mainly from **decreased protein deposition in most tissues of the body and increased fat deposition in its place**. The physical and physiological effects are **increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength**

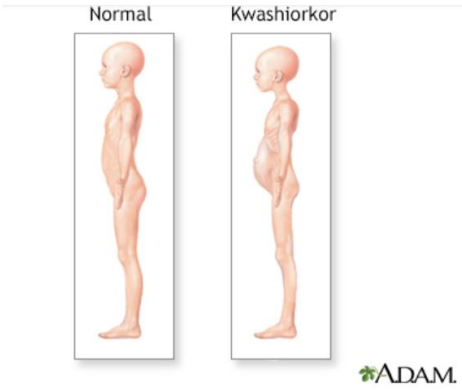
** Thus, it is possible that some of the normal aging effects result from diminished growth hormone secretion. In fact, some studies of growth hormone therapy in older people have demonstrated three important beneficial effects: (1) increased protein deposition in the body, especially in the muscles; (2) decreased fat deposits; and (3) a feeling of increased energy. Other studies, however, have shown that treatment of elderly patients with recombinant GH may produce several undesirable adverse effects including **insulin resistance and diabetes, edema, carpal tunnel syndrome, and arthralgias (joint pain). Therefore, recombinant GH therapy is generally not recommended for use in healthy elderly patients with normal endocrine function**

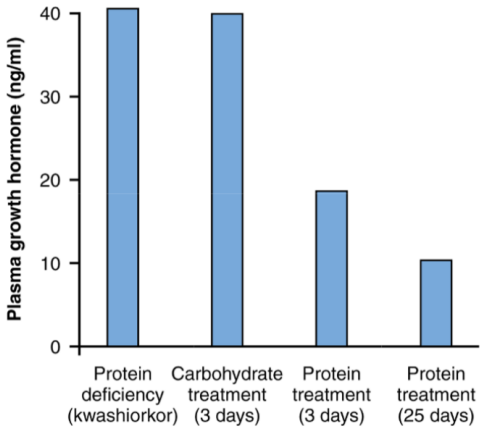
Regulation of Growth Hormone Secretion

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Increased blood amino acids (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	Growth hormone inhibitory hormone (somatostatin)
Exercise	Growth hormone (exogenous)
Testosterone, estrogen	Somatomedins (insulin-like growth factors)
Deep sleep (stages II and IV)	
Growth hormone–releasing hormone	
Ghrelin	

** ghrelin, a hormone secreted by the stomach before meals
** Under acute conditions, hypoglycemia is a far more potent stimulator of GH secretion than is an acute decrease in protein intake. Conversely, in chronic conditions, GH secretion seems to correlate more with the degree of cellular protein depletion than with the degree of glucose insufficiency. For example, the extremely high levels of GH that occur during starvation are closely related to the amount of protein depletion.

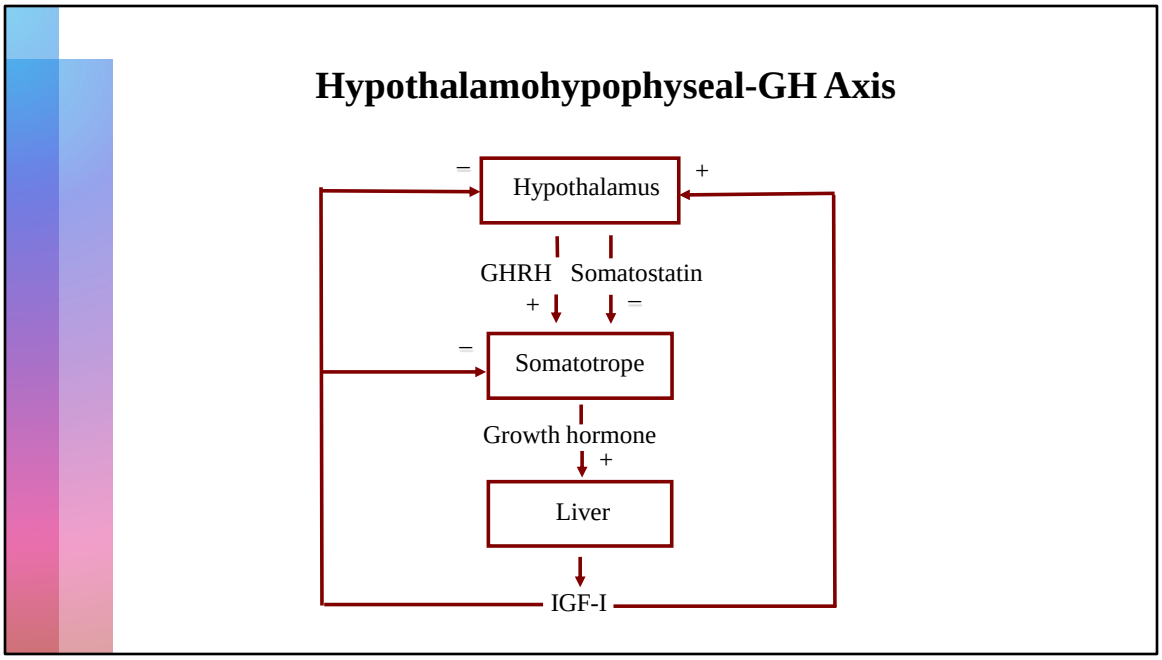
Physiological Functions of Growth Hormone



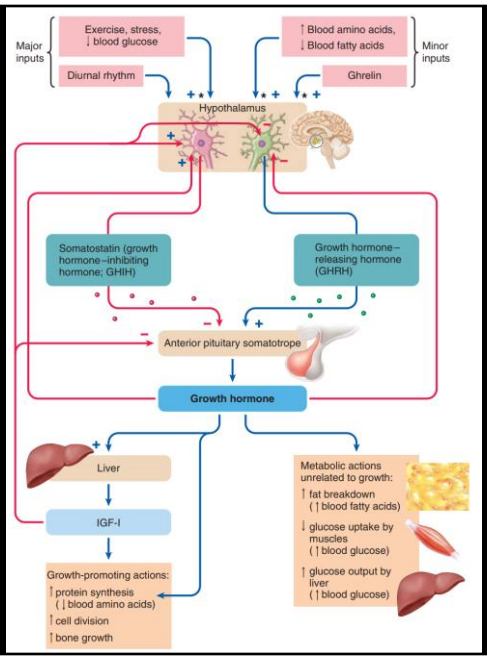


** this slide demonstrates the effect of protein deficiency on plasma GH and then the effect of adding protein to the diet. The first column shows very high levels of GH in children with extreme protein deficiency during the protein malnutrition condition called kwashiorkor; the second column shows the levels in the same children after 3 days of treatment with more than adequate quantities of carbohydrates in their diets, demonstrating that the carbohydrates did not lower the plasma GH concentration. The third and fourth columns show the levels after treatment with protein supplements for 3 and 25 days, respectively, with a concomitant decrease in the hormone.

** These results demonstrate that under severe conditions of protein malnutrition, adequate calories alone are not sufficient to correct the excess production of GH. The protein deficiency must also be corrected before the GH concentration will return to normal



When GH is administered directly into the blood of an animal over several hours, the rate of endogenous GH secretion decreases. This decrease demonstrates that GH secretion is subject to typical negative feedback control, as is true for essentially all hormones. The nature of this feedback mechanism and whether it is mediated mainly through inhibition of GHRH or enhancement of somatostatin, which inhibits growth hormone secretion, are uncertain.

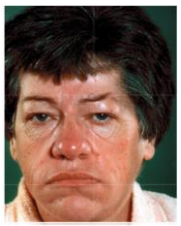

Major inputs
Exercise, stress, ↓ blood glucose
Diurnal rhythm
↑ Blood amino acids, ↓ Blood fatty acids
Ghrelin
Minor inputs
Hypothalamus
Somatostatin (growth hormone–inhibiting hormone; GHIH)
Growth hormone–releasing hormone (GHRH)
Anterior pituitary somatotrope
Growth hormone
Liver
IGF-I
Growth-promoting actions:
↑ protein synthesis (↓ blood amino acids)
↑ cell division
↑ bone growth
Metabolic actions unrelated to growth:
↑ fat breakdown (↑ blood fatty acids)
↓ glucose uptake by muscles (↑ blood glucose)
↑ glucose output by liver (↑ blood glucose)

Abnormalities of Growth Hormone Secretion

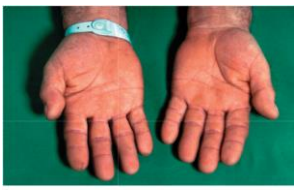
Dwarfism

- Most instances results from **panhypopituitarism** during childhood.
- All the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased.
- A person with panhypopituitary dwarfism does not pass through puberty and never secretes sufficient quantities of gonadotropic hormones to develop adult sexual functions.
- In **Laron dwarfs** and **African pygmies**, the rate of GH secretion is normal or high, but responsiveness to GH is impaired due to **mutations of the GH receptor** or a **hereditary inability to form IGF-1**, a key step for the promotion of growth by GH.

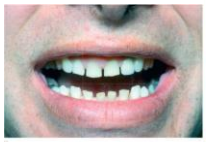
Gigantism and Acromegaly



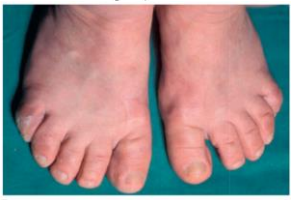
A: Typical facies.



C: Large fleshy hands.



B: Separation of lower teeth.



D: Widening of the feet.

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@Macleod's clinical examination

Gigantism

- Excess growth hormone before adolescence.
- All body tissues grow rapidly, including the bones.
- Hyperglycemia → degeneration of B cells → 10 percent will develop full-blown diabetes mellitus.
- Panhypopituitarism → general deficiency of pituitary hormones usually causes death in early adulthood.
- Treatment: microsurgical removal of the tumor or by irradiation of the pituitary gland.

Acromegaly

- Excess growth hormone after adolescence.
- Enlargement in the bones of the hands and feet and in the membranous bones, including the cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone, and portions of the vertebrae.
- the lower jaw protrudes forward
- the forehead slants forward
- the nose increases to as much as twice normal size
- the feet and hands are almost twice normal size.
- kyphosis.
- the tongue, the liver, and especially the kidneys, become greatly enlarged.

Question??

- A boy 18 years of age is brought with progressively increasing height and increase in shoe size. The parents feel that the child should have stopped growing fast by now as his siblings are much shorter than him though they are older.
- You would not expect to see:
- A) Increased IGF
- B) A macroadenoma of the pituitary
- C) Bilateral hemianopia (loss of vision)
- D) Hypoglycaemia

Growth hormone is secreted in a pulsatile pattern.