Growth Hormone: The Expansion of Available Products and Indications

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KEYWORDS

- Growth hormone • Indications • ISS • SHOX
- Turner syndrome • Prader-Willi syndrome
- Small for gestational age

Growth hormone (GH) first was isolated from the human pituitary gland in 1956, but its biochemical structure was not elucidated until 1972. The most famous person to exemplify the appearance of untreated congenital GH deficiency (GHD) was Charles Sherwood Stratton (1838–1883), who was exhibited by P.T. Barnum as General Tom Thumb and who married Lavinia Warren.[1] Pictures of the couple show the typical adult features of untreated severe GHD along with proportional limbs and trunks. By the middle of the 20th century, endocrinologists understood the clinical features of GHD. The first report of successful treatment of human GHD was in 1958, so that GH therapy now is celebrating its 51st anniversary. Raben, an endocrinologist at Tufts University School of Medicine in Boston, was able to purify enough GH from the pituitary glands of autopsied bodies to treat a 17-year-old boy who had presumed GHD.[2] A few endocrinologists then began to help parents of children who had severe GHD to make arrangements with local pathologists to collect human pituitary glands after removal at autopsy. Parents then would contract with a biochemist to purify enough GH to treat their child. Supplies of this cadaveric GH were limited, and only the most severely deficient children were treated. From 1963 to 1985, about 7700 children in the United States and 27,000 children worldwide were given GH extracted from human pituitary glands to treat severe GHD. Physicians trained in the relatively new specialty of pediatric endocrinology provided most of this care, but, in the late 1960s, there were only

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100 such physicians in a few dozen of the largest university medical centers around the world. To maximize procurement, purification, distribution, and clinical investigation, the National Institutes of Health and the College of American Pathologists formed the National Pituitary Agency (NPA) in 1960.[3] Treatment was reserved for only the most severe cases of GHD and, because of scarce supplies, was discontinued when girls reached 5 ft and boys reached 5.5 ft. Identification of the biochemical structure of GH in 1972 became the catalyst for the development of recombinant DNA-derived human GH, the gene for which first was cloned in 1979. The discovery was fortuitous considering the identification in 1985 of four young adults in the United States with the fatal, slow viral (prion-mediated) Creuzfeldt-Jacob Disease (CJD), who had been treated with GH from the NPA in the 1960s.[4] The connection was recognized within a few months, and use of human pituitary GH rapidly ceased. Between 1985 and 2003, 26 (out of 7700 patients treated) cases of CJD occurred in adults in the United States who had received NPA GH before 1977; 135 other cases were identified around the world. As of 2003, there had been no cases identified in people who received only GH purified by the improved 1977 methods.

A new American biotechnology company, Genentech (San Francisco, California), developed in 1981 the first recombinant human GH (rhGH) by a biosynthetic process called inclusion body technology.[5] Later, an improved process to develop rhGH was developed called protein secretion technology.[6] This is currently the most common method used to synthesize rhGH, known generically as somatotropin. Discontinuation of human cadaveric GH led to rapid US Food and Drug Administration (FDA) approval of Genentech's synthetic methionyl GH, which was introduced in the United States in 1985 for the therapy of severe childhood GHD. Although this previously scarce commodity was suddenly available in bucketfuls, the price of treatment ($10,000 to 30,000 per year) was extraordinary for a pharmaceutical at that time.

With the development of rhGH, an unlimited commercial source became available, allowing for an ever-growing list of FDA-approved indications for GH use in non-GH deficient children and for additional indications in adults:

- Children with chronic renal insufficiency (CRI) in 1993
- Turner syndrome (TS) in 1996 to 1997
- Prader-Willi syndrome (PWS) in 2000
- A history of small for gestational age (SGA) in 2001
- Idiopathic short stature (ISS) in 2003
- Short stature homeobox (SHOX) gene deficiency in 2006, Noonan syndrome (NS) in 2007
- Adults with severe GHD and for HIV wasting in 1996
- Short bowel syndrome in 2003.

APPROVED BRANDS AND INDICATIONS

Introduction

The first available rhGH, Protropin, was a polypeptide hormone produced by inclusion body recombinant DNA technology. Protropin had 192 amino acid residues and a molecular weight of about 22,000 d. The product contained the identical sequence of 191 amino acids constituting pituitary-derived human GH and an additional amino acid, methionine (MET), on the N-terminus of the molecule. Protropin was synthesized in a special laboratory strain of *Escherichia coli*, which had been modified by the addition of the gene for human growth hormone (hGH). This Met-GH was not a pure GH and, therefore, caused some patients to produce antibodies against the product.[7]