

The Section on **ENDOCRINOLOGY** Newsletter

Volume 14

Fall 2005

Inside this Issue

- **Co-Editors Column: On The Use of New Therapies Without Data**
- **Point and Counterpoint: Subclinical Hypothyroidism**
 - 1) Treatment Recommended
 - 2) The Case for Not Treating
- **IGF-I Deficiency and IGF-I Treatment: Issues and Conundrums**
- **Growth Hormone Stimulation Testing in Children: Time to Stop**
- **Update on the Lawson Wilkins Pediatric Endocrine Clinical Research Network**
- **Pediatric Insulin Pump Therapy: Marketing Strikes Back!**
- **Accelerator Versus Hygiene: Newer Hypotheses for the Causation of Type 1 Diabetes**

Chairperson's Column

Surendra Varma, MD

I am pleased to inform you that the Section on Endocrinology (SOEn) Executive Committee is very well qualified in every aspect and is very proactive. We are privileged to have such a strong Executive Committee.

This year has started very well for our section. Dr. William Clarke has taken over the role as the Section Program Chairperson for National Conference and Exhibit (NCE). For the 2006 NCE, Dr. Clarke has proposed several very interesting and challenging programs that will benefit all the pediatricians. I sincerely hope that all proposals are approved. Endocrinology continues to be well represented at the NCE meetings. The SOEn has continued to provide quality programs to the pediatricians.

The Executive Committee has reviewed the Academy's special report "Pediatric Subspecialty Workforce: Public Policy and Forces for Change." The senior author of this report is Ethan Jewett, MA, Senior Health Policy Analyst in the Division of Graduate Medical Education and Pediatric Workforce. I am very indebted to his precise analysis of the subspecialty work force situation specifically of pediatric endocrinology. On page 6 of this newsletter is a Subspecialty Workforce Fact Sheet for Pediatric Endocrinology. Figure 1 shows the data regarding pediatric endocrinologists by professional activity and demographic profile respectively and the Table shows current facts regarding our subspecialty. The full report and more information is available on the Committee on Pediatric Workforce Web Site at: <http://www.aap.org/workforce/copwssw.htm>

The SOEn is very keen to initiate an annual award to be presented to a pediatric endocrinologist for a life-long distinguished service and educational contributions in our field. The proposal has been formulated and it will be submitted through Academy channels for review and approval. We are currently working on identifying potential sources of funding to support the award.

I am pleased to announce that our section has actively collaborated with the Section on Ophthalmology to develop the Clinical Report, "Screening for Retinopathy in the Pediatric Patient With Type 1 Diabetes Mellitus." The Clinical Report was published in the July 2005 issue of *Pediatrics* and replaces the 1998 Policy Statement with the same title. I convey my thanks and gratitude to the members of the Executive Committee for their contributions.

Our interactions and liaison with Lawson Wilkins Pediatric Endocrine Society (LWPES) and Pediatric Endocrinology Nursing Society (PENS) are very effective and mutually beneficial. I reported our sections' activities to the executive committee of the LWPES at their annual meeting. Dr. Janet Silverstein has been designated by LWPES to provide their report to our executive committee on a periodic basis. In addition, we are happy to have continuous interactions with the PENS. Ms. Kelly Behm, Past-President, is very active in interacting and communicating with our section. She makes concerted efforts to attend our Executive Committee Meetings on a regular basis. The National School Nurses Association (NASN) has asked for a representative from our section and Dr.

continued on page 2

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Co-Editor's Column: On the use of new therapies without data

*Stephen Kemp, MD
Department of Pediatrics
University of Arkansas
Little Rock AR*

One of the important emphases of our training in Pediatric Endocrinology has been evidence-based medicine. We spent a lot of our time evaluating studies as a way of deciding how we should treat patients. I have noticed a lot of chatter on the list-serve and have learned from talking to colleagues that some of us seem to be using therapies for new indications without a lot of data behind them. As a case in point, I would point out the attempts to get children (usually those being treated with growth hormone) to grow more by delaying puberty, either with the use of Lupron to delay puberty or more recently with an aromatase inhibitor to interfere with the effect of estrogen in promoting fusion of the epiphyses.

What is the evidence that these therapies are effective? There is a body of publications regarding the use of Lupron combined with growth hormone, compared to using GH alone. It appears that the greatest benefit of adding Lupron is when the child actually has early puberty, but if therapy is started late, say after the bone age is 12 years, the benefit seems to be small—perhaps not as much as an extra inch. Lupron is expensive, is rather invasive (an IM injection), and delays puberty in children who may already be troubled by being behind their peers in pubertal development.

Aromatase inhibitors should in theory be a better option. These agents are less expensive, and do not interfere with normal androgenization of puberty. Unfortunately, the literature lists few studies of the use of these agents with GH in order to maximize growth before epiphyseal closure. In a recent report (Mauras et al., *J Pediatr Endocrinol Metab* 2004 12;17(12):1597-606) the authors report that they did not find any differences in bone age advancement or predicted adult height in the subjects who received anastrozole, 1 mg daily, for a year, in addition to GH despite a 60% decrease in plasma estradiol levels (using an ultrasensitive recombinant cell bioassay). Perhaps in this study there was just not had enough time to see a difference. In an earlier report, Dunkel and Wickman (*J Steroid Biochem Mol Biol* 2003;86:345) had reported more optimistic results—an increase of 5 cm in adult height prediction at 18 months after one year of therapy with a different aromatase inhibitor, letrozole, when given together with testosterone in boys with constitutional delayed puberty. The study design was very different and in addition, letrozole may be more a more potent aromatase inhibitor than anastrozole.

In either case, it would seem that (consistent with our training regarding evidenced-based practice) we should be putting our energy into studying this potential therapy, using controlled clinical trials, rather than adopting it into our practice without having the data to know whether it is truly effective. While awaiting such data, one suggestion is that anyone using existing drugs for new indications employ consistent and conservative criteria for use, consistent dosing, and a standardized follow-up protocol, so that they are able to objectively evaluate in their own small group of patients whether the desired effect is in fact observed.

continued from page 1

Silverstein has kindly agreed to serve in this role. Dr. Francine Kaufman is our liaison with Academy Task Force on Obesity. This task force is very active and we acknowledge Dr. Kaufman's valuable contributions in their deliberations.

In August, I attended a consortium of American Board of Pediatrics regarding future process for various subspecialties' maintenance of certification. The quality improvement issues have been discussed and there is no concrete resolution yet.

I also attended the Annual Leadership Forum of the academy. It is heartening to know that the Academy is very much interested in supporting all sections' activities.

I am very grateful to Dr. Paul Kaplowitz for editing our section's newsletter. It takes good time and effort on his part to put it all together. He has been fortunate to solicit help from Dr. Steve Kemp, who is a section member from Little Rock, Arkansas. The executive committee and I are very grateful for their contributions.

During my tenure as chair, my goal is that our section becomes more active in protecting the interests of our section members and continues to provide quality educational programs for the pediatricians. I will be honored to receive feedback from all of you. You may contact me at my email address surendra.varma@ttuhsc.edu. I will try my best to address the issue and respond to you in a very timely fashion.

Lastly, but not the least, I duly acknowledge the contributions of Ms. Laura Laskosz who is our section manager. Without her help our task will be too difficult.

My best wishes for the forth-coming holidays and the New Year.

Sincerely,

Surendra Varma, MD, FAAP
Chairperson, Section on Endocrinology

Point and Counterpoint

Editors Note: The question of what to do with the child with a normal free T4 and a slightly elevated TSH is one that continues to divide the endocrine community. We here present 2 viewpoints on managing this common problem, one by Dr Stephen LaFranchi, and a response by the Newsletter co-editor. We will publish selected responses to these articles in the next issue.

Subclinical Hypothyroidism: Treatment Recommended

*Stephen LaFranchi, MD
Department of Pediatrics
Division of Endocrinology
Oregon Health & Science University
Portland, Oregon*

Subclinical hypothyroidism (SCH) is a mild form of thyroid failure defined by thyroid function tests that show a serum TSH level above the reference range together with serum free T4 or T4 in the normal range for age. Generally, most clinicians would agree to treat patients with a sustained TSH >10 mU/L. For this debate, therefore, we have agreed to focus on the patient with a mild TSH elevation. Using current, sensitive, 3rd generation TSH assays, this could be considered in the range of 6 to 10 mU/L for younger children and somewhat lower, 4.5 to 10 mU/L for adolescents.

SCH represents the most common disturbance of thyroid function in children. The prevalence of SCH in the US adult population is estimated at 4% to 8.5% (1). The 1988 to 1994 National Health and Nutrition Examination Survey (NHANES III) reported that approximately 2% of children 12 to 19 years of age (the youngest group examined) had a serum TSH >4.5 mU/L, the cutoff designated for hypothyroidism (2). It was estimated that only 10% had overt hypothyroidism (low free T4 or T4, elevated TSH); therefore the majority were felt to have SCH.

Almost all hypothyroid etiologies have been reported to cause SCH. This includes the most common cause of acquired hypothyroidism, autoimmune thyroid disease (AITD), and also the disorders that carry an increased risk of AITD: type 1 diabetes mellitus, Down syndrome, and Turner syndrome. Various studies show that somewhere between 20% and 40% of such children have positive antithyroid antibodies, 5% to 15% develop SCH, while a smaller percent develop overt hypothyroidism. SCH has also been reported in children post irradiation for head and neck tumors, and in children treated with anticonvulsants. SCH is more common in regions of high iodine intake vs. low iodine intake.

There is no consensus on whether or not to treat individuals with SCH. Even in adults, where endpoints are easier to measure and some evidence-based medicine exists, treatment is controversial. In 2004, Surks et al. carried out a meta-analysis of 195 published studies in adults (1). In assessing the quality of evidence on "strength of association" of a serum TSH between 4.5 and 10 mU/L, the authors concluded there was "good" evidence for progres-

continued on page 4

The Case for Not Treating Children With Subclinical Hypothyroidism

*Paul Kaplowitz, MD
Department of Endocrinology
Childrens National Medical Center
Washington, DC*

Much has been written over the past 5-10 years concerning the pros and cons of treating patients with a normal T4 and mild elevation of TSH. Even though several prospective studies have been done in adults looking at the rate of progression to overt hypothyroidism, the issue of treatment vs no treatment has still not been resolved. There has to date been little written about this entity in children (reviewed by Dr LaFranchi), in part because no controlled pediatric studies have been done. However, I will argue, in large part based on my own experience, that there is no compelling reason to treat most of these children because very few progress to overt hypothyroidism over a period of several years.

For starters, I question one of the premises accepted by people who favor treatment that "the pituitary gland knows best", and that if the TSH falls outside the 95% confidence range, this represents solid evidence that the pituitary gland has found the ability of the thyroid to produce an adequate amount of thyroid hormones wanting. There are situations in which we ignore what the TSH tells us when thyroid hormone levels tell a different story. For example, it is common for children with congenital hypothyroidism to have TSH levels as high as 30 with high-normal free T4 levels, a situation which has been attributed to an altered thyroid-pituitary feedback system developing in a hypothyroid environment (1). In hyperthyroid patients, we don't continue to treat aggressively with antithyroid medication when the free T4 and T3 have dropped to subnormal levels, just because the TSH remains suppressed.

I would argue that in most children with normal free T4 and mildly elevated TSH are "euthyroid outliers", rather than mildly hypothyroid patients whose thyroid is being inexorably albeit slowly destroyed by the immune system. Few have classic hypothyroid symptoms and many have been found while being evaluated for obesity, when testing because a parent has a history of a thyroid disorder (perhaps a borderline high TSH), or when testing a hyperactive child for possible *hyper*thyroidism. It has been my policy to withhold treatment in such patients (unless there is a goiter, which suggests underlying thyroid disease) and to have the thyroid tests repeated in 6-12 months. I try to have this done by the primary care physician, who is instructed to refer the patient if the TSH increases

continued on page 5

sion to overt hypothyroidism. They concluded there was “insufficient” evidence to show an association with elevations in total and LDL cholesterol, adverse cardiac end points, systemic hypothyroid symptoms, and neuropsychiatric symptoms. In addition, Surks et al. concluded that evidence was either “insufficient” or there was “no evidence” for benefits of thyroid hormone treatment for these clinical conditions. It should be added that they reached the same conclusions for a serum TSH >10 mU/L (only an elevation in serum cholesterol and LDL cholesterol was deemed to demonstrate “fair” evidence). This suggests to me that either there really is no evidence of benefit, or, just maybe, there have not been enough good randomized clinical trials (RCT). Surks et al. concluded “The consequences of subclinical thyroid disease (serum TSH 4.5–10.0 mU/L) are minimal and we recommend against routine treatment of patients with TSH levels in these ranges.” If evidence is insufficient after examining 195 studies in adults, what chance do we have of finding evidence in children?

In an attempt to address this issue, the first question might be, “what do we know about the natural history of thyroid function in children with SCH?” In one study by Moore of 18 children with SCH (aged 5 to 19 years), 7 were treated while 11 never received thyroid hormone. After a mean of 5.8 years of follow-up, 7 patients were now euthyroid, 10 continued to have SCH, while one developed overt hypothyroidism (3).

The second question might be, “what do we know about clinical effects, if any, from SCH in children?” I was able to find four published reports addressing this issue. A unique feature of children is growth; if SCH has a clinical impact, an effect on growth would be the obvious parameter to examine. Unfortunately, there is little data on this point, and what little there is is flawed. Cetinkaya et al. reported an increase in growth velocity in prepubertal and pubertal Turkish children with SCH treated with L-thyroxine over 12 months compared to pretreatment growth rates (4). However, SCH was defined by an exaggerated TSH response to TRH; none of the basal serum TSHs were >5 mU/L. Chase et al. also reported an improvement in growth

velocity in children with SCH associated with type 1 diabetes mellitus treated with L-thyroxine, though the best response was seen in children with TSH levels >10 mU/L, i.e., more significant SCH (5). Neither of these studies included an untreated group with SCH. Continuing in the theme of SCH in children with type 1 DM, the third study by Mohn et al. reported that children with SCH (mean TSH 7.6, range 5.5 to 19.9 mU/L) had significantly more symptomatic hypoglycemic episodes by review in the 12 months preceding diagnosis (5.5 episodes/wk vs. 1.6 episodes/wk in controls), which decreased with L-thyroxine treatment back to the frequency seen in controls after 12 months of treatment (2.4 episodes/wk vs. 1.6) (6). These investigators stated that SCH “did not affect growth” (no data reported). The fourth study by Toscano et al. examined myocardial function in children with Down syndrome and SCH (mean TSH 7.8 mU/L). None of 16 children who underwent echocardiographic analysis of left ventricular mechanics had evidence of myocardial impairment (7).

In summary, there are only a handful of studies examining the effect of L-thyroxine treatment in children with SCH. What evidence there is seems to suggest that about half of children with SCH will have persistent SCH over several years, with perhaps 10% developing overt hypothyroidism; the other half will revert to euthyroidism. Some studies appear to show a treatment effect on growth, some do not. One study shows an improvement in a clinical feature (hypoglycemia in children with type 1 DM), while another did not (myocardial function in children with Down syndrome).

Lacking convincing evidence, should we draw the same conclusions for children as adults? Children are different from adults in that they are undergoing the dynamic processes of growth and pubertal development. Thyroid hormone plays a critical role in these processes. Although evidence is lacking, from my perspective there are “physiologic” reasons in favor of maintaining strict euthyroidism. I recommend L-thyroxine treatment for the following reasons:

1. It is impossible to know if the “normal” free T4 or T4 is really normal for a particular patient.
2. A minority of children will progress to overt hypothyroidism with re-

sultant clinical manifestations before periodic monitoring allows detection of this change.

3. If a goiter is present, lowering of TSH to normal should decrease goiter size (at least whatever increase is owing to the increased TSH).
4. Lowering TSH to normal may “put the gland at rest” and in theory slow the autoimmune process, perhaps allowing a greater chance for recovery to a euthyroid state.

For me, this boils down to a positive “risk:benefit ratio” in favor of treatment in children. There may be potential to do some good, and, providing one is careful with dosing and monitoring, one can avoid adverse effects. SCH is a disorder where sub-replacement dosing should work fine. Once growth and pubertal development are complete, thyroid hormone treatment can be stopped and thyroid function reassessed. Lastly, SCH is a relatively common problem in children crying out for someone to undertake a prospective, randomized clinical trial so we get the “evidence” we are lacking.

References:

1. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228-238.
2. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III) *J Clin Endocrinol Metab* 2002;87:489-499.
3. Moore DC. Natural course of “subclinical” hypothyroidism in children and adolescence. *Arch Pediatr Adolesc Med* 1996;150:293-297.
4. Cetinkaya E, Aslan AT, Vidinlisan S, Ocal G. Height improvement by L-thyroxine treatment in subclinical hypothyroidism. *Pediatr Internatl* 2003;45:534-537.
5. Chase HP, Garg SK, Cockerham RS, Wilcox WD, Walravens PA. Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabet Med* 1990;7:299-303.

continued on page 5

“Point”

Continued from page 3

6. Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F. The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med* 2002;19:70-73.
7. Toacano E, Pacileo G, Limongelli G, et al. Subclinical hypothyroidism and Down's syndrome; studies on myocardial structure and function. *Arch Dis Child* 2003;88:1005-1008.

“Counterpoint”

continued from page 4

to greater than 10. In nearly all cases in which I am aware of the outcome, the TSH has either remained in the 5.5-10 range or decreased into the high-normal range. I recently had a case of a patient who had an initial TSH of 8.4, which which decreased slightly to 6.0 a month later, and by the time I saw her 4 months after than, it had normalized to 1.0. Thus, transient mild hypothyroidism may be more common than we realize, but we won't detect it if we start treatment after 1-2 slightly elevated TSH levels. In the few patients where the TSH has increased into double digits, most have been in the 10-15 range, with still normal free T4 levels. Furthermore, I often stop thyroid hormone for at least a month in children who were started on it by other physicians several years earlier, if the reason for starting it was a TSH of 5-10. About half the time, the TSH off treatment is normal and half the time, it remains in the 5-10 range. Only about 10% of such patients have had overtly hypothyroid tests off treatment. This is not what one would expect if the slightly increased TSH in a child was often an early sign of a failing thyroid gland. Although good pediatric data is lacking, one recent study in adults is instructive. Of 107 Spanish patients over age 55 with subclinical hypothyroidism, the rate of progression to overt hypothyroidism was 1.76, 19.67, and 73.47 cases per 100 patient-years in subjects with initial TSH values between 5.0-9.9, 10.0-14.9, and 15.0-19.9 mU/liter (2). This study supports the use of a TSH cut-off of 10 for watching vs treating subclinical hypothyroidism.

What could be the cause of the persistent mildly elevated TSH, if not early autoimmune

thyroiditis? I can imagine a couple of possibilities. First, about 2.5% of “normal” individuals will have a TSH which is more than 2 SD above the mean, so as for any other lab test, finding a marginally elevated TSH should not be equated with a disease state in the absence of supporting evidence. Second, some of these children could produce a TSH molecule of reduced bioactivity, such that it takes 2-4 times as much TSH to elicit the same biological effect as “normal” TSH. Decreased bioactivity of TSH has been reported in central hypothyroidism (3), but an attempt to find this in children with Down syndrome and mildly elevated TSH was unsuccessful (4). Third, there may be subtle genetic variations in the TSH receptor molecule which render it less efficient at converting TSH binding into a biological response. At the recent meetings on Lyon, a group from Italy reported that 3 of 12 patients with normal thyroid hormone levels and TSH of 5-10 had mutations in the TSH receptor gene. In such cases, the mild elevation of TSH would be relatively stable over a period of many years. Since the pituitary-thyroid feedback loop is intact, one can often (though in my experience, not always) decrease TSH into the normal range by giving thyroid hormone. The question is whether doing so is of any benefit to the child, as no one has yet demonstrated that mild TSH elevation is by itself harmful. It is assumed that if we normalize the TSH, we will be helping the child (or at least preventing symptomatic hypothyroidism down the road) without any good evidence to back it up.

I agree with Dr. LaFranchi that it is time for some prospective pediatric studies in which patients are followed for several years either on or off treatment to establish the natural history of this common condition in children and to see if treatment has any benefit. In the meantime, many of us will elect to just observe these children or have them monitored by their PCP. I review the test results of 5-10 such cases a month and if I were to treat all of these children, it would significantly impact on the space available in my clinic to see patients with conditions for which treatment is known to be effective. Given the shortage of pediatric endocrinologists in many parts of the US, I believe we need to rely more on our pediatrician colleagues to keep an eye on the majority of these patients. Even the occasional child

who is lost to follow-up and does become overtly hypothyroid before diagnosis will suffer no irreversible harm. While treatment with periodic monitoring of free T4 and TSH levels is safe, the cost of many years of thyroid hormone therapy and regular visits to an endocrinologist in such a large number of children is hardly trivial.

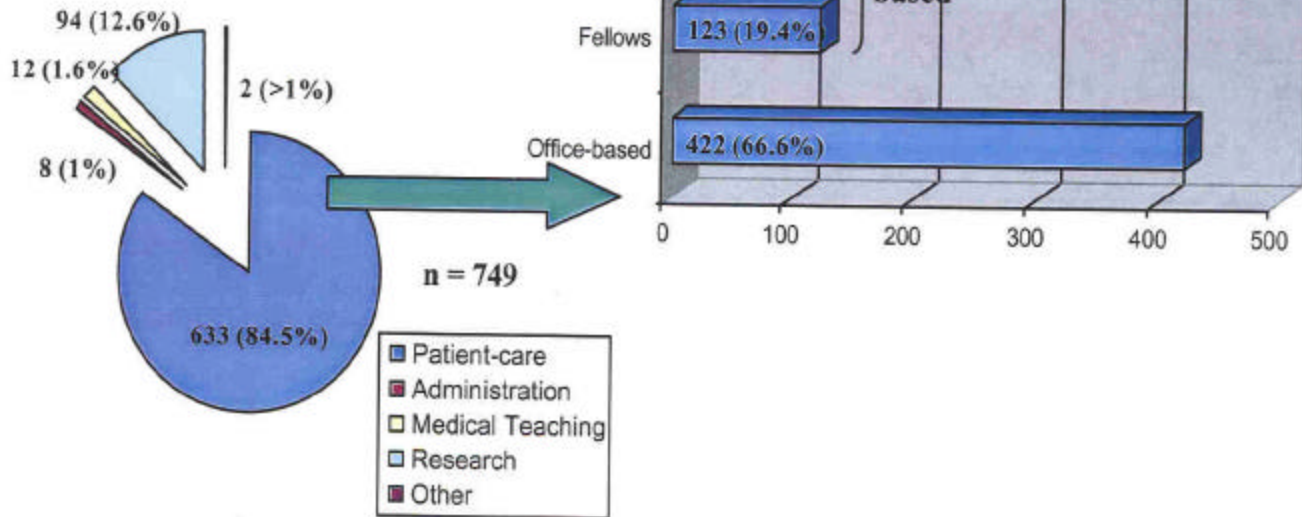
References:

1. Redmond GP, Soyka LF. Abnormal TSH secretory dynamics in congenital hypothyroidism. *J Pediatr*. 1981; 98:83-5.
2. Diez JJ, Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab* 2004;89:4890-7.
3. Persani L et al. Circulating thyrotropin bioactivity in sporadic central hypothyroidism. *J Clin Endocrinol Metab*. 2000;85:3631-5.
4. Konigs CH et al. Plasma thyrotropin bioactivity in Down's syndrome children with subclinical hypothyroidism. *Eur J Endocrinol*. 2001;144:1-4.
5. Bal M, Barp L, Cassio A, et al. Analysis of TSHR gene in patients with isolated hyperthyrotropinemia. *Hormone Res* 2005;64(S1):102a.

Subspecialty Workforce Fact Sheet: Pediatric Endocrinology, July 2005

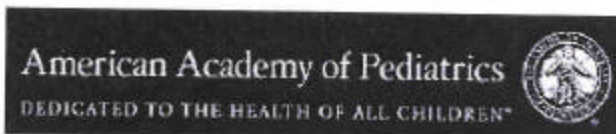
**Fig 1. Pediatric Endocrinologists
by Professional Activity**

Source: American Medical
Association Masterfile, 2003.



Facts at a Glance

Characteristic	Data	Source
Mean Age	45.9	AMA Masterfile, 2003
Percent Male	63%	Stoddard et al, 2000
Percent White	82%	Stoddard et al, 2000
Average Salary	\$130, 245	AMGA, 2003
Patient Wait for Referral	9 weeks	NACHRI, 2004
Accredited fellowships	67 programs	ACGME, July 2005
Filled fellowship positions	190 positions	ACGME, July 2005



AAP Division of
Graduate Medical Education &
Pediatric Workforce

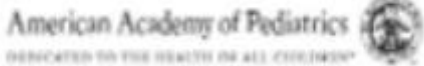


Give \$75 for the 75th!



Help us celebrate our 75th anniversary by donating \$75 to Friends of Children Fund. Your donations help support AAP programs that address emerging issues in children's health.

Call us at (888)700-5378 or donate online at www.aap.org/donate



Welcome New Members!

The following people have joined the section or reactivated their membership since July 1, 2006. If you know of others who might be interested in joining our section, please have them call 800/433-9016, ext. 5897 for an application or visit the web site www.aap.org. For More Information, please visit the AAP Membership web site at www.aap.org/member/memcat.htm. Current members of the Academy in good standing are eligible to apply online by following the instructions below:

1. Log on to the AAP Member Center (www.aap.org/moc)
2. Once logged in, click on "Member Services" (located on the right side of the screen)
3. Click on the link titled, "Online Section Membership Application"
4. Once the form appears, follow the simple instructions shown:

- Select the Section(s) that you are interested in
- Complete the demographic information (optional)
- Select the "Submit" button

May 2005

Fellow:

Gregory Germain, MD, FAAP

June 2005

Fellow:

Maria Bournias, MD, FAAP

Resident Fellow:

Renee de la Torre, MD

July 2005

Fellows:

Maria Dominicis, MD, FAAP
 Louise Greenspan, MD, FAAP
 Christopher Houk, MD, FAAP
 Maria Macapagal, MD, FAAP
 Carol O'Shea, MD, FAAP

August 2005

Fellows:

Rachana Sureka, MD, FAAP
 Mark Vanderwel, MD, FAAP

August 2005

Resident Fellows:

Michael Aguinaldo, MD
 Waleed Alqurashi, MD
 Nofil Arain, MD
 Romina Barral, MD
 Julia Burger, MD
 Suzanne Covington, MD
 Rachel Darling, MD
 Arlen Foulks, DO
 Ramla Habib, MD
 Adam Horne, MD
 Amy Hurley, MD
 Hye Kim, MD
 Kenneth Kim, MD
 Jennifer Krick, MD
 Ngoe Le, MD
 Danial Lee, MD
 Anitha Malaisamy, MD
 Robin Mayfield, MD
 Maireade McSweeney, MD
 Eduard Panosyan, MD
 Bhaskari Peela, MD, MBBS
 Tamara Peterson, MD
 Rebecca Riba, MD
 Seth Septer, DO
 Ana Stoica, MD
 Sri Wijegoonaratna, MD
 Mary Younger, MD
 Kimberly Zencka, MD

September 2005

Resident Fellows:

Dalia Al-Abdulrazzaq, MD
 Michelle Batthish, MD
 Nalina Chandrasekharan, MD
 Ashley Cox, MD
 Capt. Marcus Luce, MD
 Dinah Morad, MD
 Eitan Weinberg, MD
 Hilde Westvik, MD

October 2005

Fellow:

Christopher Romero, MD, FAAP

Resident Fellows:

Simona Nichita, MD, Resident Fellow
 Vicki Skidmore, MD, Resident Fellow

IGF-I Deficiency and IGF-I Treatment: Issues and Conundrums

Arlan L. Rosenbloom, MD
Division of Endocrinology
Department of Pediatrics
University of Florida College of Medicine
Gainesville, Florida

The development of recombinant human IGF-I for treatment of growth disorders is being pursued along two pathways, twice daily IGF-I injections (Tercica) and once daily injection of an equimolar complex of IGF-I and IGFBP3 (SomatoKine, Insmed). In addition to the purported pharmacokinetic advantage permitting once daily injection for the latter preparation, a lower risk for hypoglycemia has been proposed (1). The commercial viability of these preparations in the broad growth market, beyond the rare growth hormone resistance due to receptor/postreceptor defects, depends on the recognition of IGF-I deficiency in a larger population who would derive specific benefits from such replacement therapy.

IGF-I deficiency defines a wide variety of congenital molecular and anatomic abnormalities and acquired conditions affecting the GHRH-GH-IGF-I axis. This terminology recognizes the central role of IGF-I in normal growth, that GH exerts its effects on growth through stimulating IGF-I synthesis. Severe IGF-I deficiency, in the absence of multiple pituitary deficiencies, such as that resulting from molecular defects of the GH gene, GHRH receptor deficiency, and GH receptor mutations, results in mature stature 4-12 SD below the mean, the result of growth rates that are approximately half normal (2). The expanded somatomedin hypothesis states that a critical part of the effect on growth of GH is its stimulation of the differentiation of prechondrocytes into early chondrocytes, which then secrete IGF-I (autocrine and paracrine) that in turn stimulates clonal expansion and maturation of the chondrocytes, or growth. At least 20% of growth is considered to be the result of this local production (as opposed to hepatic endocrine production) of IGF-I (2).

Circulating IGF-I is largely bound in a ternary complex with IGFBP3 and acid labile

substance (ALS) which are also synthesized as a direct result of GH action and deficient in IGF-I deficiency states caused by GH deficiency or GH receptor dysfunction. Numerous other IGF binding proteins have varying functions in different tissues. Particularly intriguing is the abundant IGFBP2, which is elevated with severe IGF-I deficiency, and increases further with IGF-I administration; in the GH resistant patient, this increase in IGFBP2 may provide the buffering that is unavailable from IGFBP3 (3).

The presence of milder forms of IGF-I deficiency has been suggested by the observation of low IGF-I concentrations in some 25-40% of children with "idiopathic" short stature (4). One explanation for this phenomenon has come from the recent observation that approximately half of children with Noonan syndrome have a mutation affecting GH signaling that results in lower IGF-I and IGFBP3 concentrations than in those children with Noonan syndrome who do not have this mutation, but are equally short (5). A precise definition of partial IGF-I deficiency, however, remains elusive. This conundrum parallels that of GH deficiency, in which: 1) response to rhGH treatment only correlates with successful replacement therapy when there is unequivocal deficiency; 2) inadequate response to GH stimulation occurs without endocrine disease, particularly with deprivation or chronic illness; 3) assays vary from laboratory to laboratory; 4) intraindividual variability in response to stimulation occurs; and 5) the definition of normal GH concentrations is arbitrary. The situation may be more problematic for defining IGF-I deficiency compared to GH deficiency because of even greater concern about the IGF-I assay (6). Whether the IGF-I response to GH stimulation to define IGF-I deficiency will be any more informative than GH testing has been in defining GH deficiency remains to be seen.

The most extensive experience with recombinant human IGF-I replacement has been in about 100 patients with GH unresponsiveness, mostly due to GH receptor deficiency/Laron syndrome with a few GH gene deletion patients who developed inactivating

antibodies. Growth responses to twice daily injection in these patients are dramatic, but significantly less than with GH replacement therapy for GH deficiency. This attenuated response is likely the result of absence of the direct effect of GH on the prechondrocyte and associated paracrine/autocrine concentrations of IGF-I, rather than defective transport and delivery as the result of IGFBP3 deficiency (which is not corrected by such treatment) (7). Trough levels of IGF-I (before the 12 hourly injection) are in the low normal range, and profound tissue effects (acromegaloid changes, lymphoid hyperplasia) indicate substantial drug delivery. Particularly informative was the observation that Laron syndrome patients with normal IGFBP3 concentrations, presumed to have intracellular defects resulting in IGF-I deficiency, had growth responses to rhIGF-I indistinguishable from those of subjects with inability to generate IGFBP3 (8). Furthermore, inadequate binding of exogenous rhIGF-I should increase the risk for hypoglycemia; however, placebo controlled study of IGF-I treatment of children with GHRD showed no increase in hypoglycemia over a six-month period (9). More recent study of children with low IGF-I and IGFBP3 levels monitored over a 24-hour period at the end of two weeks of rhIGF-I treatment failed to demonstrate hypoglycemia (10). These data suggest that the sole advantage of the IGF-I/IGFBP3 combination in growth hormone insensitivity may be its pharmacokinetic profile permitting once daily injection. In subjects with molecularly proven GHRD, twice daily IGF-I and once daily IGF-I/IGFBP3 in comparable dosage produce similar maximal concentrations of IGF-I and areas under the curve, but the Tmax for the combination is double that of the IGF-I alone (11). Considering that the IGF-I/IGFBP3 combination lacks the ALS component of the physiologic circulating ternary complex, the specific role of this component, and the effect of its absence on the value of the preparation, are unclear.

The value of IGF-I administration to children with idiopathic short stature and subnormal

Continued on page 9

circulating IGF-I concentrations remains to be demonstrated. There is no evidence that such individuals respond less well to GH administration than do ISS patients with more normal IGF-I levels. Because IGF-I suppresses GH secretion, administering IGF-I to GH sufficient individuals might have the counterproductive effect of diminishing chondrocyte proliferation and autocrine/paracrine IGF-I production. It may be that a combination of IGF-I and GH will be most effective, adding a third arm to studies comparing GH and IGF-I that are obviously necessary (4). That treatment with both IGF-I and GH may be most effective in GH responsive individuals who are either GH deficient or GH suppressed by exogenous IGF-I is suggested by studies in hypophysectomized rats in whom giving both hormones resulted in more growth than either alone, and GH alone was more effective than IGF-I alone (12).

References

1. Kemp SE, Thrailkill KM. SomatoKine: is there a use in treating growth disorders? *Curr Opin Investig Drugs*. 2005; 6:373-7.
2. Rosenbloom AL, Connor EL. Hypopituitarism and other disorders of the growth hormone (GH)-insulin like growth factor-I (IGF-I) axis. In: Lifshitz F (ed) *Pediatric Endocrinology: fourth edition*. New York: Marcel Dekker pp. 47-86, 2003
3. Vaccarello MA, Diamond FB Jr, Guevara-Aguirre J, et al. Hormonal and metabolic effects and pharmacokinetics of recombinant human insulin-like growth factor-I in growth hormone receptor deficiency/Laron syndrome. *J Clin Endocrinol Metab* 1993; 77:273-80.
4. Rosenfeld RG The IGF system: new developments relative to pediatric practice. *Endocr Dev* 2005; 9:1-10.
5. Binder G, Neuer K, Ranke MB, Wittekindt NE. PTPN11 mutations are associated with mild GH resistance in individuals with Noonan syndrome. *J Clin Endocrinol Metab*. 2005 Jun 28; [Epub ahead of print]
6. Quarmby V, Quan C, Ling V, et al. How much insulin-like growth fac-

tor I (IGF-I) circulates? Impact of standardization on IGF-I assay accuracy. *J Clin Endocrinol Metab* 1998; 83:1211-6.

7. Guevara-Aguirre J, Rosenbloom AL, Vasconez O, et al. Two year treatment of growth hormone receptor deficiency (GHRD) with recombinant insulin-like growth factor-I in 22 children: Comparison of two dosage levels and to GH treated GH deficiency. *J Clin Endocrinol Metab* 1997; 82:629-33.
8. Laron Z, Klinger B, Eshet R, et al. Laron syndrome due to a postreceptor defect: response to IGF-I treatment. *Isr J Med Sci* 1993; 29:757-63.
9. Guevara-Aguirre J, Vasconez O, Martinez V, et al. A randomized double-blind, placebo-controlled trial of safety and efficacy of recombinant insulin-like growth factor-I in children with growth hormone receptor deficiency. *J Clin Endocrinol Metab* 1995; 80:1393-8.
10. Guevara-Aguirre J, Guevara-Aguirre M, Rosenbloom AL. Absence of hypoglycemia in response to varying doses of recombinant human insulin-like growth factor-I (rhIGF-I) in children and adolescents with low serum concentrations of IGF-I. *Pediatric Academic Societies*. Washington, DC. Poster Symposium. May 15 2005
11. Camacho-Hübner C, Storr HI, Miraki-Moud F, et al. Pharmacokinetic studies of rhIGF-I/rhIGFBP-3 complex administered to patients with growth hormone insensitivity syndrome (GHIS). 85th Annual Meeting of the Endocrine Society, San Diego, California, June 2005.
12. Fielder PJ, Mortensen DL, Mallet P, et al. Differential long-term effects of insulin-like growth factor-I (IGF-I), growth hormone (GH), and IGF-I plus GH on body growth and IGF binding proteins in hypophysectomized rats. *J Clin Endocrinol Metab* 1996; 137:1913-20.

Upcoming Meetings

Paget Disease and Bone/Fibrous Dysplasia: Advances and Challenges
January 12 - 14, 2006
Fort Lauderdale, FL
www.paget.org

AACE 15th Annual Meeting and Congress
April 26 - 30, 2006
Chicago, IL
www.aace.com

PAS Annual Meeting 2006
April 29 - May 2, 2006
San Francisco, CA
www.pas-meeting.org

Tissues
May 14 - 17, 2006
Prague, Czech Republic
www.ectsoc.org

Endocrine Society's 88th Annual Meeting
June 24 - 27, 2006
Boston, MA
www.endo-society.org

American Society for Bone and Mineral Research Annual Meeting
September 15 - 19, 2006
Philadelphia, PA
www.asnbr.org

77th Annual Meeting of the American Thyroid Association
October 12 - 15, 2006
Phoenix, AZ
www.thyroid.org

AAP National Conference and Exhibition
Date and Location TBD
www.aap.org

Growth Hormone Stimulations Testing in Children: Time to Stop

Darrell M. Wilson, MD
Department of Pediatrics
Stanford University Medical Center

Growth hormone deficiency (GHD) in children is a rare but serious disorder with implications well beyond the decision to start treatment with growth hormone (GH). Hypoglycemia in infants, failure to detect intracranial pathology, or death from other associated hypothalamic/pituitary hormone deficiencies are but a few of the potential consequences of true GHD. Clearly, we need to use the best possible tools at our disposal to diagnose GHD. Given the episodic nature of GH secretion, measurement of GH concentrations on a single sample is rarely useful. For nearly half a century, growth hormone stimulation tests (GHSTs) have played a significant role in the diagnosis of GHD. Changes in how GHSTs are performed and interpreted in children, however, have rendered GHSTs unreliable[1].

At the beginning of the GH era, GHST were performed at a small number of centers which used consistent GH assays and much lower peak GH cutoffs (ranging from 3 to 5 ng/mL) were used to declare a patient GH sufficient. Over the years, the technology for GH assays has changed. Measuring the same samples, many of the newer GH assays report lower concentrations of GH than do the older assays[2]. Ironically, even as modern GH assays were reading lower, the cutoff for passing a GHST were progressively increased; first to 7 ng/mL, and then 10 ng/mL. In the quest for improved sensitivity, specificity has dropped to stunning low levels. In one NIH study[3], Marin et al reported that a full 78% of prepubertal normally growing children fail to pass a GHST by achieving a peak GH of 10 ng/mL or greater, the currently accepted cutoff for normal GH response. Moreover, both the short and long term repeatability of GHSTs within an individual is quite poor. As just one example of the short-term studies we reviewed[1], Tassoni et al[4] repeated GHSTs in 49 short children one to three weeks apart. Using a cutoff of 7 ng/mL, 42% of patients had discordant results. Loche et al[5] retested 33 prepubertal children with heights more than two standard

deviations below the mean 1 to 6 months after they had “failed” two GHSTs (cutoff < 10ng/mL) and found the 85% subsequently passed a third GHST. Long-term repeatability is also quite poor. When repeatability, or precision, is so inadequate, a diagnostic test just cannot be very helpful clinically. Perhaps surprisingly, lowering the diagnostic cutoff doesn’t seem to improve repeatability of GHSTs.

Fortunately, other diagnostic approaches to GHD have also made GHSTs unnecessary in childhood [6]. As with most of pediatrics, the diagnostic pathway starts with an age appropriate history and physical examination. Neonatal hypoglycemia, micropenis, intracranial pathology, as well as the more obvious problems with growth velocity, are among a few of the features summarized by Pandian and Nakamoto that increase the likelihood of hypothalamic/pituitary dysfunction, including GHD [2]. Among patients suspected of having GHD, insulin-like growth factor-I (IGF-I) and its binding protein 3 (IGFBP-3) can provide clinically useful estimates of endogenous GH activity. Other hormone assays, including the prostatic T₄ and the cosyntropin-stimulated cortisol, neither of which were available at the time GHSTs were first instituted, can provide information on the secretion of other pituitary hormones. Increasingly, direct genetic testing for mutations associated with GHD are available.

Modern cranial MRI, with its impressive resolution, can reveal subtle abnormalities in the hypothalamic/pituitary area that are associated with GHD[7]. With the exception of those with specific genetic causes, GHD is very rare among those with a normal cranial MRI. In combination with specific laboratory tests, short and poorly growing children can be successfully evaluated for GHD without using GHSTs (see [6] for one suggested algorithm).

Because of the issues summarized above, we stopped performing clinical GHSTs here at Stanford University about a decade ago. Nationally, the frequency of GHSTs among children treated with GH has decreased as well, falling from 89% in the late 1980s to only

52% most recently [8]. I believe that data demonstrate that GHSTs, as currently done in children, are not reliable. Moreover, they are expensive and, on occasion, dangerous.

While I believe the data clearly demonstrate the inadequacy of GHSTs for making or refuting the diagnosis of GHD, a common query frequently follows: “What should we do with that large group of short kids with normal cranial MR and IGF-1 at the low end of the expected range?” This question implicitly links GH therapy to GHSTs. While GHD is clearly an indication for GH therapy, GHD is not the only indication for GH therapy. The FDA has recently added idiopathic short stature to the growing list of approved indications for GH therapy in children. To continue to use an unreliable test, which many very normal children will fail, to “justify” a trial of GH therapy is disingenuous at best. Given solid alternative approaches exist to make the diagnosis of GHD, I believe it is time to stop performing GHSTs in children.

References

1. Gandrud, L.M. and D.M. Wilson, Is growth hormone stimulation testing in children still appropriate? *Growth Horm IGF Res*, 2004. 14(3): p. 185-94.
2. Pandian, R. and J.M. Nakamoto, Rational use of the laboratory for childhood and adult growth hormone deficiency. *Clin Lab Med*, 2004. 24(1): p. 141-74.
3. Marin, G., et al., The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. *J Clin Endocrinol Metab*, 1994. 79(2): p. 537-41.
4. Tassoni, P., et al., Variability of growth hormone response to pharmacological and sleep tests performed twice in short children. *J Clin Endocrinol Metab*, 1990. 71(1): p. 230-4.

continued on page 14

Update on the Lawson Wilkins Pediatric Endocrine Clinical Research Network

*Gail E. Richard, MD
Department of Pediatrics
Department of Endocrinology
Children's Hospital and Regional Medical Center
Seattle, WA*

A new clinical research network for doing collaborative research in pediatric endocrinology has recently been announced by the Lawson Wilkins Pediatric Endocrine Society. In 2003 a generous donation by the Nordstrom and Gittinger families allowed planning to begin for an infrastructure for collaborative research by members of the Lawson Wilkins Pediatric Endocrine Society. This donation also funded an initial study for the network entitled "Natural History of Idiopathic Diabetes Insipidus".

The process of developing the network began with concept approval by the LWPES Executive Committee in January 2004. A conference was held in Chicago in September 2004 in Chicago at which a Steering Committee selected by the LWPES Executive Committee heard about the experiences of other collaborative pediatric research networks. Representatives of the Neonatal Network, Children's Oncology Group, The Cystic Fibrosis Therapeutics Development Network, Pediatric Emergency Care Applied Research Network, The Glaser Pediatric Research Network, and Childhood Arthritis & Rheumatology Research Alliance gave presentations describing their mission, governance and operations. Representatives from the FDA, NIH and the pharmaceutical industry also contributed their perspectives.

By the end of the conference the following mission and vision statement had been written:

Vision: To be the premier network for Pediatric Endocrine collaborative research

Mission: To advance the care of children with endocrine diseases and conditions by conducting the highest quality collaborative research

Values: scientific rigor, collegiality, inclusiveness, flexibility, openness

Goals:

- To conduct studies of natural history and epidemiology of pediatric endocrine disorders
- To conduct outcomes research for pediatric endocrine disorders
- To conduct or facilitate therapeutic trials for pediatric endocrine disorders
- To conduct studies that increase knowledge of the pathophysiology of pediatric endocrine disorders
- To establish a DNA repository of samples from children and youth with pediatric endocrine disorders
- To establish a tissue bank of samples from children and youth with pediatric endocrine disorders

Subsequently at the May, 2004 annual meeting of the LWPES in San Francisco, input was gathered from LWPES members regarding the structure and function of the network. This input led to the formation of a network open to participation by all LWPES members rather than a network with a limited number of designated centers.

The network will provide a managed and maintained web based infrastructure to facilitate collaborative research. Services provided will include assistance with study design to optimize and facilitate collaboration among many centers, assistance with IRB document preparation, assistance with budgeting for network usage, centralized data collection and analysis, as well as on-line meeting capability for study teams, collaboration groups and committees. The network does not have at this time the ability to fund future studies, this it will remain the responsibility of the principal investigator to obtain funding. It is anticipated that the existence of the network will allow collaborative research to be done with significantly less work on the part of the principal investigator and in a much more timely fashion than would otherwise have been possible.

In the past year two general announcements have gone out to the LWPES membership inviting participation in the inaugural study "Natural History of Idiopathic Diabetes Insipidus". Several centers have indicated an interest in participation, and IRB applications are in progress. The study remains open and participation by more centers would be welcome.

LWPES members can access more information about the network through the Members section of the LWPES website.

Pediatric Insulin Pump Therapy: Marketing Strikes Back

*Stephen, W. Ponder, MD, FAAP, CDE
Professor of Pediatrics
Director, Children's Diabetes and
Endocrine Center of South Texas
Driscoll Children's Hospital*

Insulin pump therapy is now a mainstay in the practice of pediatric endocrinology. As remarkable as pump therapy might seem, the secret of its success lies in the quality of not only the patient's grasp of diabetes self care, but the ongoing input from a knowledgeable diabetes care team.^{1,2} Competitive market forces have resulted in rapid advances in the sophistication of the currently available insulin pump devices, with therapeutic advances rolling out with each new pump upgrade. These same market forces have effectively saturated the specialist insulin pump market, resulting in more aggressive efforts to recruit non-endocrine specialists into prescribing pump therapy. True, the majority of patients with diabetes are managed by non-specialists, by virtue of our relatively low numbers and geographic distribution. Nonetheless, insulin pump therapy is complex and time consuming to deliver, requiring access to diabetes educators and dietitians to leverage the best outcomes under most circumstances.

There has been a noticeable shift in marketing strategies on the part of some insulin pump manufacturers. More and more primary care providers are being approached by families inquiring about obtaining a pump for their child or teen with diabetes. Realizing this trend, pump companies have made primary care providers aware of their training programs offered to new pump users. In most cases, the company can fund a start up training, which may vary widely in the time spent and depth of information provided. The trainer may be a company employee or a free lance pump trainer. This approach is not controlled or overseen in any way and is, for all practical purposes, dictated by the individual pump company.

Given that many providers assume, or are led to believe, that thorough and comprehensive training is being provided, there is an inherent risk for poor outcomes created

by this approach. The busy practice of most general pediatricians or family medicine doctors does not lend itself to a lengthy visit to review insulin pump self-management skills and troubleshooting abilities. Furthermore, many docs may still be struggling with basic pump operations themselves and could be using their first patients as part of their learning curve. Without an experienced pump prescriber to assist them, most non-specialists will muddle through the best they can, yet may not be able to demonstrate the same clinical outcome as physicians specializing in this form of diabetes care.

One example of this recently took place in Texas. A general physician practicing in a rural area was approached by a pump company representative. The physician was advised that if he prescribed five pumps, then he would be eligible to be sent for a training to become a "pump expert". Of course, the initial pumps would need to be from this company. In fact, the physician went as far as to post a billboard with a photo of him holding up an insulin pump stating that he would prescribe pump therapy. A mother of a 4 year boy with type 1 diabetes saw this physician and had her son placed on the pump. The training lasted a couple of hours and was conducted by a company sponsored educator. For the next four months, the mother never gave a bolus for meals, believing that the pump provided all the insulin he needed. She would deliver an occasional correction dose, and that was all. Ultimately, the child presented to a local emergency room with severe hypoglycemia. The hemoglobin A1C was in the double digits. Upon further review, the pump was set at a single rate which was too high for the overnight hours, yet clearly inadequate to meet his daily needs, given the mother never provided bolus doses, resulting in chronic daytime hyperglycemia. Upon arrival the knowledge base of the mother regarding the pump was extremely limited. Following admission and stabilization, the family was re-educated over four days and continued on the pump, with subsequent improved A1C outcomes.

This case points out the hazards of insulin pump therapy in inexperienced hands. At this

time, no standards exist on how to select a pediatric pump candidate and how to train and follow up the outcomes of pump therapy. The American Diabetes Association position statement on pump therapy only refers to "thorough patient education" in regards to how patients should be prepared for pump therapy.³ The need for skilled professional care from a team is emphasized in their statement, as is the need for careful patient selection. However, we need to expand this to more specific curricular goals which would be not only age-appropriate, but also emphasize ongoing family involvement with day to day insulin pump therapy. The recent report of missed meal boluses as a major contributor to elevated A1c values underscores the need for greater parental involvement.⁴ There are several areas for improvement. First of all, pump companies need to defer from direct marketing their products to primary care providers. It is too easy to mislead these providers with promises of how their trainers can meet all their patient's needs when in reality the long term aspects of pump therapy are left almost entirely to the provider. Educational guidelines for pre-pump, pump-start and post-pump training should be developed by independent bodies, not by industry alone. With a few notable exceptions, the majority of primary care physicians are not formally prepared to prescribe pumps, much less maintain and adjust them. It is ill conceived to think that the companies themselves can and will police themselves in this regard. The example above demonstrates the consequences of lack of guidelines for this process. We have allowed "the fox to guard the henhouse," as they say.

Recently, I submitted a resolution to the Annual Leadership Forum (ALF) regarding the need for guidelines for training families of children using the insulin pump. The resolution was accepted and sent to the AAP Committee on Endocrinology for further action. The Academy needs to step up and develop guidelines for pre-pump education, pump initiation, and post-pump follow up.

continued on page 14

Accelerator Versus Hygiene: Newer Hypotheses for the Causation of Type 1 Diabetes

Denis Daneman MB BCh FRCPC
Chief, Division of Endocrinology
The Hospital for Sick Children
Toronto

Although knowledge accumulated over the past 20-25 years has added enormously to our understanding of pathogenetic mechanisms in type 1 diabetes, a unifying hypothesis that convincingly accounts for disease causation remains elusive. In this report, two relatively recent hypotheses, the "Accelerator" (1) and "Hygiene" (2) hypotheses will be discussed.

The Accelerator Hypothesis, which was first proposed by Terence Wilkin, from the UK, in 2001, argues that, rather than there being two separate disorders, type 1 and type 2, diabetes should in fact be viewed as a single disease (1, 3). According to this hypothesis, the two types of diabetes are distinguished only by the rate of β -cell loss, and the specific 'accelerator(s)' that are involved. Wilkin and his colleagues propose the existence of three such 'accelerators': the first is the intrinsic (genetic) potential for a high rate of β -cell apoptosis, an essential but insufficient step in the pathophysiology of diabetes. The presence of this accelerator sets the stage for diabetes development, while its absence protects against it. Data supporting the existence of the first accelerator are limited but provocative: e.g., in vitro (over)expression of the anti-apoptotic gene bcl-2 may lead to protection of β -cells against cytokine-induced and oxidative damage (4). Similarly, both GLP-1 and GLP-2 exert antiapoptotic actions in vivo, with preservation of β -cell mass and gut epithelium, respectively. In addition, GLP-1 and GLP-2 promote direct resistance to apoptosis in cells expressing GLP-1 or GLP-2 receptors. (5). These studies do suggest that there may be some pathways that either protect the β -cell mass or expose it to risk of damage. It is not certain whether the rate of β -cell apoptosis contributes in any way to the pathogenesis of diabetes or whether either type 1 or 2 diabetes can occur independently of this facilitatory mechanism.

The second accelerator is insulin resistance,

a consequence of weight gain and sedentary lifestyle, although inherent differences in insulin sensitivity may also play a role. Insulin resistance is central to the Accelerator Hypothesis' attempts to link the two types of diabetes. Insulin resistance puts pressure on a β -cell mass already at risk for accelerated apoptosis, facilitating the expression of clinical diabetes. A strong case can be made for a role for insulin resistance in both type 1 diabetes and obesity. Childhood obesity is associated with insulin resistance, particularly in those ethnic groups at highest risk for early onset of type 2 diabetes. Also, recent data from Wilkin's group provide support that increasing weight and, by inference, insulin resistance, may precipitate earlier expression of type 1 diabetes in childhood. However, earlier onset does not necessarily imply causation, but rather perhaps facilitation of expression of type 1 diabetes. There are supportive data from Sweden and Belgium which found that, while the overall incidence of type 1 diabetes did not increase in the <34 or <40 years age group respectively, the median age at diagnosis decreased significantly. This shift to younger age at diagnosis may reflect at least in part the heavier weight of the population. There is no doubt that insulin resistance plays a role in the course of type 1 diabetes in teens. What remains uncertain is whether there is an *a priori* role for insulin resistance in the pathogenesis of type 1 diabetes, or whether insulin resistance associated with type 1 diabetes is simply the result of the degree of peripheral hyperinsulinism required to match the quantity and quality of caloric intake and lack of physical activity, i.e. a type 2 diabetes picture developing on the background of typical type 1 diabetes. This latter phenomenon has sometimes been referred to as "double diabetes."

The third accelerator is found only in those with the genetic predisposition to β -cell autoimmunity. The metabolically more active β -cell in insulin-resistant (accelerator 2) subjects with a genetically high rate of apoptosis (accelerator 1) is more likely to undergo rapid functional deterioration and manifest typical type 1 diabetes. In the absence of this immune accelerator, apoptosis is slower and

progression is towards type 2 diabetes.

Supporters of the Accelerator Hypothesis point out the major facts underpinning the hypothesis: first, the rise in childhood obesity parallels the rise in both types of diabetes in childhood, and, second, the decreasing age of onset of type 1 diabetes in heavier children. Detractors argue that there is sufficient evidence to support the autoimmune model for type 1 diabetes etiology without having to implicate the other accelerators, and that data supporting the other accelerators' role in type 1 diabetes remains conjectural at best. The association of type 1 diabetes with HLA markers and other IDDM susceptibility genes provides a clear separation from type 2 diabetes, as does the usually more rapid progression of clinical disease in type 1 versus type 2 diabetes.

The other hypothesis, the Hygiene Hypothesis, arises from observations that atopic disorders, specifically asthma, occur more frequently in affluent than traditional societies, that their prevalence increases with societal modernization, and that they are less frequent in children in large families or those in daycare (2). Parallels exist between these reports in atopic disorders and those in type 1 diabetes (6). Observations such as these have led some investigators to wonder whether those children that develop atopic diseases or type 1 diabetes may be less exposed to infections or other immune challenges early in life which act as "protective environmental influences". This may account for the increase in the incidence of type 1 diabetes that occurs rapidly in migrant populations as they move from low to high incidence regions of the world. An example of this has been the very rapid rise in type 1 diabetes incidence in South Asian immigrants to the United Kingdom.

Although there are some compelling epidemiological data, this hypothesis lacks scientific support in the etiology of type 1 diabetes. However, Edwin Gale from the UK has postulated that the decline in the prevalence

continued on page 14

of pinworm infestation due to improved living conditions might explain some of the changing epidemiology of both atopic disorders and type 1 diabetes (2). In his view, pinworms might have immunomodulatory effects, perhaps in conjunction with other factors controlling development of the mucosal immune system.

Both the Accelerator and Hygiene Hypotheses broaden the perspectives of those studying the etiology and pathogenesis of type 1 diabetes. What will it take to move the credibility of one of these hypotheses forward? For the Accelerator Hypothesis, it will take time. Either the line between type 1 and type 2 diabetes will become fuzzier as childhood obesity increases worldwide or the distinction may become more definite if the epidemic of obesity can be stopped. For the Hygiene Hypothesis it would be demonstration of specific protective effects of one or more infectious agents that are prevalent in societies with low type 1 diabetes incidence, but absent or relatively infrequent in low incidence areas. Much work remains to be done.

References:

1. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type 1 and Type II diabetes. *Diabetologia* 2001; 44:914-22.
2. Gale EAM. A missing link in the hygiene hypothesis. *Diabetologia* 2002; 45:588-594.
3. Betts PR, Mulligan J, Ward P, Smith B, Wilkin TJ. Increasing body weight predicts the earlier onset of insulin dependent diabetes in childhood: Testing the 'Accelerator Hypothesis' (2). *Diabet Med* 2005; 22:144-51.
4. Tran VV, Chen G, Newgard CB, Hohmeier HE. Discrete and complementary mechanisms of protection of beta-cells against cytokine-induced and oxidative damage achieved by bcl-2 overexpression and a cytokine selection strategy. *Diabetes*. 2003; 52:1423-32.
5. Drucker DJ. Glucagon-like peptides: regulators of cell proliferation, differentiation, and apoptosis. *Mol Endocrinol*. 2003; 17:161-71,

2003.

6. Kaila B, Taback SP. The effect of day care exposure on the risk of developing type 1 diabetes: a meta-analysis of case-control studies. *Diabetes Care* 2001; 24:1353-8.

Continued from page 12

Advanced pumping techniques must also be addressed after the initial training. Current practices rarely involve follow up training by pump company trainers unless asked by the prescriber. Even when this is done, this service may not be available due to reimbursement issues. I hope that readers of this newsletter will consider the impact of aggressive insulin pump marketing on the well being of children with diabetes. Pump therapy is an invaluable tool in the management of children with diabetes of all ages and should not be limited. As leaders in the proper endocrine care of children, we need to advocate for the best standards of training for our patients not only at the onset of their pump use, but throughout it.

References:

1. Tamborlane WV, Fredrickson LP, Ahern JH. Insulin pump therapy in childhood diabetes mellitus: guide lines for use. *Treat Endocrinol*. 2003;2(1):11-21
2. Torrence T, Franklin V, Greene S. *Insulin Pumps*. *Arch Dis Child* 2003;88:949-953
3. Position statement of the American Diabetes Association. Continuous Subcutaneous Insulin Infusion. *Diabetes Care* 27 (Suppl. 1):S110, 2004
4. Burdick J, Chase HP, Slover RH, Knievel K, Scrimgeour L, Maniatis AK, Klingensmith GJ. Missed Insulin Meal Boluses and Elevated Hemoglobin A_{1c} Levels in Children Receiving Insulin Pump Therapy. *Pediatrics* 2004;113:221-224

5. Loche S., B.C., Maghnie M., Faedda A., Tziialla C., Autelli M., Casini M.R., Cappa M., Results of early reevaluation of growth hormone secretion in short children with apparent growth hormone deficiency. *J Pediatr*, 2002. 140: p. 445-449.
6. Badaru, A. and D.M. Wilson, Alternatives to growth hormone stimulation testing in children. *Trends Endocrinol Metab*, 2004. 15(6): p. 252-8.
7. Coutant, R., et al., Growth and adult height in GH-treated children with non-acquired GH deficiency and idiopathic short stature: the influence of pituitary magnetic resonance imaging findings. *J Clin Endocrinol Metab*, 2001. 86(10): p. 4649-54.
8. Wilson, D.M. and J. Frane, A brief review of the use and utility of growth hormone stimulation testing in the NCGS: Do we need to do provocative GH testing? *Growth Horm IGF Res*, 2005. 15 Suppl A: p. 21-5.

**AAP Section on Endocrinology
Executive Committee
2005 - 2006**

Chairperson

Surendra Varma MD

Executive Committee

Stuart Brink, MD
William Clarke, MD
Kenneth Copeland, MD
Paul Kaplowitz, MD
Susan Rose, MD

Immediate Past Chairperson

Janet Silverstein, MD

Liaison

Pediatric Endocrine Nursing Society
Kelly Behm, RN, BSN
Newsletter Editors
Paul Kaplowitz, MD
Stephen Kemp, MD

Statements and opinions expressed in this publication are those of the authors and not necessarily those of the American Academy of Pediatrics.

