

## Combined Hyperglycemic Hyperosmolar Syndrome with Diabetic Ketoacidosis as the Presentation of Diabetes Mellitus Type 2 in an Adolescent Female



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### Introduction

Type 2 diabetes mellitus and insulin resistance, while once thought to be illnesses of adulthood, are becoming a much greater concern in pediatrics. Coinciding with the increase in obesity seen worldwide is the increasing incidence of childhood type 2 diabetes (1). This presents management dilemmas for clinicians in the acute care setting because there are little data available to support evidence-based practice. Further complicating this is the finding that many patients presenting with acute manifestations of type 2 diabetes mellitus, the most critical being the hyperglycemic hyperosmolar syndrome (HHS), are mistakenly diagnosed with diabetic ketoacidosis (DKA) and treated accordingly (2, 3).

The management of HHS does differ from that of pediatric DKA specifically regarding the amount of fluid administered and timing of insulin administration. Typically, patients with HHS require aggressive fluid resuscitation with cautious use of insulin contrasting with pediatric patients in DKA in whom the standard of care is iv insulin at 0.1 U/kg-h with no more than 4 liters of iv fluids per m<sup>2</sup>/d to avoid complications of cerebral edema (4). The dilemma facing emergency room and intensive care unit (ICU) physicians is worsened by the fact that some 25% of children and adolescents diagnosed with type 2 diabetes mellitus present with classic DKA

(1). Rather than the autoimmune  $\beta$ -cell destruction seen in type 1 diabetes mellitus, these patients have glucose toxicity leading to impaired insulin secretion as well as insulin signaling in the skeletal muscle leading to ketosis (5).

Here we present a young adolescent female later diagnosed with type 2 diabetes mellitus who exhibited features of both DKA and HHS during her acute presentation along with a review of the literature on HHS in children.

### Case Presentation

A 13-yr-old Native American female was transported to the emergency room after being found lying unresponsive on the floor by a sibling. The family reported polyuria and polydipsia for the preceding week, which they noted after she was diagnosed with a tooth abscess. There was no known history of such symptoms previously. She had been taking antibiotics and oral opiates during that week for management of the abscess. There was a maternal grandmother who died recently from complications related to type 2 diabetes mellitus but no other first- or second-degree relatives with a history of diabetes mellitus.

Physical exam showed a severely dehydrated and minimally responsive obese adolescent female. Weight was 85 kg (>95th percentile). Vital signs were significant for tachycardia (heart rate 160),

tachypnea (respiration rate 40), and hypotension (blood pressure 85/40). There was acanthosis nigricans noted in her cervical region, axilla, and antecubital fossa bilaterally. Lungs were clear to auscultation, and abdomen was soft without masses.

Because of the history of opiate use, a trial of Narcan and a 1-liter bolus of normal saline were given without improvement in her neurological status. Bedside blood sugar check read "HI." Laboratory studies showed venous blood gas pH of 7.22, CO<sub>2</sub> of 15, O<sub>2</sub> of 149, and HCO<sub>3</sub> of 6. Urinalysis showed specific gravity of 1.010, glucose greater than 1000 and 1+ ketones. Urine drug screen was negative. The presumed diagnosis of DKA was made, and she was given 7 U of regular insulin by iv push along with two more normal saline boluses. Metabolic panel showed sodium of 134 mEq/liter (Corrected 157), potassium 5.1 mEq/liter, chloride 98 mEq/liter, CO<sub>2</sub> 8 mEq/liter, BUN 76 mg/dl, creatinine < 0.1 mg/dl, glucose 1552 mg/dl, calcium 12.0 mg/dl, albumin 4.5 g/dl, ALT 104 U/liter, AST 47 U/liter, T. Bili 0.6 mg/dl, and alkaline phosphatase 183 U/liter. Serum ketones and lactic acid were negative. Amylase was 202 U/liter with lipase 4455 U/liter. Serum osmolality was 410 mOsm/kg. A computed tomography scan of her head revealed no evidence of cerebral edema.

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## LETTER FROM THE EXECUTIVE DIRECTOR

As I prepare to retire as Executive Director of the Endocrine Fellows Foundation, I wish to express my very special “thank you” to the hundreds of Fellows I have had the opportunity to meet and visit with over the past 10 years. I was privileged to be a witness to the growth and development of so many Endocrine Fellows as you participated in the various programs offered by the EFF. I have developed many personal friendships through these years that I hope continue as I am a retired citizen.

A special “thank you” is also extended to the Endocrinology Program Directors in over 400 locations across the country. You supported me through the years with your counsel, guidance, and most importantly, your friendship as we worked on the advancement of EFF programs for Fellows. Thank you for your contributions toward EFF symposia, preceptorship programs, *EndoTrends*, etc.

I want to express a special appreciation to the many wonderful ladies and gentlemen I have met from the pharmaceutical industry who, while supporting the activities of the EFF, also supported me.

A personal “thank you” to my assistant, Sharnetha Harris, whose loyalty, devotion, and assistance to me added so greatly to my fulfillment in my role as Executive Director over these many years.

A “thank you” that cannot be measured, and for which there are no sufficient adjectives, is directed to the EFF Board of Directors. All of you became my mentors as well as friends and supporters rather than just being my “bosses.” The 10 years have been indescribable—thanks to you.

I wish continued success to the EFF and know the Foundation will continue to flourish and provide incomparable educational opportunities for Endocrine Fellows.

Sincerely,  
Marilyn Fishman



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## EndoTrends

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## Combined Hyperglycemic Hyperosmolar Syndrome with Diabetic Ketoacidosis as the Presentation of Diabetes Mellitus Type 2 in an Adolescent Female

The patient was transferred to the ICU and started on normal saline at 250 ml/h with dopamine and norepinephrine for blood pressure support. She required 19 liters of fluid resuscitation in addition to inotropic pressors during the first 30 h to return her to and maintain normal blood pressure. Insulin was held until she was hemodynamically stable and no decline in blood glucose was being achieved with rehydration. At that time, she also had worsening acidosis (pH 6.97). We elected to start insulin, (~20 h into ICU stay), at a rate of 0.025 U/kg·h and slowly titrate to a peak of 2.2 U/kg·h to achieve a rate of decline in blood sugar of approximately 100 mg/dl·h. Her hospital course was further complicated by respiratory arrest, occurring 36 h after initial presentation, necessitating 4 d of mechanical ventilation.

Blood glucose levels normalized and she was weaned off inotropes on hospital d 3. Her pancreatitis resolved with bowel rest on hospital d 4 and she was started on naso-gastric feeds. She was

extubated on hospital d 6 and started on a low-fat diet with sc insulin. She was discharged home on hospital d 15 on a regimen of twice daily (70/30) premixed insulin and the ADA diet. Diabetes auto-antibodies (Gad-65, islet cell, and insulin) were all negative.

### Discussion

HHS and DKA are the most significant and potentially fatal acute complications of diabetes mellitus and may be the presenting manifestation (4). Because of the increased mortality associated with HHS, compared with DKA, (15–25% vs. 3–4%) early recognition is important (1, 6). Diagnostic criteria for HHS include severe hyperglycemia (>600 mg/dl), hyperosmolality (> 350 mOsm/kg), and absence of or minimal acidosis with hypertriglyceridemia, pancreatitis, venous thrombosis, and adult respiratory distress syndrome (4). Precipitating factors reported have included infections or medications known to cause hyperglycemia (6).

Our patient's initial presentation met the criteria for HHS, but her worsening

acidosis without an increase in lactic acid level argues that there was a component of DKA, suggesting a mixed picture. We chose to manage her with fluid alone initially to restore circulating volume particularly because a steady decline in blood sugar was being achieved initially with rehydration alone. Our concern was decreasing her serum osmolality before restoring circulating blood volume might further compromise blood pressure. Prior reports have shown that correction of the hyperglycemia before adequate rehydration can lead to secondary oliguria and hypotension (7). This scenario, termed "latent shock of dehydration," suggests that dehydration is the prevailing mechanism behind the critical condition in HHS and aggressive iv fluid repletion is needed (3, 6).

This case report highlights the worsening problem of childhood obesity and the associated increase in pediatric type 2 diabetes mellitus. Key learning points include 1) the need for early screening as many patients diagnosed

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with HHS had been seen by medical providers preceding their presentation; 2) the significant role dehydration plays and thus the requirement for aggressive fluids contrary to traditional teaching for DKA; and 3) the possibility that a mixed picture of DKA and HHS can be present. Furthermore, because of the scarcity of randomized trials available consensus statements regarding the management of type 2 diabetes mellitus in childhood need to be developed.



### Case Report

## Hypothyroidism Followed by Hyperthyroidism in Allogenic Bone Marrow Transplant

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### Introduction

Patient was originally diagnosed with aplastic anemia in 1991 and underwent a related donor allogenic bone marrow transplant with total body irradiation conditioning. His posttransplant course was complicated with persistent autoimmune hemolytic anemia requiring a prolonged course of steroids lasting years. In 1998 at the age of 14, the patient was found to be hypothyroid and referred to pediatric endocrinology. He was started on thyroid hormone replacement with a TSH of 86. Throughout 2002, patient was followed in pediatric endocrinology for hypothyroidism and hypogonadism. His TSH remained persistently elevated thought to be secondary to medical noncompliance. He had an elevated LH of 439 (0.2–5) and elevated FSH of 12 (2–9.2). Total testosterone was 121 (200–620). Patient was started on testosterone enanthate 50 mg im monthly.

From 2002 to present, the patient was followed by a local endocrinologist who had stopped his thyroid hormone replacement because of normalization of his thyroid function tests. Now the patient presents to adult endocrinology at the age of 22 with a 1-yr history of a 70-lb weight loss, palpitations, diarrhea,

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and tremor. His only medication is propranolol, recently started for the palpitations. Patient smokes less than one pack of cigarettes daily and drinks alcohol socially on the weekends. Family history was negative for thyroid disease or autoimmune diseases. Review of systems is otherwise negative. Physical exam was notable for a well-appearing young adult with sparse facial hair and eunuchoid features. There was no exophthalmos, lid lag, lid retraction, or conjunctival injection. Neck exam revealed a symmetric, smooth goiter three times normal size with no bruits or tenderness to palpation. Heart rate was increased at 120 beats/min. Reflexes were 2+ in bilateral biceps tendons with brisk return phase. Testicles were Tanner stage II, and adrenarche was Tanner stage IV.

Laboratory studies were ordered with normal ranges in parentheses: TSH <0.004 (0.4–5.5), free thyroxine 3.2 (0.7–2.2), free  $T_3$  1171 (230–420), TSH receptor antibody 50.1 (0–1.0), thyroid-stimulating Ig 212 (0–129), thyroid peroxidase antibody 100 (0–34), anti-thyroglobulin antibody <20 (0–40), LH 35.8 (0.9–10.6), FSH 33.8 (2.0–17.7), and total testosterone 453 (270–1194). A nuclear medicine thyroid scan with

Tc-99 pertechnetate revealed a diffusely enlarged thyroid with homogenous uptake and no hot or cold defects. Nuclear medicine thyroid uptake with nine microcuries of I-131 was 20% at 4 h and 41% at 24 h (normal uptake <30%).

The patient was diagnosed with Graves' disease. Treatment options were discussed including anti-thyroid drugs, radioactive iodine ablation, or surgery. Given the patient's history and risk of aplastic anemia and agranulocytosis with anti-thyroid drugs, the patient was treated with 9.81 millicuries of I-131. Six weeks after ablation, patient's thyroid function had improved with free thyroxine of 1.4 (0.72–2) and free  $T_3$  of 388 (230–420).

### Discussion

Endocrine dysfunction is common after allogenic bone marrow transplantation (BMT) and primarily affects the gonadal, thyroid, and GH axes (1). In our patient, it was assumed that he had primary gonadal failure from the total body irradiation. His thyroid disease pathophysiology was less clear.

Two mechanisms have been described in the pathogenesis of autoimmune thy-

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roid disease after allogenic BMT, which include “adoptive immunity” and mechanisms related to graft-*vs.*-host disease (GVHD) (2). After pretransplantation conditioning, the host immune system is effectively destroyed and replaced with immunity primarily of donor origin. In adoptive immunity with regards to the thyroid, the host receives a clone of donor lymphocytes that can infiltrate the thyroid and produce antibodies against it (3). The lymphocytes can be analyzed by fluorescence *in situ* hybridization to determine the chromosomal origin, or DNA analysis by evaluation of short tandem repeats can determine lymphocyte origin (4).

GVHD can be an acute or chronic complication of allogenic BMT. Subacute thyroiditis, low T<sub>3</sub> syndrome, and subclinical hyperthyroidism are the most frequent thyroid disorders from GVHD (1). Autoimmune thyroid disease is also associated with GVHD. Thymic damage induced by acute GVHD is believed to cause the immunodeficiency and autoimmunity manifested in chronic GVHD (5). Mulligan and Kronenberg (6) report one case of autoimmune hyperthyroidism thought to be due to chronic GVHD with negative antibody status in the donor.

In our patient, the initial hypothyroidism could be secondary to donor acquired Hashimoto’s thyroiditis, TSH receptor-blocking antibodies, or total

body irradiation. Antibodies to the TSH receptor are polyclonal and two different populations can coexist in the same patient. These include the TSH receptor stimulating antibodies and TSH receptor-blocking antibodies (7). The hypothyroidism would be explained by an abundance of the blocking type antibody compared with the stimulating antibody.

The future development of Graves’ disease in our patient 16 yr after the BMT also has several etiologies that include a genetic predisposition, donor acquired TSH receptor-stimulating antibodies, or native autoimmunity. Individuals with aberrant expression of HLA-DR3 antigen expression are at increased risk for the development of Graves’ disease (8). In theory, there can also be reactivation of the host immune system after chronic immunosuppression with persistence of host intrathyroidal lymphocytes producing antibodies (3, 9).

To our knowledge, this case represents the first case report of a patient with a history of allogenic BMT developing hypothyroidism then hyperthyroidism. To date, the patient’s lymphocytes have not been tested to determine the origin. Given the patient’s lack of chronic-*vs.*-host disease, we postulate that his autoimmune thyroid disease was acquired by adoptive immunity. It remains unclear whether the hypothyroidism was

due to Hashimoto’s thyroiditis or TSH receptor-blocking antibodies given the high titers of both. The hyperthyroidism is assumed to be secondary to acquired TSH receptor-stimulating antibodies given the high titer.

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## Persistent Hypoglycemia: Normal Variation or an Insulin-Mediated Process?

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### Case Presentation

Mr. R.G. is a 25-yr-old male with no significant past medical history who was found difficult to arouse by his girlfriend after a night of heavy alcohol use. Upon the arrival of emergency response personnel to his home, his fingerstick capillary blood glucose was 47 mg/dl. His vital signs were otherwise

stable: temperature 97.7 F, pulse 74, and blood pressure 128/74 mm Hg. Dextrose was administered with improvement in his symptoms shortly thereafter, and he was transported to the emergency department at our institution.

Upon arrival, his capillary blood glucose level was 79 mg/dl. He was alert

and oriented, in no apparent distress, and reported no complaints. Physical exam revealed a well-developed, well-nourished young male (BMI of 23 kg/m<sup>2</sup>). Cardiopulmonary, abdominal, and neurological exams were unremarkable. Upon further questioning, he reported no food consumption for approximately 20 h before presentation. His alcohol

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intake, however, during that time period was significantly more than usual, at approximately 10 beverages over the 20 h. He denied any recent illnesses or strenuous exercise before the event. He reported no prescription or over-the-counter medication use. He did not smoke but did acknowledge occasional marijuana use. His maternal great-grandfather had a history of type 2 diabetes, but there was no family history of spontaneous hypoglycemia or islet cell tumor.

Laboratory measurements of a routine complete blood count and chemistry panel were unremarkable, as were a liver function panel: total bilirubin 0.5 mg/dl, direct bilirubin 0.2 mg/dl, ALT 12 U/liter, AST 23 U/liter, alkaline phosphatase 44 U/liter, albumin 4.9 g/liter, total protein 7.7 g/dl. Serum amylase was 46 U/liter, lipase 19 U/liter, and a urine toxicology screen was negative for amphetamines, barbituates, cocaine, opioids, or benzodiazepines. Neither a serum ethanol level nor evaluation for ketones were performed. The patient was admitted to the hospital for further observation.

Initial morning labs revealed the following significant values: insulin 29  $\mu$ IU/ml (reference 0–16  $\mu$ IU/ml); C-peptide 5.3 ng/dl (reference 0.8–3.1 ng/dl), which approximates 1765 pmol/liter; (1) and  $\beta$ -hydroxybutyrate 0.07 mmol/liter (reference < 0.28 mmol/liter), although the concurrent serum glucose with these measurement was normal at 83 mg/dl. During the course of his hospital stay, capillary and blood glucose levels ranged from 33 to 177 mg/dl, taken preprandially and postprandially, while maintained on intermittent dextrose-containing iv fluids. He remained asymptomatic and exhibited no neuroglycopenic symptoms during the entire 10-d hospitalization.

Further testing after a fasting period of approximately 9 h, obtained when capillary blood glucose was 42 mg/dl, revealed: serum glucose 49 mg/dl; insulin 3  $\mu$ IU/ml (0–16  $\mu$ IU/ml); C-peptide 2.4 ng/dl (reference 0.8–3.1 ng/dl), which approximates 799 pmol/liter; (1) and  $\beta$ -hydroxybutyrate 0.08 mmol/liter (ref-

erence < 0.28 mmol/liter). A serum proinsulin level later obtained when capillary blood glucose was 69 mg/dl was 48.8 pmol/liter (reference < 18.8 pmol/liter). Serum glucagon concentration was not measured. A serum sulfonyleurea level was negative. An ACTH stimulation test was normal, with an unstimulated ACTH level of 18 pg/ml and the cortisol response from 12.8  $\mu$ g/dl (baseline) to 34.6  $\mu$ g/dl (60 min). IGF-I concentration was 172 ng/ml (reference 126 to 382 ng/ml). IGF-II concentration was ordered but not reported due to laboratory error. Insulin, islet cell, adrenal, and thyroid peroxidase autoantibody titers were negative. Fractionated plasma free metanephrine concentrations were within the normal range, and serum TSH was 0.3  $\mu$ IU/ml. Total testosterone and LH concentrations were 842 ng/dl (reference 241 to 827 ng/dl) and 6.3 mIU/ml (reference 1.5 to 9.3 mIU/ml), respectively. Both abdominal computed tomography and magnetic resonance imaging studies were unremarkable and showed no abnormalities in the pancreas, adrenals, or liver. He was discharged with instructions to check his capillary blood glucose levels at least three times daily and avoid any heavy alcohol use, strenuous exercise, or skipped meals (*i.e.* to eat a small meal at least every 6 h) until seen in follow-up. He was given glucose tablets and taught the use of an emergency glucagon pen.

The patient was seen in the endocrinology clinic 4 d after hospital discharge. A log of his capillary blood glucoses checked three times daily ranged from 51 to 102 mg/dl. He again denied any neuroglycopenic symptoms aside from the initial episode that had prompted the hospital admission more than 1 wk prior.

In the past 16 months since his initial presentation, the patient has repeatedly declined another hospital admission to attempt the definitive 72-h fast and further assess his abnormal laboratory results obtained previously. He continues to keep a log of capillary blood sugar values recorded at various times (usually preprandially or before heavy

exercise), with values ranging from 32 to 105 mg/dl. His capillary blood glucose machine has been checked against serum laboratory measurements on several occasions, and no significant differences were found between the two readings. He continues to deny any neuroglycopenic symptoms, including during occasional sports activity or with consumption of one to two alcoholic beverages weekly. He reports eating three regular meals each day and denies having the need to use any of the glucose tablets or the emergency glucagon pen.

## Discussion

First reported in 1938 by Whipple, the triad of hypoglycemia is described by low plasma glucose, hypoglycemia symptoms, and the improvement of symptoms with correction of the blood sugar concentration (2). Plasma glucose concentrations in healthy individuals can range from 60 to 100 mg/dl, and when levels decrease below this range, several physiologic mechanisms (*e.g.* glucagon, epinephrine, GH, and cortisol) are usually employed to counterbalance the effects of hypoglycemia (3, 4). Various stages of neuronal cell death and clinical neurocognitive impairment occur with hypoglycemia, (5) and diffusion-weighted magnetic resonance imaging may help distinguish acute hypoglycemic changes from old ischemic lesions (6). In nonhospitalized patients, hypoglycemia is most common in patients with diabetes mellitus, particularly those managed with insulin. Hypoglycemia in patients without preexisting diabetes can result from factitious use of insulin or sulfonyleurea medications, alcohol consumption, an insulin-mediated process from either an insulinoma or the noninsulinoma pancreatogenic hypoglycemia syndrome (NIPHS), nonislet cell tumors that secrete insulin-like growth factors, or autoimmunity to insulin or the insulin receptor.

Alcohol consumption has been shown to not only cause hypoglycemia from decreased gluconeogenesis and the depletion of glycogen stores, but from the

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impairment of the counterregulatory hormone response, (7) particularly that from GH (8, 9). Flanagan *et al.* (10) showed that the combination of gin and tonic in otherwise healthy individuals is able to induce reactive hypoglycemia, due primarily to the suppression of the epinephrine and growth hormone responses after acute ingestion. However, a retrospective observational study of 584 patients who had detectable serum alcohol concentrations found that hypoglycemia (<67 mg/dl) is uncommon in the emergency department setting (0.9%), (11) and others found no statistically significant differences found in the hypoglycemia rates between intoxicated and nonintoxicated patients (12). A serum ethanol level was not obtained in our patient upon arrival to the emergency department, but he had no clinical signs of intoxication and remained persistently hypoglycemic throughout the entire hospitalization and in the subsequent months since.

Insulinomas are the most common type of tumors causing hypoglycemia, with the incidence approximating 1 to 4 per million people (13). Persistent hypoglycemia in an otherwise healthy individual raises the suspicion of an insulin-mediated process, for which Service (14) proposes several criteria to assess hypoglycemia achieved during a 72-h fast: plasma insulin  $\geq 6 \mu\text{IU/ml}$ , C-peptide  $\geq 200 \text{ pmol/liter}$  by RIA, proinsulin  $\geq 5 \text{ pmol/liter}$  by ICMA,  $\beta$ -hydroxybutyrate  $\leq 2.7 \text{ mmol/liter}$ , and  $\geq 25 \text{ mg/dl}$  glucose response to iv glucagon during hypoglycemia. The patient discussed in the present case achieved hypoglycemia within the first 9 h of fasting and exhibited some of these criteria from the available laboratory measurements obtained. Our patient was noted to achieve hypoglycemia without a definitive pattern in regards to time of day or relation to meals or activity, but usually demonstrated asymptomatic low blood sugars within 3–4 h of fasting or when without dextrose infusion. It is interesting to note that Hirshberg and colleagues (15) recently proposed the substitution of the traditionally accepted 72-h fast for a 48-h period, given the ability to achieve hypoglycemia and diagnose insulinoma in 94.5% of the 127 cases within the

first 48 h of the fast. Several more attempts to repeat the measurements were made; he was noted to have blood glucose levels at or below 40 mg/dl on multiple occasions, and the resulting laboratory values were similar to those reported above from his initial fast. Although no single set of measurements met every criteria as described by Service for an insulin-mediated process, most parameters were strongly suggestive.

The presence of an insulin-mediated process, as suggested to be present in our patient by several of his laboratory measurements, without a discrete pancreatic mass is termed NIPHS and was first described by Service and colleagues in 10 subjects (16, 17). The pathologic changes seen with this syndrome, nesidioblastosis (the proliferation of abnormal B cells throughout the pancreas; also known as endocrine cell dysplasia, islet cell hyperplasia, islet cell hypertrophy, microadenomatosis, and islet hypertrophy), accounts for approximately 0.5–7.0% of all adult cases of hyperinsulinemic hypoglycemia (18). The successful control of hyperinsulinemic hypoglycemia in nesidioblastosis has been described with 70% distal pancreatectomy (18).

Nonislet cell tumor hypoglycemia (NICTH) has been described only sporadically over the past 40 yr as a cause to persistent hypoglycemia (19). Tumors can originate from mesenchymal tissue (*e.g.* fibrosarcomas, mesotheliomas, leiomyosarcomas, hemangiopericytomas), epithelial tissue (*e.g.* hepatomas and gastric, pancreatic exocrine, and lung carcinomas), or hematopoietically (19). These tumors, usually large, are usually located intrathoracically and retroperitoneally, although one report recently described the atypical first presentation of NICTH in a lower extremity mass (20). IGF-II produced by these tumors activate both insulin receptors (to induce hypoglycemia directly) as well as IGF-I receptors in the pituitary and pancreas, thereby further suppressing the growth hormone compensatory response (19). The IGF-I level in our patient was within the normal reference range, and we plan to

reattempt assessment of his IGF-II level, although there was no suggestion of tumor by the several imaging modalities mentioned above.

Additionally, hypoglycemia can rarely result when endogenous antibodies bind to insulin or activate the insulin receptor (21). This syndrome usually is accompanied by other positive serum titers of autoimmunity (22), which the patient in the current case did not exhibit. Finally, the persistence of hypoglycemia in the current case, in the absence of neuroglycopenic symptoms, may represent a set point error in glucose homeostasis, similar to that described in a 39-yr-old female who had chronic, persistent, and asymptomatic glycopenia ranging from 35 to 45 mg/dl without an explainable etiology (23).

Interestingly, the patient in the current case, although he continues to demonstrate intermittent low capillary blood glucose concentrations, has not had any clinical sequelae of hypoglycemia since his hospitalization. The possibility that he may have an insulin-mediated process has been explained to him, and he declines further workup through a repeat hospitalization and monitored 72-h fast for hypoglycemia. We continue to counsel him to be cognizant of the symptoms of neuroglycopenia, particularly in the setting of heavy alcohol consumption or in preparation of strenuous exercise. He remains asymptomatic more than 16 months after his initial presentation.

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### Case Report

## Permanent Neonatal Diabetes with Autoimmunity

Juliana Austin, M.D. and Bruce Boston, M.D.  
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### Introduction

This is the case of permanent neonatal diabetes in a child with autoimmunity. The patient also has a strong family history of diabetes and thyroid disease. This report discusses the different forms of early onset diabetes and speculates on the most likely diagnosis in this child.

### Case Report

CD is a 20-month-old male with permanent neonatal diabetes now presenting with gastrointestinal complaints. He was born with intrauterine growth retardation (1860 g) at 38 wk gestation. His blood sugars increased to 360 over the first 24 h of life. He was initially started on an insulin drip and subsequently transitioned to sc insulin. He is currently on insulin of 0.5 U/kg·d with HbA1cs of 8.3–9.4%. He now presents with symptoms of gas, diarrhea, and bloating. His height and weight are at the 25th percentile.

His family history is significant for a brother with type 1 diabetes that was

diagnosed at 11 months of age. His brother is currently 6 yr old on 0.5 U/kg·d of insulin with HbA1cs of 6–7.7%. His brother is positive for glutamic acid decarboxylase (GAD) 65 antibody and negative for islet cell antibody. Their mother had gestational diabetes during both pregnancies. Their maternal grandmother has type 2 diabetes mellitus. There is a strong family history of hypothyroidism. There are other distant family relatives with early onset type 1 diabetes (see pedigree in Fig. 1). One family member with type 1 diabetes died of unexplained kidney disease.

CD was evaluated for celiac disease. Tissue transglutaminase was above 100 U/ml (nl 0–4), and AntiGliadin IgA was 22.7 U/ml (nl 0–5). Biopsy confirmed villous atrophy and lymphocytic infiltration, consistent with the diagnosis of celiac disease.

He was also evaluated for thyroid disease: TSH of 7.66  $\mu$ IU/ml (nl 0.465–4.680), free T<sub>4</sub> of 1.11 ng/dl (nl 0.78–2.19), thyroglobulin Ab of <20 (nl <20),

anti-thyropoxidase of 21 IU/ml (nl < 35).

Neonatal diabetes genetic screening was done. His KCNJ11 sequence was not associated with neonatal diabetes. His glucokinase sequence was identical to the reference sequence, with no sequence variants detected. It was very unlikely that his IPF1 sequence was to be associated with neonatal diabetes.

Type 1 diabetes mellitus antibodies were obtained: GAD 65 antibody was below 0.2 (nl <1) and islet cell antibody was negative.

So what kind of diabetes is this?

### Differential Diagnosis for Early Onset Diabetes

#### Neonatal diabetes

Neonatal diabetes is rare, with an incidence of 1 in 400,000 births (1). The onset of neonatal diabetes is within the

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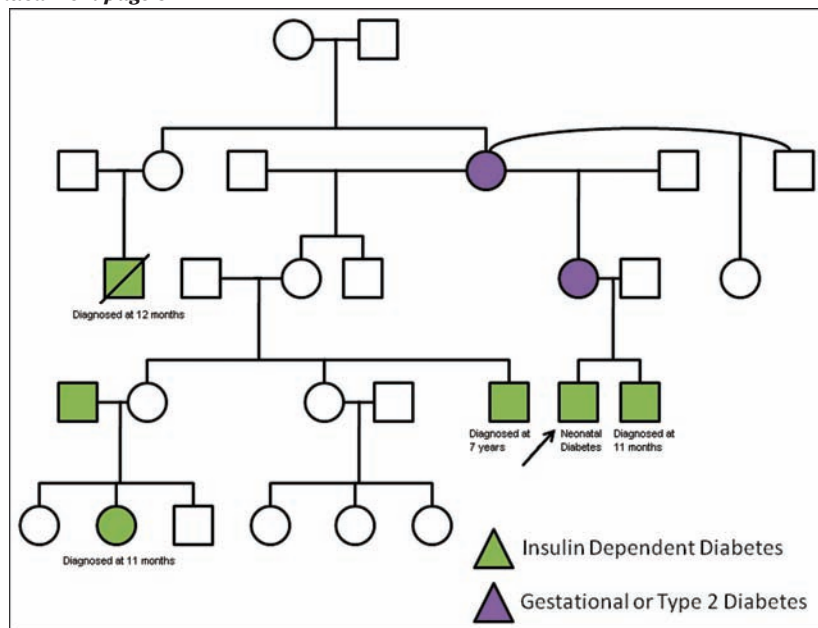


Figure 1. Family pedigree.

first few months of life. Intrauterine growth retardation is usually present at birth because insulin plays a crucial role in fetal growth, especially during the last trimester of pregnancy. Neonatal diabetes is characterized by hyperglycemia and pronounced glycosuria, leading to severe dehydration and metabolic acidosis, but minimal or no ketonuria. Basal plasma insulin may be normal, but insulin response to glucose load is low to absent. Long-term follow-up of a cohort of patients with neonatal diabetes has shown that approximately 40–50% were permanent and 50–60% were transient, but 60–70% of those who were had transient neonatal diabetes recurred at 7–20 yr of age (2).

**Transient neonatal diabetes.** The transient form spontaneously resolves within 3–6 months (3). This may be due to a functional delay in  $\beta$ -cell maturation. In the transient form, patients are younger at the diagnosis of diabetes, more likely to have intrauterine growth retardation, and less likely to develop ketoacidosis than patients with permanent neonatal diabetes. During the active phase, insulin administration is mandatory (1–2 U/kg·d). Because the syndrome usually resolves by 2–3 months of age, recurrent hypoglycemia allows for gradual reduction in insulin

administration with eventual discontinuation of exogenous insulin. There is a suggested genetic component as transient neonatal diabetes has been reported in siblings. A gene for transient neonatal diabetes had been localized to the long arm of chromosome 6 at 6q24. Transient neonatal diabetes mellitus is associated with paternal uniparental disomy of chromosome 6 or paternal duplications in this region (4). Differential methylation of a subportion of this region has been demonstrated in patients with transient neonatal diabetes whether they do or do not have uniparental disomy or paternal duplications of chromosome 6 (5). This suggests that transient neonatal diabetes may be associated with a specific methylation imprint on chromosome 6 that is paternally expressed. This gene may have an important function in normal pancreatic development.

**Permanent neonatal diabetes.** Neonatal diabetes may be permanent if associated with the rare syndrome of pancreatic agenesis. Homozygous or compound heterozygous mutations in the gene for insulin promoter factor-1 (IPF1, also known as PDX-1) has been associated with two cases of pancreatic agenesis, leading to pancreatic exocrine and endocrine deficiencies (6, 7). IPF-1 is a transcription factor that is required for

normal development of the pancreas, and, in mature islet cells, for activation of insulin gene transcription in response to increased blood glucose concentrations. Heterozygous mutations of IPF1 are the cause of Maturity Onset Diabetes of the Young (MODY) 4 and some forms of late-onset type 2 diabetes (8).

Homozygous or compound heterozygous mutations in the glucokinase gene have also been associated with permanent neonatal diabetes. Glucokinase catalyzes the first and rate-limiting step of glycolysis. In pancreatic  $\beta$ -cells, glucokinase activity determines the rate of ATP production in response to the blood glucose concentration, thereby functioning as the  $\beta$  cell's "glucose sensor." An increase in the intracellular ATP concentration then triggers insulin release. Loss-of-function mutations in glucokinase reduce the efficiency with which pancreatic  $\beta$ -cells use glucose for ATP production, so that higher than normal blood glucose levels are necessary to generate an intracellular ATP concentration sufficient to trigger insulin release. Homozygous mutations in glucokinase impair the  $\beta$ -cell's glucose sensing ability severely enough to cause permanent neonatal diabetes (9–11). Heterozygous mutations of glucokinase cause MODY 2 (12), which is usually associated with a family history of gestational diabetes.

Heterozygous activating mutations in the KCNJ11 gene, which encodes for the Kir 6.2 protein subunit of the ATP-sensitive potassium channel, is one of the most common causes of permanent neonatal diabetes (13). Insulin release depends on closure of the ATP-sensitive potassium channel, which is triggered by an increase in the intracellular ATP level in response to a high blood glucose concentration. Gain-of-function mutations in KCNJ11 reduce the sensitivity of the ATP-sensitive potassium channel to ATP. Consequently, the mutated ATP-sensitive potassium channel stays open despite an increase in intracellular ATP concentration, preventing insulin release in response to high

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blood glucose levels and causing permanent neonatal diabetes.

Heterozygous activating mutations of ABCC8, which encodes the SUR1 subunit of the ATP-sensitive potassium channel, can also lead to permanent neonatal diabetes (14). These patients, however, retain sensitivity to sulfonylureas and can achieve euglycemia with treatment with sulfonylureas alone.

### **Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)**

Mutations in the FOXP3 (forkhead domain-containing protein) gene leads to IPEX (15). The major features include early onset diabetes (often neonatal) and diarrhea with small intestinal pathology such as villous atrophy and inflammatory infiltrate. Other features include severe failure to thrive, eczema, hemolytic anemia, thrombocytopenia, and hypothyroidism. Type 1 diabetes autoantibodies (GAD, insulin autoantibodies, islet cell antibody) are frequently positive, in addition to antibodies to the thyroid gland and various other organs (16). These children usually die within the first year of life from overwhelming sepsis (17).

### **Wolcott-Rallison syndrome**

Wolcott-Rallison syndrome is an autosomal recessive disorder characterized by infancy-onset (often within the neonatal period) diabetes associated with a spondyloepiphyseal dysplasia (18). In addition, there is a constellation of other features including hepatomegaly, mental retardation, renal failure, and early death (19). The gene, EIF2AK3 (eukaryotic translation initiation factor-2 kinase 3), is located on 2p12 and is highly expressed in islet cells as a regulator of protein synthesis (20).

### **Permanent Neonatal Diabetes with Cerebellar Hypoplasia**

PTF1A encodes for the pancreas transcription factor 1 $\alpha$ , which is essential for normal pancreatic and cerebellar development. Homozygous mutation in this gene is associated with dysmorphic features (low-set ears, triangular facies, talipes equinovarus, and joint stiffness),

microcephaly, neonatal diabetes, recurrent apneic attacks, and absent cerebellar tissue on brain imaging (21). All children described with this condition have died in infancy, not from diabetes but from associated respiratory failure secondary to the brain anomalies.

### **Discussion**

This is a case of permanent neonatal diabetes with evidence of autoimmunity. Although the patient has celiac disease, he does not have antibodies consistent with type 1 diabetes. However, we know that not all cases of type 1 diabetes have positive antibodies. HLA typing is currently pending.

Given his family history, his findings could be consistent with a homozygous or compound heterozygous mutation in the glucokinase gene leading to glucokinase deficiency. This would be consistent with his mother's history of gestational diabetes and the additional family history of diabetes. However, the genetic screening was negative for glucokinase mutations. Similarly, his genetic screening for IPF1 was negative, and his findings are not consistent with homozygous mutations of the IPF1 gene because his exocrine pancreatic function is intact. Mutational analysis of the KCNJ11 are not consistent with neonatal diabetes. This leaves the possibility of ABCC8 gene as a cause of permanent neonatal diabetes in this patient. This does not, however, explain the finding of autoimmunity in this patient or throughout his family. He does not have additional findings consistent with Wolcott-Rallison syndrome or permanent neonatal diabetes with cerebellar hypoplasia.

The findings in this case are most likely consistent with IPEX. As previously mentioned, IPEX is X-linked and the inheritance pattern of diabetes within this family is consistent with an X-linked process. The major features of IPEX include early onset diabetes (often neonatal, as in his case) and diarrhea with small intestinal pathology such as villous atrophy and inflammatory infiltrate. He does not have type 1 diabetes antibodies; however, these are not always present. He does, however, have autoantibodies for celiac disease. Al-

though these children usually die within the first year of life with overwhelming sepsis, it is possible that he has a less severe mutation of the FOXP3 gene. This patient is currently awaiting genetic testing.

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## Preceptorial in Metabolic Bone Diseases, College of Physicians & Surgeons, Columbia University

The preceptorial in Metabolic Bone Diseases, sponsored by the Endocrine Fellows Foundation, was held at Columbia University Medical Center, Division of Endocrinology for a 2-week period from April 28–May 9, 2008. The faculty of the Metabolic Bone Diseases Unit, including Drs. John P. Bilezikian, Ethel S. Siris, Elizabeth Shane, Shonni J. Silverberg, Mishaela Rubin, Aubrey Stoch, Jack Tohme, Jessica Fleischer, Marcella Walker, Adi Cohen, Donald McMahon, Stavroula Kousteni, Emily Stein, Serge Cremers, David Dempster, Robert Lindsay, Felicia Cosman, Jeri Nieves, and Thomas Jacobs, as well as other participating Columbia faculty (Gerard Karsenty, Patricia Ducey, Ronald Staron, Thomas Nickolas, Wylie Hembree, and Alison Pack) all taught in this comprehensive introduction to basic and clinical aspects of this field. Drs. Adrianna Dusso (Washington University School of Medicine) and John Adams (UCLA) served as guest faculty members. As illustrated by the schedule of activities, the Fellows gained comprehensive exposure to all the important metabolic bone diseases as well as engaged in discussions related to mechanisms, pathophysiology, evaluation, and therapeutics.

The Fellows who were selected (see photograph) learned in an environment that was workshop oriented. There was ample time, thus, not only for formal presentation of material that covered fundamental

principles of basic and clinical bone physiology and pathophysiology, but also for active dialogue between the instructors and the Fellows. The Fellows were also introduced to key areas of research such as protocol design, acquisition, interpretation of data, and statistical testing. Additionally, the Fellows attended conferences, clinical case discussions, the Metropolitan New York Bone Club, and research seminars. The Fellows had the opportunity to investigate a topic of particular interest to them

and to present their work to the Faculty at the end of the preceptorial period.

The Preceptorship in Metabolic Bone Diseases has been held at Columbia now for over 10 yr. As has been the case without exception in the past, this most recent program was met with great enthusiasm by the Fellows who were fortunate to be selected to attend this highly popular program of the Endocrine Fellows Foundation.



Left to right: Robert Levine, M.D.; Marina Voltchenok, M.D.; Reena Khurana, M.D.; Dima Yeshou, M.D.; Norma Lopez, M.D.; Mentor of the Columbia Preceptorship, John P. Bilezikian, M.D.; Vasanthi Narayan, M.D.; Rudolph Mendoza, M.D.; Krupa Doshi, M.D.; Lekshmi Nair, M.D.; and Marissa Grotzke, M.D.



## LETTER TO THE EDITOR

Dear Editor:

This letter is in response to an e-mail sent to you regarding our recent case report, which was published in *EndoTrends*, Vol. 15, Issue 2, 2008, and titled "Aggressive Pheochromocytoma: Is There a Place for Innovative Medical Therapies?"

It has been brought to the authors' attention that the use of the term RET mutation was used to describe the mutation associated with Von Hippel Lindau Syndrome (VHL). The correct mutation involves a mutation in the VHL gene. This was an unintentional, but significant, oversight on the authors' part and we regret having missed this before submitting our final draft.

We take full responsibility for this error.

The authors of the e-mail to the editor also stated that while patients with a pheochromocytoma due to MEN2 and the RET mutation would theoretically respond to tyrosine kinase inhibitors, patients with pheochromocytoma and the VHL gene mutation would likely respond to VEGF inhibitors. Newer tyrosine kinase inhibitors inhibit multiple receptors including VEGF and PDGF, both of which are implicated in the pathogenesis of VHL tumors. Additionally, some of the newer tyrosine kinase inhibitors have been used successfully in patients with renal cell carcinoma, a common tumor in some types of VHL (1). The patient we described had a

very aggressive pheochromocytoma resulting from his VHL and could potentially benefit from treatment with a newer tyrosine kinase inhibitor, such as Sorafenib.

We would like to thank the editors for the opportunity to correct our error and to clarify the potential use of tyrosine kinase inhibitors in aggressive pheochromocytomas.

Sincerely,

David Podolsky, M.D.

Kathleen Colleran, M.D.

### Reference

1. Potti A, George D. Tyrosine kinase inhibitors in renal cell carcinoma. *Clin Cancer Res.* 2004; 10:6371S-6376S.



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Articles should range from 800–1000 words or two to four typewritten pages. Exceptions for longer or shorter articles may be made based on content. Submissions should include an original manuscript (including all applicable bibliographic references), a diskette containing the article (Word 6.0 preferred, ACSII format also accepted), plus any accompanying photographs, charts, or graphs (graphic accompaniment to submitted articles is highly encouraged).

Figures should be submitted as TIFF or EPS files. Photoshop files are also acceptable. Please submit artwork at the size it should be printed. See <http://cjs.cadmus.com/da> for additional information. Please provide a good quality hard copy for each figure submitted. Please send figures on CD or disk rather than e-mail.

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If you have a topic that you think would be of interest to our readers, please forward your submission to The Endocrine Fellows Foundation, c/o Association Resources, 342 North Main Street, West Hartford, CT 06117. For questions, please call (877) 877-6515 or fax 860-586-7550.

## EMPLOYMENT OPPORTUNITIES

### Clinical Research Position in Diabetes

The Great Plains Diabetes Institute and two of its Centers for Innovation—the KU Diabetes Center and the Cray Diabetes Self-Management Center, based on the campus of the University of Kansas Medical Center in Kansas City, KS—are pleased to announce a faculty position in Endocrinology effective fiscal year 2009 (to be filled between August 2008 and June 2009).

Twenty-five percent effort will be directed toward direct patient care, to include diabetes outpatient clinic and rotations within the KU Hospital supervising residents, students, and fellows in the consultative management of diabetes and endocrine disorders. Limited formal teaching to first- and second-year medical students and students in allied health will be required. Seventy-five percent effort for the first three years will be allotted to establishing a research program in diabetes. The candidate is expected to achieve regional and national leadership in diabetes by implementing and evaluating new treatments in diabetes or methods of delivering health care to people with diabetes.

Candidates must possess an M.D. or D.O. with board eligibility or certification in Internal Medicine and Endocrinology or Metabolism and have undertaken at least 3 yr of postdoctoral fellowship with clinical and research emphasis on diabetes, obesity, islet cell biology, and/or insulin action and including at least one year of research training in diabetes or diabetes-related health care delivery or outcomes research. The ability to compete for external funding in clinical research related to diabetes, with special emphasis on health care delivery, outcomes, or patient or professional education is expected.

The Great Plains Diabetes Institute represents a collaboration of regional institutions that includes Children's Mercy Hospitals and Clinics and St. Luke's Hospital. The University of Kansas Medical Center has made a major commitment to excellence in the form of a 10-year plan (<http://www.kumc.edu/evc/TheTimeIsNow.pdf>) that includes commitment of \$45 million to diabetes. This includes the hiring of 30 new faculty members (20 in diabetes and 10 in obesity) and a significant expansion of research facilities. Among the faculty to be hired are eminent scholars in islet biology and health care delivery/outcomes research.

The KU Diabetes Center has a strong history of research in diabetes and its complications ([http://alliedhealth.kumc.edu/documents/research/from\\_benchandbeyond/unlocking\\_diabetes.pdf](http://alliedhealth.kumc.edu/documents/research/from_benchandbeyond/unlocking_diabetes.pdf)) and has the goal of becoming an NIDDK-designated Diabetes Research and Training Center (DRTC) within ten years. It has strong ties with KU-Lawrence and its School of Pharmacy, which ranks number four in the nation in NIH fund-

ing and with the Office of Therapeutics, Discovery and Development (OTDD) located on the Kansas City campus.

The Cray Diabetes Self-Management Center is a fully endowed diabetes center located within KU Hospital. It is embarking on several projects that will provide innovative health care delivery and support of primary care personnel throughout the state of Kansas, as well as lead efforts in clinical research in diabetes. It currently is providing leadership for a regional one-stop, cradle-to-grave diabetes clinic that will represent collaboration among the leading health care delivery institutions in the region.

The above takes place within an ambitious initiative for Kansas City and the region, under the leadership of the Kansas City Area Life Sciences Institute, to bring Kansas City to the forefront of bioscience endeavors (see [http://www.gkccf.org/leadership.aspx?ekfrm=250&menu\\_id=74](http://www.gkccf.org/leadership.aspx?ekfrm=250&menu_id=74)). Within this initiative is envisioned a strong focus on translational research, a major priority for the Great Plains Diabetes Institute.

The position we seek to fill represents a unique opportunity to become part of an exciting initiative in its early stages and to play a major role in its formation.

For further information about the position and the above initiatives, please contact: Dr. David C. Robbins, M.D., Professor of Medicine, Director, Great Plains Diabetes Institute, University of Kansas School of Medicine, Kansas City, KS 66160. Phone: 913-588-0277 (office); 816-810-7373 (cell); fax: 913-588-1149; e-mail: [drobbins@kumc.edu](mailto:d Robbins@kumc.edu).

### Board Certified or Board Eligible Endocrinologist

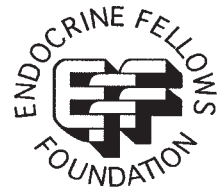
**San Antonio, Texas.** We are seeking a Board Certified or Board Eligible Endocrinologist doctor to work in an eight-physician Endocrine group at the Texas Diabetes Institute (TDI). The TDI is a 153,000 square foot state-of-the-art facility devoted to the care of patients with diabetes and includes all medical and surgical subspecialties devoted to the comprehensive care of the diabetes patient. The Endocrine physicians must be capable of interacting with a large Diabetes/Endocrine group at the University of Texas Health Science Center including seven other Endocrine physicians. The physician will have a faculty appointment as a Clinical Assistant Professor at the UTHSCSA. The University of Texas Health Science Center at San Antonio (UTHSCSA) is an equal opportunity affirmative action employer. The UTHSCSA offers a competitive salary and generous benefits package. **All faculty appointments are designated as security-sensitive positions.** Interested candidates should contact Ralph A. DeFronzo, M.D., Deputy Director at TDI, Professor of Medicine, and Chief of the Diabetes Division, UTHSCSA (210-567-6691), and e-mail a copy of their CV to [Albarado@uthscsa.edu](mailto:Albarado@uthscsa.edu).

**To All Program Directors:**

**Please help us update our database so that**

**ALL of your Fellows will receive our valuable information, such as:**

- *EndoTrends* – A quarterly publication published by EFF to disseminate clinical and research findings of interest to Fellows
- Research Grants – Grants awarded annually during two award cycles, Spring and Fall.
- Scientific Forums – Travel grants are offered to one Fellow from each accredited training program.
- Preceptorship – The EFF offers two-week preceptorial programs designed to provide fellows the opportunity to work with mentors in specific areas of endocrinology and metabolism.



***Incoming and Current Fellows:***

Name: \_\_\_\_\_ Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

Fellowship Year: 1st 2nd 3rd– Completion date of Fellowship: \_\_\_\_\_ E-Mail \_\_\_\_\_

Name: \_\_\_\_\_ Phone: \_\_\_\_\_ Fax : \_\_\_\_\_

Fellowship Year: 1st 2nd 3rd– Completion date of Fellowship: \_\_\_\_\_ E-Mail \_\_\_\_\_

Name: \_\_\_\_\_ Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

Fellowship Year: 1st 2nd 3rd– Completion date of Fellowship: \_\_\_\_\_ E-Mail \_\_\_\_\_

Name: \_\_\_\_\_ Phone: \_\_\_\_\_ Fax: \_\_\_\_\_

Fellowship Year: 1st 2nd 3rd– Completion date of Fellowship: \_\_\_\_\_ E-Mail \_\_\_\_\_

**(Completion Date Is Very Important)**

(If supervising more than three fellows, please copy the form)

**Endocrine Specialty: (Circle One)    Adult    Pediatrics    Reproductive Endocrinology**

Hospital/University Affiliation: \_\_\_\_\_

Mailing Address: \_\_\_\_\_

***Outgoing Fellows are:***

Name: \_\_\_\_\_

Name: \_\_\_\_\_

New Address: \_\_\_\_\_

New Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

(If supervising more than two outgoing fellows, please copy the form.)

Program Director: \_\_\_\_\_ Telephone: \_\_\_\_\_

E-Mail: \_\_\_\_\_ Fax: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

**Please Fax Form To: 860-586-7550**

**Endocrine Fellows Foundation, c/o Association Resources, 342 North Main Street,  
West Hartford, CT 06117**

**Toll Free: 877-877-6515**

## EndoTrends QUESTIONNAIRE:



***EndoTrends* is published by the Endocrine Fellows Foundation to provide important, useful, and interesting medical and other relevant information to Endocrine Fellows, young practicing endocrinologists, and the clinical endocrine community in general.**

**To help us improve our news magazine and increase its value to you, I would appreciate your thoughts about the following three items:**

**1. What is your general impression of the educational value of *EndoTrends*?**

**Excellent**                       **Somewhat valuable**                       **Satisfactory**

**2. What sections of *EndoTrends* would you like to have emphasized, de-emphasized, or eliminated?**

<b>Case Reports</b>	<b>Program Articles</b>	<b>Miscellaneous</b>
<b>More/Less</b>	<b>More/Less</b>	<b>More/Less</b>

**3. Your suggestions for publishing additional types of material:**

**Name (Optional)\_\_\_\_\_**

**Please Tear Out and Fax Form to (860) 586-7550  
Or mail to: Endocrine Fellows Foundation  
c/o Association Resources, 342 North Main Street,  
West Hartford, CT 06117  
(877) 877-6515**