

Concerns about Growth Hormone Experiments in Short Children

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Since 1958, human growth hormone (hGH) has been extracted from cadavers for use in children who do not produce normal amounts. The hormone increases the height of hormone-deficient short children, although they typically remain much shorter than average. Since the early 1980s, genetic engineering has permitted the mass-production of hGH without resorting to cadavers. However, prior to 2003, the U.S. Food and Drug Administration (FDA) approved hGH for use only in hormone-deficient children and other limited indications: chronic renal insufficiency, Prader-Willi syndrome, children born small for gestational age, and Turner syndrome.

In 1989, researchers at the National Institutes of Health began experiments to test hGH in children who were not deficient in growth hormone but were simply short. Other research teams had found that the hormone does not cause any change in growth rate for 20 to 50 percent of non-hormone-deficient children. The remaining 50 to 80 percent show short-term increases in growth, although final adult height is affected only modestly.¹⁻⁹ An FDA report¹⁰ found that non-hormone-deficient children, by an average age of 18.8 years, gained an average of 2.8 to 5 cm (1 to 2 inches) beyond predicted height after an average of 4.4 years of treatment. This means, for example, that a child predicted to reach a height of 5'0" without treatment will be only 5'1" to 5'2" with treatment. A higher dose used in another study with injections 6 times per week for an average duration of 5.3 years resulted in a mean gain in adult height of 7 cm, or about 2.7 inches.¹⁰

In 2003, the FDA approved the use of hGH in non-hormone-deficient short children. The long-term risks of hGH injections in children who already produce adequate growth hormone are not known. Possible risks of such treatment relate both to the multiple injections the children receive and to the drug itself:

Injections: Children can receive from 156 to 312 injections of hGH per year for 2 to 5 years or more.¹⁰ The psychological effects of repeated injections on children or on family relationships are not fully known, but investigators have found that, among hospitalized children, hypodermic needles are the most stress-provoking stimulus encountered.¹¹ Diabetic children

describe injections as one of the top stressors in their medical treatment.¹²

Studies of families with diabetic children have also found that the parental attention required for chronic medical treatment can lead to resentment on the part of siblings and can even affect the parental relationship.¹³ It is not known whether similarly disruptive effects occur with the introduction of chronic hGH treatment.

Increased Stigmatization: Growth hormone injections and the repeated examinations required may build or reinforce a negative self-image and stigmatization. In some cases of hormone-deficient children, unrealistic expectations for growth following hGH therapy have led to disappointment and depression.^{14,15} Available evidence does not show that hGH improves social adjustment, even when such treatment increases the final height of hormone-deficient children who have emotional problems.¹⁶

Cancer Risk: Growth hormone causes the liver to increase its production of insulin-like growth factor (IGF-I), which is thought to play a role in breast cell growth and lactation. Elevations of blood levels of IGF-I are associated with a greater risk for prostate and breast cancer.^{17,18} In laboratory tests, IGF-I encourages breast cancer cells to multiply and is more potent in this regard even than estrogens.^{19,20} Slight elevations of growth hormone, with corresponding increases in IGF-I, may be one reason why tall women have a higher risk of breast cancer, compared to shorter women.^{21,23} One study showed that women over 5'6" have double the risk of women below 5'3", particularly for premenopausal breast cancer.²¹

Several cases of leukemia have been reported in hormone-deficient children receiving hGH, but there is little evidence implicating hGH as a cause. Hormone deficiencies can be caused by brain tumors, which are sometimes treated with radiation. The leukemia may be linked to the radiation or to underlying genetic abnormalities rather than to the hGH.

In approving hGH for use in non-hormone-deficient children, the Food and Drug Administration

cited a “16-year safety history.”¹⁰ However, increased risk of hormone-related cancers may not be detected until after a longer latency period.

Renal Effects: For children who have kidney problems, growth hormone may aggravate their already poor kidney function, possibly by increasing the rate of blood flow through the kidney and the rate at which the kidneys filter the blood. One case report describes a child with preexisting kidney disease who went into end-stage kidney failure after treatment with hGH.²⁴

Metabolic Changes: Growth hormone increases the metabolism, that is, the rate at which the cells of the body consume fuel and nutrients. Some children may become unusually lean, losing body fat and becoming inappropriately muscular.²⁵

Antibody Production: In some children, hGH stimulates the production of antibodies to growth hormone. It is presumed that these antibodies will not interfere with their own growth hormone,²⁶ but researchers are monitoring this possibility.

Cost: Treatment with hGH costs approximately \$20,000 per child per year. Of all children born in the U.S. each year, 90,000 will be below the third percentile for height. A single year’s treatment of the 90,000 nine-year-olds below this height standard, for example, would cost \$1.8 billion dollars. Given this expense, such treatment would necessarily be restricted to certain groups.

The Psychology of Short Stature

The intellectual capacity of growth hormone-deficient short children is usually normal. Most achieve an educational level comparable to their siblings, although some do not.²⁷ Some hormone-deficient children have shown problems on visual-motor tests,²⁸ and rates of employment and marriage are far below average.^{16,29} The emotional maturation of growth hormone-deficient children is often normal³⁰ but varies widely.^{31,32} Many have poor self-esteem and tend to avoid aggressiveness.^{14,16}

Short children who are not hormone-deficient generally have no resulting intellectual or academic problems.³³ Children who are either unusually tall or short often have somewhat lower self-esteem, compared to children who are nearer average height.^{34,35} Short children may favor individual activities to socializing in large groups, and some have less maturity in social judgment.³⁶ Adolescence temporarily increases these characteristics.³⁷ However, children differ from each other in many ways aside from height, all of which can affect their self-confidence in peer relationships during adolescence.

Several steps can improve the adjustment of short children. Parents and teachers can be helpful by reacting to children according to their age, not their height,³⁸ contrary to the natural tendency to treat short children as if they are younger than their chronological age. Teasing and names linked to size can be avoided. Role-playing helps children to

anticipate and cope with difficult situations, such as bullying. Involvement in sports for which smaller size is advantageous (e.g., gymnastics) or for which size is not a factor (e.g., skiing, swimming, golf) can be encouraged.

Counteracting prejudice and feelings of shame related to race, gender, disabilities, and other characteristics has long been a goal of both public and private programs, but there has been no major effort to reduce such feelings based on stature.

There may be any number of ways of addressing the stigma of short stature. Psychological approaches³⁸ to improve adjustment in children who are having difficulties merit further investigation before hormonal treatments are used, particularly since hormonal treatments will have, at best, a partial effect.

Summary and Recommendations

The most important concern about hGH use is cancer risk. Because the drug elevates insulin-like growth hormone levels, increased cancer risk is a possibility, and no evidence yet discounts this risk. Other potential risks include the pain or discomfort of the repeated injections, increased stigmatization, renal effects, metabolic changes, and antibody production.

Children are not fully capable of informed consent and cannot adequately weigh the risks or benefits of hGH treatment. Both parents, children, and their physicians may tend to overestimate the potential benefits of hormone treatment and may overlook other ways of handling short stature.

The following recommendations are indicated:

- The therapeutic use of hGH in children should be limited to those with growth hormone deficiencies and diagnosed medical conditions.
- Children who have received hGH should be monitored for biological and psychological effects over the long term.
- Non-pharmacologic interventions to counteract the stigma of short stature should be investigated.

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