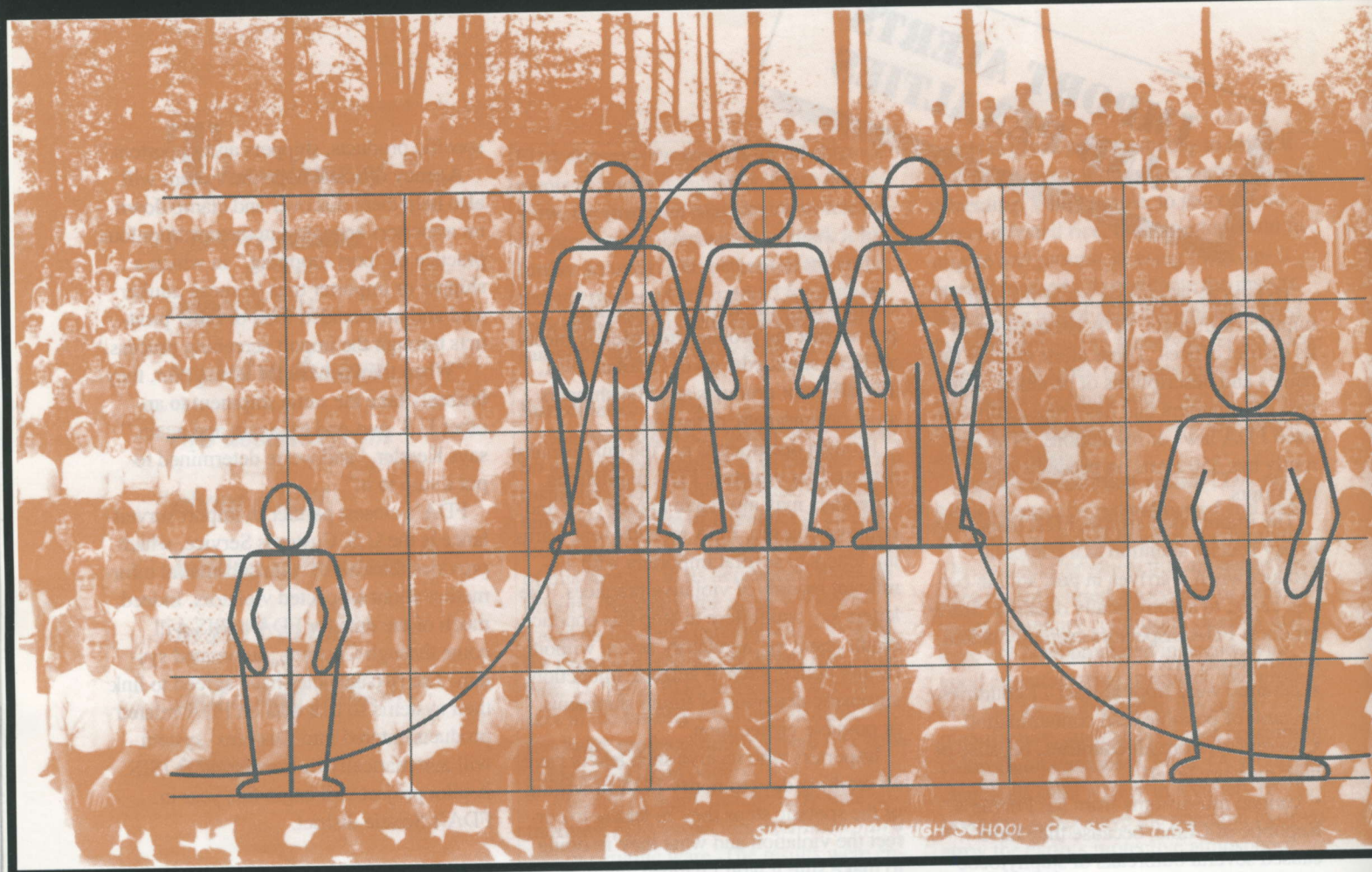


THE LONG AND SHORT OF IT



NEW MEDICATIONS FOR GROWTH DISORDERS

Many homes have pencilled lines on a wall that chart the rapidly rising height of children, and often even the most picky pint-sized eaters will be inspired to chow down if they are told the food will make them "big and strong."

When a child's growth or development goes awry, it often dismays parents and prompts them to seek medical help. Whether or not there is actually a physical abnormality, when a child's growth varies greatly from the average, social and emotional problems may result. A child who is significantly

shorter than his or her friends or one who has delayed or precocious (early) puberty, for example, may be shunned or ridiculed by other children.

Several new drugs can set a child's abnormal growth back on track. In the late 1980s, the Food and Drug Administration approved Protropin and Humatrope, two synthetic forms of human growth hormone, to treat children with small stature. These drugs can boost the growth rate of children deficient in the hormone, preventing extremely short adult stature.

(Growth hormone extracted from cadaver pituitaries was used to treat such

children before the development of synthetic human growth hormone. But the discovery in April 1985 that some of the natural growth hormone was contaminated by a microbe that causes a fatal brain illness known as Creutzfeldt-Jakob disease prompted officials to stop its use.)

In delayed puberty, it is development of sexual characteristics rather than final height that is impeded. Physicians use sex hormones and their chemical cousins experimentally to boost the growth and development of these "late bloomers." (See accompanying article.)

At the opposite extreme, some children

by MARGIE PATLAK



develop adolescent sexual characteristics at a very young age and stop growing much earlier than normal so that they grow up to be short adults. To treat this condition, known as precocious puberty, two synthetic hormones, called histrelin acetate (Supprelin) and nafarelin acetate (Synarel), were approved by FDA in the past two years.

Ethical Dilemmas

Although these treatments may benefit children with extreme cases of short stature, or delayed or precocious puberty, their use in borderline children—those on the short end of the measuring stick, for example, but not rock bottom on the charts—is raising some thorny ethical issues.

Short stature doesn't always stem from

a disease, for example, but often is part of the normal variation in height and is inherited from short parents.

Physicians are wary of treating normal short children with growth hormone for merely cosmetic or social reasons, especially since the benefits and adverse effects of the hormone treatments on these children are not fully known. The decision of which children to treat rests with physicians and parents. It cannot wait until the child matures to adulthood and is able to make his or her own decision, since growth hormone is not thought to be effective in full-grown adults.

"Often it isn't the kids who are worried about being short, but their parents," points out pediatric endocrinologist Gilbert August, M.D., of George Washington University. "These parents, who are short

A doctor's diagnosis is necessary to tell whether a child on either end of the height curve has a growth disorder.

themselves, vicariously relive through the child their own failures in high school about not being able to make the team, etc. I've often joked that if you could just do a 'parentectomy' these kids would be fine."

But even without parental pressures, short stature can be costly in our society, which values height. Some scientists cite studies showing success is tied to inches, with taller people making more money or having more prestigious jobs on average than shorter individuals.

Drawing the line between normal growth and development and medical disorder is not always clear-cut. Growth disorders can be difficult to diagnose because of the wide variation in normal growth rates, and researchers are just beginning to tease apart the various hormones and other factors that govern a child's growth and entrance into puberty.

Growth Hormone Deficiency

One of the more challenging growth disorders to diagnose is a growth hormone deficiency. It affects only 15,000 to 20,000 children in this country. Some children with a growth hormone deficiency have normal growth rates the first few years of life. This growth abnormality is suspected if a child is between 3 and 12 years of age and growing less than 2 inches a year for an extended period.

But before diagnosing growth hormone deficiency, physicians first rule out several more common conditions that can temporarily slow growth, including a deficient diet, abnormal digestion, stress, hypothyroidism, diabetes, brain tumor or injury, and chronic illness, such as severe asthma or a kidney disorder.

An inherited tendency to be on the short side of normal, as evidenced by a child's short parents, can also explain a slow growth rate. Children may have delayed

As in normal puberty, in precocious puberty the brain secretes luteinizing hormone-releasing hormone (LHRH), which prompts the pituitary gland to release gonadotropins. These hormones then stimulate girls' ovaries to make estrogen and progesterone, and boys' testes to make testosterone. These hormones spur the development of secondary sexual characteristics and trigger growth spurts.

puberty, in addition, which can temporarily retard growth. (See accompanying article.)

Once these factors are ruled out, using various blood, cell and urine tests and x-rays, standard growth hormone stimulation tests are usually done. Growth hormone levels are measured in the blood after the child is given certain drugs known to prompt growth hormone secretion.

Low levels of growth hormone in these tests signal a classic growth hormone deficiency. Children's growth hormone levels may hover around the somewhat arbitrary "normal" cutoff point in these tests, however. Whether these children have a true growth hormone deficiency can't be known for certain, especially because growth hormone stimulation tests are not considered precise or sensitive.

Other children may "pass" growth hormone stimulation tests even though they may have a growth hormone disorder. For example, growth hormone stimulation tests can't detect children who secrete adequate quantities of an abnormal form of growth hormone that is unable to prompt normal growth. Also, some children may secrete normal amounts of growth hormone when stimulated by the tests, but don't make enough of the hormone under normal circumstances. Both types of children may benefit from growth hormone therapy.

It is known that radiation therapy or brain tumors can cause growth hormone deficiency, but in most cases the causes are not known. Decades of experience

with growth hormone therapy have shown, however, that it works in nearly all children accurately diagnosed with the condition even if the cause cannot be pinpointed.

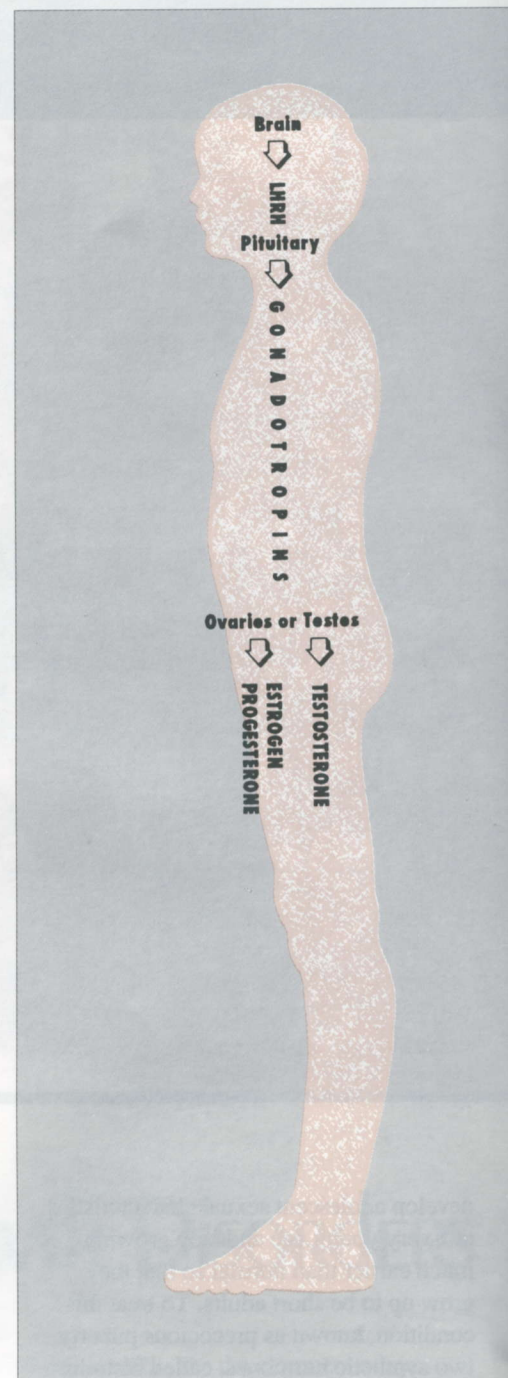
Growth hormone therapy is given by injection, either daily or several times per week. Parents are trained to give these injections unless the children feel comfortable doing it themselves. Therapy continues until the end of puberty, when bone growth stops, or sooner, if both family and doctor feel the child has reached an acceptable height.

The sooner before puberty therapy begins, the greater the height that can be achieved. There is no firm evidence tying growth hormone therapy to any significant side effects when it is used properly. Reports that the therapy can boost the likelihood of developing leukemia, or other disorders have not been confirmed, although long-term studies are addressing this.

Giants in the Making

Even less common than growth hormone deficiency is growth hormone excess, which can cause gigantism. One such person with this condition in the 1930s was nicknamed the "Alton Giant," after his Illinois hometown. He reached a height of nearly 9 feet and a 37 shoe size, according to the Life book *Growth*.

Fewer than 50 such "giants" have been reported in the medical literature. Most owed their amazing growth to pituitary tumors that prompted excessive production of growth hormone. Other symptoms that often accompany pituitary tumors are



headaches, dizziness, vomiting, and vision disturbances such as double vision.

Nearly all pituitary tumors can be detected with CT (computerized tomography) scans or magnetic resonance imaging (MRI) scans. Patients with these tumors are treated with surgery, radiation, or an experimental drug that mimics the natural compound somatostatin, which inhibits the release of growth hormone. These treatments can sometimes stem excess growth hormone production and re-

turn a child's growth rate to normal.

Excess growth hormone production should be suspected if a child is exceptionally tall and growing unusually fast. The vast majority of such children, however, do not have abnormal growth hormone production, but are merely following in their tall parents' footsteps.

Precocious Puberty

Some children are tall for their age and grow faster than expected because they are undergoing precocious puberty. Although the onset of puberty varies considerably, sexual development before age 8 in girls and age 9 in boys is generally considered precocious puberty. This condition can occur as early as in infancy. About one child of every 10,000 in the United States starts puberty prematurely, according to the National Institute of Child Health and Human Development.

The hormonal changes responsible for early puberty are usually the same ones that trigger normal puberty. The brain secretes pulses of a hormone called luteinizing hormone-releasing hormone (LHRH), which prompts the pituitary gland to release hormones called gonadotropins. These hormones, in turn, stimulate the ovaries and testes to make sex hormones that cause the development of sexual characteristics as well as trigger a growth spurt.

Consequently, children who start puberty prematurely are initially tall for their age. But the sex hormones also cause growth to stop earlier than normal so the children may not achieve their full height



Children's growth patterns may be inherited and can vary widely, just as there is great variation within the normal range in the heights of adults. Such variety enables, for example, a 6-foot-2-inch woman to get a book from a high shelf for a 5-foot man.

LATE BLOOMERS

Children with delayed puberty are exceptionally short for their age, and have no need for the bras or shavers that are standard equipment for their adolescent peers.

Girls are considered delayed if they don't show any signs of puberty by age 12 or 13, boys by age 14 or 15. At the age when most children experience a pubertal growth spurt, delayed children continue growing at the same slower rate, making them short for their age. Once late bloomers complete puberty, however, their height catches up to that of their peers. About 1 out of every 100 children has delayed puberty.

A red flag for such late bloomers is x-ray evidence that bone maturation lags behind what is expected for the child's age. The degree of bone maturation is appropriate for the child's height, however. Rarely, puberty is delayed or never occurs because of a central nervous system disorder such as hypopituitarism, or because of abnormalities in the sex chromosomes.

Chronic illness, malnutrition, or emotional stress can also delay puberty. But usually doctors are unable to detect a cause for delayed puberty. Children with delayed puberty often have a parent who was a late bloomer, and the condition is neither a physical abnormality nor a sign of disease, but nevertheless can have social and psychological ramifications.

Adolescents with delayed puberty, like children with precocious puberty, are often teased or sometimes even ostracized by their peers. A major source of anxiety for these children, especially boys, is short stature.

In several studies, an experimental drug known as oxandrolone—a synthetic compound similar to the male hormone testosterone—boosted growth rates of boys with delayed puberty. Given daily in low doses by mouth, oxandrolone doesn't usually prompt puberty, studies suggest, nor does it appear to affect final height, although more studies are needed to firmly establish this. It mainly accelerates children's growth so their heights reach those of their peers already undergoing puberty. Several studies found no short-term side effects tied to oxandrolone therapy.

To boost sexual development, doctors may treat late bloomers with sex hormones, though this use is experimental. Testosterone given monthly by injection

to boys usually induces sprouting of pubic and facial hair and the enlargement of the penis. The therapy sometimes makes boys more aggressive and may have other side effects. Girls given female hormones—estrogen or estrogen and progestin combinations—often develop breasts and start to menstruate. Potential side effects of this therapy include nausea, fluid retention, depression, and circulatory disorders.

There is concern that sex hormone treatments might limit final height, as they do in precocious puberty. But recent research suggests that low doses of these hormones do not rob late bloomers of inches.

Oxandrolone, testosterone, estrogen, and progestin are usually only given for about six months to a year to children with delayed puberty. At this point, studies show, most children have entered puberty and no longer need the drugs. ■

—M.P.

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potential. Boys may not grow taller than 5 feet 2 inches, and half of the girls do not exceed 5 feet.

The cause of precocious puberty in girls with the condition often is not known. Rarely, early puberty in girls is prompted by tumors, brain disorders, injuries, or infections. Also, in rare cases, girls have hormone-secreting tumors or cysts in the ovaries or adrenal glands that prompt what is known as pseudoprecocious puberty. (Unlike children undergoing true precocious puberty, girls with pseudoprecocious puberty don't ovulate, and boys with the condition don't generate sperm.) Precocious puberty in boys, in contrast, is often caused by brain tumors. The rare boys who undergo pseudoprecocious puberty, in addition, often have tumors in the adrenal glands or the testicles.

Doctors can determine what type of precocious puberty a child has from blood hormone levels and CT or MRI scans of the head, adrenal glands, or sex organs.

Early puberty is inherited in nearly 1 out of 10 boys with the condition. The tendency to start puberty prematurely can be passed directly from father to son, or indirectly from the maternal grandfather through the mother (who does not start puberty early herself) to her son. Premature puberty is inherited in fewer than 1 in 100 girls with the condition.

"Precocious puberty is a problem," points out FDA pediatric endocrinologist Saul Malozowski, M.D., "because a child who experiences it has the sex drive of

someone with [adolescent levels] of sex hormones, but lacks the emotional maturity to deal with it."

Because precocious puberty often limits height, and is accompanied by teasing by a child's peers, doctors usually recommend treating the condition. Such treatment aims to halt or even reverse the condition.

If puberty is being prompted by tumors, radiation treatment or surgical removal of such tumors may be recommended. But often such removal—especially of brain tumors—is not feasible. Moreover, even when surgery is performed, it may not successfully stop sexual development.

Consequently, most doctors prefer to treat children with precocious puberty with drugs that restore the normal hormonal balance in the body. The two newly approved drugs Supprelin and Synarel can stop the accelerated growth and stem or sometimes reverse sexual development in children with true precocious puberty. Supprelin injections can be given at home by a parent. Synarel is given via a nose spray.

These drugs mimic LHRH. Daily doses apparently stem the pituitary gland's responsiveness to the natural hormone. The child's own secretion of LHRH, consequently, no longer triggers sex hormone production. Within weeks of beginning treatment, menstruation and ovulation, or sperm production, usually stop. After several months, many girls' developed breasts shrink and their pubic hair may fall out. The penis and testicles usually shrink back

to normal size in boys, and pubic and facial hair often disappear.

The most frequent side effects of these drug therapies are light vaginal bleeding within the first month of treatment in girls, and in both sexes, redness, swelling, and itching at the injection site for Supprelin. Therapy is stopped when a child reaches the appropriate age for the onset of puberty.

Psychological Boosts Needed, Too

Most children on the fringes of what's considered "normal" for growth and development need to be reassured that their unique way of growing up is worthwhile, according to pediatric endocrinologist Leona Cuttler, M.D., of Case Western Reserve University in Cleveland.

"The need to be like everybody else is so strong in children," she says. "It's important to emphasize to them the wide range of what's considered normal for height and development."

In her clinic, she adds, social workers and psychologists assess and help improve, if necessary, the psychological well-being of children with short stature or delayed or precocious puberty. How well these children adjust to their height and development enters into her decision on whether to treat them.

As FDA's Malozowski points out, "the more time you spend with a patient, the less medicine you have to use." ■

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