

Special Editorial: Growth Hormone Treatment and Neoplasia—Coincidence or Consequence?

The discovery that GH action in primates was species specific and the ability to extract GH from human pituitaries ushered in the era of GH therapy for humans in the 1950s. At the outset, these were investigational programs facilitated by a centralized and usually government-sponsored distribution program that also enabled monitoring of data on beneficial or adverse effects. Recombinant DNA-derived GH became available in 1985, shortly after human-derived GH was discontinued because of the occurrence of Creutzfeldt-Jakob disease in several recipients from different countries. With the introduction of recombinant DNA-derived GH, the indications for GH replacement therapy were broadened to include Turner's syndrome, chronic renal failure, Prader-Willi syndrome, and small-for-gestational-age, in addition to established GH deficiency in children. However, monitoring of potential adverse effects was meticulously continued, facilitated by scrupulously maintained, and continually enlarging, databases involving both government and pharmaceutical companies in concert with pediatric investigators.

The Lawson Wilkins Pediatric Endocrine Society (LWPES) has closely and carefully monitored reports of adverse events via its Drug and Therapeutics Committee, which regularly informed the LWPES membership (1, 2). Early reports of an increase in childhood leukemia following GH therapy proved to be unfounded when the growing international databases were carefully monitored. Existing evidence indicates that GH treatment does NOT increase tumor recurrence in those whose primary lesion has been successfully treated. The LWPES has also endorsed the prudent policy of waiting for 1 yr after the completion of tumor treatment with no further evidence of tumor recurrence or growth before starting GH treatment in these children. Because a person treated for a malignancy is at risk for a second malignancy, ongoing surveillance of such persons is recommended, especially in those with genetic syndromes that are known to confer an increased risk of malignancy (Down's syndrome, Bloom's syndrome, Fanconi's anemia, neurofibromatosis-1). These recommendations also are part of the recent consensus conference by the Growth Hormone Research Society, which the LWPES has endorsed (3). This careful monitoring by LWPES contributes to the remarkable record of safety and efficacy of GH treatment for recommended indications in children and adolescents. Although adverse events are known to occur (raised intracranial pressure, edema, slipped capital femoral epiphyses, hyperglycemia, gynecomastia), an increased risk of cancer has not been an issue in pediatric patients treated with GH (2).

The article by Swerdlow *et al.* (4), in *Lancet*, reports on the risk of cancer in patients treated with human pituitary GH in the United Kingdom from 1959 to 1985. The cohort consisted of 1848 patients in the United Kingdom treated in childhood and early adulthood with human pituitary GH

and followed for cancer incidence through December 1995 and for mortality through December 2000. Risks of cancer were compared with that in the general population after controlling for age, sex, and calendar period. Among this cohort, risks of mortality from cancer overall was increased approximately 3-fold and from colorectal cancer and Hodgkin's disease approximately 11-fold. The incidence of colorectal cancer was increased approximately 8-fold, and both incidence and mortality of colorectal cancer as well as that of Hodgkin's disease were increased even after excluding patients whose original diagnosis gave them a higher risk of cancer.

These results are potentially important but clearly preliminary, as the authors themselves point out. Only two deaths each of colorectal cancer and Hodgkin's disease were reported. Although highly more prevalent than expected in the control population, a chance occurrence of one case or of one death each from colon cancer or Hodgkin's disease may have skewed the results. It would also be essential to know whether the incidence of such malignancies is increased in patients with GH deficiency who did not receive GH therapy. Are the incidence rates of patients with GH deficiency who are not treated with GH comparable with the matched general population? The relatively small cohort and small number of cases argue strongly for caution in the rush to judgment or conclusion. Similar concerns with leukemia proved unfounded when larger cohorts were carefully examined; some cases of leukemia actually preceded the institution of GH therapy. Failure to treat GH deficiency is itself associated with premature mortality, especially from cardiovascular causes (4).

Despite these caveats, the authors are to be applauded for bringing this issue to scrutiny. They have carefully analyzed their cohort and cautiously presented their inferences and conclusions. They provide a potential rational basis through the known effects of IGF-I on promoting cell growth and inhibiting apoptosis. They point out reported associations between status of GH excess such as acromegaly and gastrointestinal cancer, although they do not mention several reports to the contrary (5). They infer that former dosing schedules with human-derived GH may have resulted in higher IGF-I levels than are likely with modern regimens, although they cannot substantiate this assertion, nor is it likely based on GH purity, potency, and dosages used in the 1959–1985 era (6–8).

The available data in pediatrics do not support any concern for excess malignancy at this time. In the two largest international databases and surveillance studies, with a total of some 86,000 patients on GH, representing almost 250,000 GH treatment years, there is only one report of a gastrointestinal carcinoma—an adenocarcinoma in a 15-yr-old girl initially treated by radiotherapy and chemotherapy for a

brain tumor (astrocytoma). She developed gastrointestinal bleeding 3.5 yr after the start of GH therapy when the tumor was diagnosed. There is also a report of spontaneous colon cancer in a girl with Turner's syndrome many years after discontinuation of GH therapy (personal communication).

With these considerations in mind, the LWPES believes:

1. Current treatment recommendations with recombinant human GH for children with documented GH deficiency are safe and without proven increased risk of inducing malignancy (2, 9, 10). Treatment for any indication with recombinant GH therapy in children should be accompanied by regular monitoring of IGF-I and IGF-binding protein-3 concentrations to ensure that they are maintained within age appropriate limits.

2. The possible association between increased cancer incidences and/or mortality and GH treatment be further critically investigated in a large cohort, especially in those treated with human-derived GH by protocols similar to those reported by Swerdlow *et al.* (4). Large databases of such patients are available and should be critically reviewed.

3. Surveillance and monitoring of ongoing long-term results of GH therapy should be encouraged and supported.

Lawson Wilkins Pediatric Endocrine Society (LWPES) Writing Committee: Mark A. Sperling (University of Pittsburgh School of Medicine, Pittsburgh, PA), Paul H. Saenger (Albert Einstein College of Medicine, Bronx, NY), Ray Hintz (Stanford University School of Medicine, Stanford, CA), Tom Wilson (State University of New York, Stony Brook, NY), and Susan R. Rose (Cincinnati Children's Hospital Medical Center, Cincinnati, OH) on behalf of the LWPES Executive Committee and the LWPES Drug and Therapeutics Committee

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Address all correspondence and requests for reprints to: Mark A. Sperling, M.D., Department of Pediatrics/Endocrinology, Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Pittsburgh, Pennsylvania 15213-2583. E-mail: masp@pitt.edu.

Other members of the LWPES Drug and Therapeutics Committee are: Phillippe Backeljauw, M.D. (Cincinnati Children's Hospital Medical Center, Cincinnati, OH); Rosalind Brown, M.D. (University of Massachusetts Medical School, Boston, MA); Pinchas Cohen, M.D. (David Geffen School of Medicine at UCLA, Los Angeles, CA); Dana S. Hardin, M.D. (University of Texas Southwestern, Dallas, TX); Stephen F. Kemp, Ph.D. (University of Arkansas School of Medicine, Little Rock, AR); Margaret Lawson, M.D. (Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada); Sally Radovick, M.D. (The University of Chicago, Chicago, IL); Steve M. Rosenthal, M.D. (University of California San Francisco, San Francisco, CA); Lawrence Silverman, M.D. (University of Medicine and Dentistry of New Jersey-New Jersey Medical School, Camden, NJ); Phyllis Speiser, M.D. (New York University School of Medicine, New York, NY).

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