

GROWTH HORMONE AS A THERAPEUTIC AGENT

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Twenty years have passed since recombinant human growth hormone (rhGH) was approved by the FDA for clinical use in patients with growth hormone deficiency (GHD). This was a major breakthrough, as the only previous source of GH was naturally-occurring GH extracted and purified, to a variable extent from human pituitaries removed at autopsy. This human GH (hGH) was first prepared and studied by Raben¹ in 1958 and was shown to produce growth in a sexually undeveloped adolescent. The supply of hGH for investigation and/or therapy was very limited until rhGH became available in 1985, when the supply suddenly became unlimited and the new modern era of GH as a therapeutic agent began. Genentech developed the recombinant techniques to synthesize rhGH, and also developed the necessary testing leading to approval by the FDA of rhGH for human use.

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From The Editor's Desk

This issue's lead article commemorates the 50 years of human growth hormone (hGH) as a therapeutic agent and the 20th anniversary of recombinant hGH (rhGH) for the treatment of hypopituitary children. The personal recollections of Dr. Robert Blizzard bring to the reader a clear historical perspective of the developments that brought about the rise and fall of hGH. It also highlights the synthesis and approval of rhGH and the major strides made with the unlimited availability of rhGH.

We also commemorate 2 decades of *Growth, Genetics & Hormones (GGH)*. This journal was established in 1985 to provide a high-quality educational resource to physicians. The journal accomplished its mission, and more. Dr. Blizzard's leadership, the hard work of the Editorial Board, and an unrestricted educational grant from Genentech made it all possible. In 2002 www.GGHjournal.com was launched. This enabled us to bring *GGH* to most pediatric endocrinologists around the world. From their comments, we know they treasure the content and erudite comments of the Editorial Board. The on line archives of the journal constitute the repository of the fundamental advances that have occurred in the field of growth since the beginning of *GGH*.

Each year we have given readers more material and added features without an increase in budget. However, *GGH* may cease publication next year as the educational grant that we have enjoyed since its inception will not be available after April 2006. Thus, we are searching for sponsorship and have requested grant support from all manufacturers of rhGH. The pharmaceutical companies that compete for market share have a common responsibility to provide high quality educational resources to physicians who prescribe rhGH. I challenge them to promptly fill the void so we may continue bringing state-of-the-art, unbiased, valuable information in the field of growth to our colleagues worldwide. It has been estimated that the annual sales of rhGH are \$1.5-\$2 **billion**; 30% of the sales being for FDA approved indications to treat children and adults (Perls TT, Reisman NR, Olshansky SJ. *JAMA*. 2005;294:2086-2090.) Thus, there *must* be funds available to be allocated for the continuation of *GGH*, a highly regarded educational journal.

We will continue to explore sources of support to enable us to provide you with *GGH* on a complementary basis—as it has been done since 1985. On line subscribers recently received a survey to evaluate their interest in helping shape the future of the journal. I am gratified by their response; more than 40% indicated a willingness to pay for a subscription to the journal. I urge all of you to complete the one question survey (www.GGHjournal.com) or to send me a note indicating your interest in a paid subscription (editor@GGHjournal.com) so we may plan the future of *GGH*.

Respectfully,
Fima Lifshitz, MD

The 20th anniversary of FDA approval of rhGH occurs simultaneously with the 20th anniversary of the establishment of the journal, *Growth, Genetics & Hormones* (*GGH*, available at www.GGHjournal.com). *GGH* has been supported by Genentech, Inc., via an educational grant. *GGH* was the first journal established for the purpose of assimilating published information, both domestic and international, on growth problems valuable to the pediatric community (endocrinologists, geneticists, matabolists, and generalists). The current editor-in-chief of *GGH* believes that a review of the historical aspects of the development and use of hGH and rhGH should be presented during this simultaneously occurring 20th anniversary before the details are lost in obscurity.

I undertake this task as one who has been privileged to be an observer and participant in the accomplishments brought about by Genentech in creating both rhGH and *GGH*. As stated in the first issue, “*GGH* is established as an educational journal by the Editorial Board to facilitate the flow of information and commentary which provide a close look at current, and often controversial, topics in endocrinology, metabolism, and genetics, and their potential applications.”² This goal has been, and continues to be met, for 20 years. Similarly, the creation and production of rhGH have benefited many thousands of children with growth disturbances. I also undertake this task as one participating actively in the use of native GH in the 30 years preceding the launching of rhGH and *GGH*.

This review is a personal perspective and recall of the past 50 years. In that sense, it may not always be totally accurate and it does not cover all important aspects in the field. Furthermore, these historical comments are made pertaining to my own experience in the United States and, therefore, do not reflect the equally interesting experiences in Europe, South America, Australia, New Zealand, and elsewhere.

VERY EARLY HISTORICAL PERSPECTIVES (Prior to 1958)

The first human who received GH of any origin was a 3½-year-old patient with presumed GHD to whom I gave bovine GH (BGH) in 1956 (supplied by Choh H. Li). This patient received BGH daily over a 3-week period while 24-hour metabolic balance studies were performed. I personally handled all stool, urinary, and dietary samples, and performed appropriate nitrogen and calcium determinations. Neither positive nitrogen balance nor hypercalcuria markers of GH reactivity were demonstrable. The conclusion was that either BGH did not act in humans or the patient was GH insensitive. Later, in 1963 when the immunoassay for hGH became available, high levels of GH and low levels of somatomedin or insulin-like growth-factor-I (IGF-I) were found in this patient’s serum.³ At 10 years of age, the patient did not

respond to hGH. Thus, this was the first patient to be diagnosed with GH insensitivity (GHI), eventually named “Laron’s Syndrome.” Now at 53 years of age, she survives without hypoglycemia (post-pancreatectomy), is married, and has a normal-size son.

EARLY HISTORICAL PERSPECTIVES (1958-1965)

Prior to 1958 studies with GH were pursued primarily in rodents and lower mammals, chiefly in 3 laboratories (led by Choh H. Li, PhD, UC Berkeley; Alfred Wilhelmi, PhD, Emory University; and Maurice Raben, MD, Tufts University). By 1958, each utilized different extraction methods to retrieve hGH from human pituitaries. For example, Raben’s procedure used hot glacial acetic acid which destroyed TSH, LH, and FSH. Li’s method was the most elaborate as he strived to report the chemical structure of hGH, which he did twice (once incorrectly and subsequently, correctly). Wilhelmi’s procedure produced a wide array of pituitary hormones in side fractions, which could be purified and used for clinical investigation.

Initially, the collection of human pituitaries was a diverse effort. Each of the above-mentioned extractors, many other endocrinologists, and even parents of short children solicited pathologists to collect pituitaries on all autopsied patients. Pituitaries from most unembalmed and all embalmed bodies at autopsy were placed separately in acetone, and a majority of those from unembalmed bodies were frozen *en mass*. The latter yielded greater amounts of hormone and the GH was less antigenic. Individual collection programs rapidly developed, usually under the leadership of an individual pediatric endocrinologist or a university group of pediatric endocrinologists. These programs tended to be geographically proximal to the location of one of the extractors. By 1962, Raben was receiving approximately 15 000 pituitaries per year, Wilhelmi was extracting approximately 3500, and Li a few less. Approximately half of the hGH extracted was kept for the extractor’s scientific use and the other half was returned to pediatric endocrinologists for clinical investigation of their patients. By 1959, I and a few others were studying presumed GHD patients with native hGH collected and extracted by these methods.

Initially, about 1 mg of hGH was obtained per unembalmed pituitary. Since 1 mg of hGH was needed to treat one patient per day, 365 pituitaries were needed per patient per year. From 20 000 pituitaries extracted per year, about 10 000 mg were available for pediatric endocrinologists. Thus, only 30 patients could receive a full course of therapy. The fascinating story of the collection of pituitaries, for extraction of hGH initially and other hormones subsequently, is a tale of intrigue and secrecy. A black-market competition for pituitaries developed. Scientific collegiality and secrecy occurred simultaneously. Clinical investigation produced many successes and too many disappointments.

In 1961, The National Institutes of Health (NIH) asked me to establish the National Pituitary Agency (NPA) to collect pituitaries on a national basis to counter the ever-growing black market for pituitaries, and to nationally organize and guide the collection, extraction, and distribution of hGH initially and other hormones later. To sell the concept of establishing the NPA was no easy task. Understandably, the extractors and involved pediatric endocrinologists had concerns about collection turfs. After extensive discussions and persuasion, an agreement of extractors, endocrinologists, and pathologists was finally attained. Each participant would be entitled to receive the same amount of pituitaries and/or hGH as he/she had received the previous year. The National Institute of Arthritis and Metabolic Diseases (NIAMD) entered into a contractual agreement with The Johns Hopkins University (my base of operation) to support the necessary personnel (other than myself), office expenses, and payments to pathologists of \$2 for the services rendered to collect, store, and deliver each pituitary to the NPA.

Funding for this agency was not available until 1963 (approximately 2 years later). Thus, I had to locate funding from other sources to implement the program. The initial success was due to many dedicated persons including Alfred Wilhelmi, PhD; William Daughaday, MD; Eugene Latimer, MD, physician coordinator; Ms. Dorothy Miller, executive secretary; and many others. The NPA was assisted by parents such as Fred and Gwen Mahler, who had 2 children with genetic GHD. Mr. Mahler, a TWA pilot, arranged transporting frozen pituitaries in the cockpits of planes from major cities in the US to the NPA in Baltimore. Mrs. Mahler, a retired TWA flight attendant, organized other retired TWA flight attendants on a national basis ("TWA Clipped Wings") to raise and donate thousands of dollars annually, for at least 6 years, to fund expenses of the NPA and the Human Growth Foundation which was created by parents of children with growth disturbances.

Of interest are the very crude methods (by today's standards) utilized for the collection and handling of the pituitaries and extracted GH. The hGH was received from the extractors at the NPA in small mason jars. It was transferred by a spatula to wax paper and placed on a simple analytical balance. One mg of hGH was weighed and placed in a small sterile screw cap vial which then was sealed. Multiple vials were then transferred via parcel to the physician investigators, along with 5- or 10-mL vials of various solvents, depending upon which hormone was dispensed. The most disagreeable solvent was 0.1% HCl, which was necessary to use in order for the Raben hGH to go into solution. Patients much preferred hGH from sources other than Raben.

In those early days, no bio-potency was determined and hGH was dispensed and injected on a milligram weight basis. Not until 1965 were potency estimates utilized.

Subsequently, assays utilized the growth rate of the tails of rats injected with hGH. The concentrations between batches varied from 0.5 to 2.0 units/mg of hGH. Reading the literature of that period is confusing since often only the milligram designation was used. The amount of hGH extracted per pituitary steadily improved. By 1977 when Albert Parlow, MD, became the single extractor of all human pituitaries in the US, the amount of hGH obtained per pituitary was several times greater than that obtained in 1960. Because of Parlow's efforts the supplies of hGH greatly increased. Remarkably, the hGH distributed never led to infections or adverse reactions until the occurrence in 1985 of the first case of Creutzfeldt-Jacob disease (CJD) resulting from the injection of apparently prion-contaminated hGH given many years earlier.

The treatment of patients was on the basis of investigation proposed by clinical research protocols on grant applications submitted to the NPA. Board review was the mechanism used to assess the proposals and to fairly distribute the extracted hGH. By law, the NIH could not support clinical treatment but could support investigative therapy. By 1963, substantial investigative therapy had been accomplished. An Editorial Commentary⁴ in 1963 by myself stated that: (1) hGH had been proven to be effective for periods up to 5 years, (2) in the first few months of therapy linear growth accelerated 6 or 7 times the pretreatment period, (3) the effectiveness of the hormone gradually waned, (4) there were no significant side effects detected, and (5) the dosage and schedules in therapy varied widely, but approximately 300 to 500 mg of hGH were required per year for each child treated. Therefore, widespread use was not possible even if a pituitary from each autopsy performed in the US was collected, as even this would only permit therapy in about 4000 patients. The editorial comment also stated that there was reason to believe that the short stature of Turner syndrome and other types of short stature were amenable to therapy. This fact was confirmed several years later. Also stated was the prediction that when hGH would become available in sufficient quantities it would have a breadth of application approaching that of cortisone.

HISTORICAL PERSPECTIVES (1965-1975)

In 1965, a Ross research conference on hGH was held at The Johns Hopkins Hospital, Baltimore, Maryland. The proceedings⁵ summarized the state of knowledge at the time, including that in 1962 a radioimmune assay for hGH was published,⁶ which permitted insight into GH's action in relation to diagnosis and treatment. By 1966, Alfred Wilhelmi, PhD; Robert Ryan, MD, Mayo Clinic; and Brij Saxena, PhD, Cornell University Medical College, were extracting and purifying TSH, ACTH, LH, and FSH from pituitaries. This ultimately permitted immunoassays for each of these hormones to be developed. It was possible, therefore, to significantly extend investigation of normal and abnormal endocrine physiology, and the

interrelations of hormones of the pituitary, the gonads, and the adrenals at adolescence. In the late 1960s, the development of a constant withdrawal pump by Avinoam Kowarski, MD and his collaborators⁷ made it possible to measure integrated concentrations of hGH over various periods of time, which advanced the capability to better understand GH physiology and production in relation to age, gender, and the effect of sex steroids.

The success of collection of pituitaries for hGH therapy, and the accumulation of knowledge derived from the use of hGH, was not without disappointments. In 1965, in a major US city the press learned that pituitaries were being collected by the medical examiner's office and shipped to the NPA. The diener was being paid the customary fee of \$2/pituitary for collecting, storing, and shipping the pituitary glands. However, he also collected gold from the mouths of autopsied corpses, and used the money gained from his supplemented income to build a swimming pool in his backyard called "the pit." The news transmitted by the United Press International and Associate Press did its damage. Grand Jury hearings were held in several cities, which affected the number of pituitaries collected that year. Unfortunately, there were other questionable occurrences in conjunction with the NPA's collection. One example involved an employee of the agency who executed questionable transactions for personal benefit. The tasks of the Director and the Board of Directors were not dull and were time-consuming.

GENE SPLICING AND RECOMBINANT DNA (rhGH) (1976-1985)

Based upon the laboratory demonstration that genes could be manipulated to produce useful new substances such as rhGH and rh-insulin, a remarkable story of a scientific revolution unfolded. This manipulation relied upon a controversial new area of research known as recombinant DNA engineering or, more popularly, as gene splicing. Stephen Hall has told the fascinating stories of the race to identify and duplicate the structures of genes (ie, insulin, GH, and somatostatin), the incorporation of these into bacteria, and by 1985 the production of these hormones in mass quantities. His book, *Invisible Frontiers*⁸ (Oxford University Press, New York, NY, 1987) is a "must read" for anyone interested in this field. Hall describes the molecular biology which challenged the accomplishment of making these hormones available as therapeutic agents, as well as the personal and professional interrelationships between the scientists. The result is a remarkable documentary of the multiple facets which transected medical science, therapeutic treatment, the pharmaceutical industry, and medical ethics into an entire new world in a 10-year period.

The mass production of specific hormones such as rhGH required identification of the gene structure of the desired hormone, duplicating that structure, determining

a way to mass produce the gene, splice the human gene into the gene structure of a bacteria so that the bacteria would produce the desired hormone in large quantity, purify the hormone, test the potency and possible toxicity in non-human mammals, and then test the hormone's potency, effectiveness, and possible toxicity in humans. The concept to accomplish this was clear prior to 1975, but the competitive race to develop the methodology began by scientists in 1976 when 3 groups of scientists in the US started the race to make insulin by recombinant technology. These groups were located at Harvard (Walter Gilbert, PhD, lab chief), at University of California at San Francisco (William Rutter, PhD; Howard Goodman, PhD; and Herbert Boyer, PhD, lab chiefs), and at Genentech (Herbert Boyer). Robert Swanson was a venture capitalist who, with Boyer, had a business goal, specifically, to make and sell human insulin. In August 1978, the Genentech group succeeded. The product was sold to Lilly and operating capital for further projects was available to the Genentech scientists. Peter Seeburg, PhD, a post-doctorate fellow with Goodman at UCSF, had been working with the hGH gene splicing system and joined the Genentech group that subsequently produced rhGH.

By 1981, several pediatric endocrinologists, including myself, were in the process of establishing the protocols for clinical trials of rhGH. A key person and the first physician employed by Genentech for the establishment of the clinical endocrine projects was Ann Johanson, MD, Professor of Pediatrics, University of Virginia. By October 1985, the clinical trials were successfully completed and the FDA approved rhGH for clinical use in patients with GHD.

Serendipity was manifest. In 1985, two explosive occurrences transpired. In March, a patient who had received hGH years previously was reported to have died of CJD. Native hGH had been given to patients for 27 years without significant side effects. The question was asked, "Should hGH investigation and therapy be discontinued?" Mortimer Lipsett, MD, Director of the National Institutes of Diabetes, Digestive and Metabolic Diseases (NIDDM) quickly called a meeting at NIH to discuss the question. Twenty plus prominent physicians of various specialties were present. I led the group who believed that "One is a series of nothing," and my calculation from the data generated by the NPA that 11 miles of height had been given to GHD patients over the years persuaded the consultant group and Dr. Lipsett not to stop distribution. Upon returning home after a follow-up meeting in New Orleans, I found a letter awaiting me from parents of an adult whom I had treated with native hGH as a child. Their son had succumbed to a neuropathological disease several months previously. A third patient also was quickly recognized. The comet truly had exploded and hGH distribution had to be stopped. The second event was the approval of rhGH by the FDA in October of 1985 for

treatment of GHD patients. This was the culmination of a phenomenal development: the creation of a synthetic rhGH that was accompanied by unlimited supplies of hGH for investigation and therapy.

hGH AND rhGH FOLLOW-UP (1985-2005)

This timeframe comprises 2 major areas of interest: first, the follow-up to the use of native hGH during the prior 27-year period (1958-1985), particularly in respect to the status of CJD, and second, the legitimate and illegitimate use of rhGH.

As of January 1, 2003, CJD in the US was reported to have occurred in 26 of the approximately 7700 patients (an incidence of approximately 0.34%) who had received hGH between 1958 and 1985. The names and addresses of 6272 of these are known. The possibility exists that some of the remainder (1428) may have been lost to follow-up because of death from CJD. Distribution of the preparations used in the early years was not always from the same extractor because the NPA often had only one type of preparation to distribute, and by necessity many patients received different preparations while undergoing investigative therapy. By 1977, the Wilhelmi extraction procedure had been dramatically improved in purity and in yield by Parlow, who had assumed responsibility for purification of all hGH for the NPA. No patient started on hGH after this improvement was incorporated into the process has developed CJD. In retrospect, Wilhelmi's preparations most likely were the source of the prion contamination, but even if this is correct only a few of the preparations were probably contaminated. Multiple factors, including total dose of the contaminated preparation and genetic susceptibility undoubtedly affected whether an exposed patient developed the disease. More cases might be expected to be reported, but the pandemic projected by Daniel Gajdusek, MD, PhD, in 1985 never occurred. In April 2003, Allen Spiegel, MD, Director of NIDDK, distributed 2 reports (a comprehensive and a short form) updating the information concerning CJD and hGH. (Information can be obtained on the NIDDK website, www.nidDK.nih.gov/health/endo/pubs/cruetz/update.htm).

Other diseases which could possibly be transmitted via hGH—including HIV—have not occurred. Adrenal crisis, however, has allegedly resulted in more deaths in patients having received hGH and rhGH than has CJD. Adrenal crisis is probably not caused by hGH or rhGH, but is a result of associated ACTH deficiency in patients with hypopituitarism. The positive aspects of the follow-up to the use of native hGH are many, and most are known to the readers of *GGH*. Those wishing additional information are referred to multiple articles in the *GGH* archives (www.GGHjournal.com/search.cfm).

In respect to the illegitimate use of rhGH, unequivocally the abuse by athletes is, and should be, of primary

concern to society and should be halted. The abuse of prescribing rhGH in an attempt to retard the aging process also should receive attention. My credibility to speak regarding the latter issue is gained from personal experience as I participated in a research protocol as proband (1982–1985) to assess if hGH could *reverse* the aging process. Specifically, I received daily injections of hGH for 2.5 years; 4 other men joined me for the last 2 years.⁹ The study terminated in 1985 when CJD was reported in patients who had received hGH. As a result of these early studies and subsequent short-term reports by multiple investigators, I remain unconvinced that hGH can *reverse* the aging process. Unequivocally we should strive to eliminate the abuse of rhGH in attempts to *reverse* the aging process. Unfortunately, the much needed study to determine whether rhGH will *retard* the aging process probably will never be done, as it would require 30 years of rhGH administration to a large group of individuals beginning at the ages of 30–35 years, as well as administration of a placebo to a similar group.

SUMMARY, CONCLUSION, AND COMMENT

This abbreviated history written by my recollection of 50 years of the use of hGH as a therapeutic agent is designed to expose young physicians and others to the use of hGH and rhGH over this extended period. With the exception of Stephen Hall's insightful presentation regarding how recombinant hormones came into existence, I am unaware of any historical accounting of the 50 years of GH. I thank Dr. Fima Lifshitz and the Editorial Board of *GGH* for the opportunity to relate these historical events and to share these with the readers of *GGH*.

In conclusion, now in my golden years, I am grateful to have had the opportunity to know and collaborate with so many giants working in the field of somatotropin investigation in the past, and I continue to meet and learn from the giants working in the field today. I am also grateful, and honored, to have had the opportunity to know and collaborate with my many former fellows and colleagues, all of whom were also my mentors. I cannot possibly record here the names of these wonderful people, but each former fellow and colleague can be assured that I am writing about you. My gratitude is also expended to former and current members of the Editorial Board of *GGH*, all of whom have shared significantly in making *GGH* an outstanding journal in bringing together physicians of multiple specialties to share knowledge of common need. The initial goals of Genentech and myself as first Editor in Chief have been exceeded, and continue to be exceeded beyond expectation.

I also wish to thank my former colleagues at NIH and others for the professional opportunities that have been given to me. To Genentech, this double 20th anniversary of the marketing of rhGH and the establishment of *GGH* is worthy of commemoration. Hopefully, this article

adequately recants the significant accomplishments and value of both.

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ADDENDUM

After submitting the above manuscript I became aware that after the March, 2006 issue (Vol 22, No 1), *Growth, Genetics & Hormones* may no longer have funding and thus cease publication. This journal has accomplished the significant goals set forth 20 years ago to broaden sharing of knowledge across pediatric endocrinology, genetics, metabolism and general pediatrics. Furthermore, the same goals need to be continued, as there is still a great need for sharing of important knowledge to provide the highest level of patient care and research among geneticists, nephrologists, endocrinologists, gastroenterologists, general pediatricians and others. There is no other journal that fulfills the need. Hopefully Genentech will continue to take the lead as they have in the past in so many endeavors, and either support directly the educational grant or organize collegially collaborative support among other organizations or corporations, so that *GGH* continues to be published next year and thereafter.

ABSTRACTS FROM THE LITERATURE

Idiopathic Short Stature Children Are Poor Eaters and Are Thin

Data on the eating behaviors and nutritional status of children with idiopathic short stature (ISS) are lacking. The paper by Wudy et al assessed 214 patients with ISS from 123 families and recorded the BMI and eating behaviors with the Child Eating Behavior Questionnaire and the Food Frequency Questionnaire. Endocrine markers of body weight regulation (leptin and ghrelin) were also measured. The ISS patients had a decreased BMI (-0.33 SDS) as compared with population norms. Furthermore, they also had a decreased food responsiveness with a score of 1.9 on the Child Eating Behavior Questionnaire, as compared with a score of 2.4 for the population mean. They had reduced enjoyment of food (3.2 vs 3.9), emotional under-eating (2.6 vs 3.0), and showed increased fussiness over food (3.2 vs 2.9). "Poor" eaters showed more marked alterations in BMI and behavioral characteristics than those who were "good" eaters. Total serum ghrelin was not different among good and poor eaters, and serum leptin was moderately increased but did not differ between the groups. The authors concluded that ISS patients present altered eating behaviors that possibly contribute to their short stature.

Wudy SA, Hagemann S, Dempfle A, et al. Children with idiopathic short stature are poor eaters and have decrease body mass index. *Pediatrics.* 2005;116:e52-57.

Editor's Comment: *There are countless papers dealing with ISS and other forms of short stature, but the nutritional status and eating behaviors of the patients are rarely addressed. Indeed, low IGF-I levels are most often analyzed and considered essential for diagnosis and treatment of short stature patients, as well as for the publication of scientific papers, often without addressing body weight, dietary intake, or nutritional status. Thus, I am delighted to note the paper by Wudy and colleagues showing ISS patients presenting with alterations in eating patterns and decreased BMIs. Hopefully, these data will stimulate an interest in evaluating the role of suboptimal nutrition on the growth patterns of children with ISS and other short stature patients. This assessment should be a must before embarking in other more costly medical interventions.*

Fima Lifshitz, MD

Compliance with Medication Recommendations

Compliance is defined as "the extent to which a person's behavior coincides with medical or health advice." Despite the importance of the medication in treatment, disease prevention, and health promotion, compliance rates range from 11% to 93%. The authors reviewed pediatric

medication compliance literature based on Medline searches of: medication compliance, patient compliance, patient dropouts, or treatment refusal combined with 45 other terms including drug therapy and specific formulations or methods of drug delivery. Additionally,