Endocrine news®
JULY 2012

PLUS

Osteoporosis in Men

Health Disparities

Immortal Cells

DOPING FOR THE GOLD

The Endocrine Society

Meet Michael*

- Michael is a pediatric patient with type 1 diabetes who regularly tests his blood glucose
- He is an active child with an inconsistent meal and physical activity schedule
- He and his caregiver have demonstrated the ability to manage his diabetes, but don't want to draw attention to it

* Hypothetical patient profile.

Choose Humalog and the MiniMed Paradigm® REAL-Time Revel™ Insulin Pump for pediatric patients with type 1 diabetes

Humalog® (100 units/mL) can be used in a Paradigm Revel Insulin Pump.[1]

- Humalog in an external insulin pump is approved for use in children with type 1 diabetes 4 years of age and older
- Provides children and caregivers additional flexibility to adapt to the changing activities and meals in their life
- Reduces the number of injections and allows patients a discreet option for their diabetes management

The Paradigm Revel Insulin Pump is available in a variety of colors and has an infusion set for various body types and lifestyles.

Humalog®

Paradigm REAL-Time Revel™ MiniMed

insulin lispro injection, USP (rDNA origin)

Indication for Humalog

- Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

Select Safety Information for Humalog

- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.
- Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously.
- Hypoglycemia is the most common adverse effect of Humalog therapy. The risk of hypoglycemia increases with tighter glycemic control. Severe hypoglycemia may be life threatening and can cause seizures or death.
- Humalog should be given within 15 minutes before or immediately after a meal.
- Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

Select Safety Information for Humalog, continued

- Catheter occlusions and infusion-site reactions have been reported in patients receiving Humalog as a continuous subcutaneous infusion.
- Humalog in an external insulin pump is approved for use in children with type 1 diabetes 4 years of age and older.

Reference

1. Paradigm® REAL-Time Revel™ User Guide. Starting on Insulin.©2009 Medtronic MiniMed, Inc. 47.

Please see Important Safety Information for Humalog on next page and Brief Summary of Prescribing Information for Humalog on following pages.

Please see Important Safety Information for MiniMed Paradigm® REAL-Time Revel™ Insulin Pump on following pages.

For more information about Humalog, please call Eli Lilly and Company at 1-800-545-5979. For more information about Paradigm® REAL-Time Revel™, please call Medtronic at 1-888-350-3245.

Medtronic

Lilly

Important Safety Information for Humalog

Contraindications

- Humalog® is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

Warnings and Precautions

- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted.

  The time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.

- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

  Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

  Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.

- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

Important Safety Information for Humalog, continued

Warnings and Precautions, continued

- **Renal or Hepatic Impairment:** Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

- **Mixing of Insulins:** Humalog for subcutaneous injection should not be mixed with insulins other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.

- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

  Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.

- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see Brief Summary of Prescribing Information on following pages.

HI HCP ISI 08JUN2011

Humalog®

insulin lispro injection, USP (rDNA origin)

Paradigm REAL-Time Revel™ MINIMED

MiniMed Paradigm REAL-Time Revel Insulin Pump Indications for Use

Pump

- The Paradigm Revel insulin pump is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

MiniMed Paradigm REAL-Time Revel Insulin Pump Important Safety Information

Contraindications

- Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Successful insulin pump therapy requires sufficient vision or hearing to allow recognition of the pump signals and alarms.

Warnings

- The pump is not suitable for use in the presence of a flammable anesthetic mixture with air, oxygen, or nitrous oxide.
- Standard Luer sets are not compatible with the Medtronic MiniMed Paradigm pump. Medtronic Diabetes Paradigm reservoirs and Paradigm-compatible infusion sets are specifically designed for use with the pump.
- Do not modify your Paradigm reservoir or Paradigm-compatible infusion set.
- Do not put any other drugs/medications inside your reservoir to use with this pump. Only insulin that has been prescribed by your physician can be used in this pump.
- Do not use pump cases that have a magnetic clasp.
- Do not expose your insulin pump to MRI equipment or other devices that generate very strong magnetic fields. The magnetic fields in the immediate vicinity of these devices can damage the part of the pump's motor that regulates insulin delivery, possibly resulting in over-delivery and severe hypoglycemia. Your pump must be removed and kept outside the room during magnetic resonance imaging (MRI) procedures.
- If your pump is inadvertently exposed to a strong magnetic field, discontinue use and contact our 24 Hour HelpLine for further assistance.

Please visit http://www.medtronicdiabetes.com/about/safety.html for complete safety information.

The MiniMed Paradigm Revel Insulin Pump is Continuous Glucose Monitoring (CGM) ready. Optional glucose sensor and MiniLink® REAL-Time transmitter are available separately from Medtronic.

For information on the MiniMed Paradigm Revel Insulin Pump integrated with CGM, please contact your Medtronic representative.

Please see Important Safety Information for Humalog on opposite page.

Medtronic

Lilly

Humalog®

(insulin lispro injection, USP [rDNA origin])

Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

HUMALOG is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS

HUMALOG is contraindicated:

- during episodes of hypoglycemia
- in patients who are hypersensitive to HUMALOG or to any of its excipients.

WARNINGS AND PRECAUTIONS

Dose Adjustment and Monitoring—Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for HUMALOG may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with insulins, including HUMALOG. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life-threatening or cause death.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (e.g., amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia *[see Drug Interactions]*.

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (e.g., the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers *[see Drug Interactions]*, or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and Allergic Reactions—Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including HUMALOG *[see Adverse Reactions]*.

Hypokalemia—All insulin products, including HUMALOG, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Renal or Hepatic Impairment—Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Mixing of Insulins—HUMALOG for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If HUMALOG is mixed with NPH insulin, HUMALOG should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix HUMALOG with other insulins for use in an external subcutaneous infusion pump.

Subcutaneous Insulin Infusion Pumps—When used in an external insulin pump for subcutaneous infusion, HUMALOG should not be diluted or mixed with any other insulin. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days. HUMALOG should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with HUMALOG may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure *[see Dosage and Administration and How Supplied/ Storage and Handling]*.

Drug Interactions—Some medications may alter insulin requirements and the risk for hypoglycemia or hyperglycemia *[see Drug Interactions]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia *[see Warnings and Precautions]*.
- Hypokalemia *[see Warnings and Precautions]*.

Clinical Trial Experience—Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of Treatment-Emergent Adverse Events during HUMALOG clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)	Total (n=167)
Flu syndrome	28 (34.6)	28 (32.6)	56 (33.5)
Pharyngitis	27 (33.3)	29 (33.7)	56 (33.5)
Rhinitis	20 (24.7)	25 (29.1)	45 (26.9)
Headache	24 (29.6)	19 (22.1)	43 (25.7)
Pain	16 (19.8)	14 (16.3)	30 (18.0)
Cough increased	14 (17.3)	15 (17.4)	29 (17.4)
Infection	11 (13.6)	18 (20.9)	29 (17.4)
Nausea	5 (6.2)	13 (15.1)	18 (10.8)
Accidental injury	7 (8.6)	10 (11.6)	17 (10.2)
Surgical procedure	5 (6.2)	12 (14.0)	17 (10.2)
Fever	5 (6.2)	10 (11.6)	15 (9.0)
Abdominal pain	6 (7.4)	7 (8.1)	13 (7.8)
Asthenia	6 (7.4)	7 (8.1)	13 (7.8)
Bronchitis	6 (7.4)	6 (7.0)	12 (7.2)
Diarrhea	7 (8.6)	5 (5.8)	12 (7.2)
Dysmenorrhea	5 (6.2)	6 (7.0)	11 (6.6)
Myalgia	6 (7.4)	5 (5.8)	11 (6.6)
Urinary tract infection	5 (6.2)	4 (4.7)	9 (5.4)

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)	Total (n=1423)
Headache	63 (11.6)	66 (9.3)	149 (10.5)
Pain	77 (10.8)	71 (10.0)	148 (10.4)
Infection	72 (10.1)	54 (7.6)	126 (8.9)
Pharyngitis	47 (6.6)	58 (8.2)	105 (7.4)
Rhinitis	58 (8.1)	47 (6.6)	105 (7.4)
Flu syndrome	44 (6.2)	58 (8.2)	102 (7.2)
Surgical procedure	53 (7.4)	48 (6.8)	101 (7.1)

Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Lipodystrophy

Long-term use of insulin, including HUMALOG, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy [see Dosage and Administration].

Weight gain

Weight gain can occur with insulin therapy, including HUMALOG, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulin, including HUMALOG, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Adverse Reactions with Continuous Subcutaneous Insulin Infusion (CSII)

In a 12-week, randomized, crossover study in adult patients with type 1 diabetes (n=39), the rates of catheter occlusions and infusion site reactions were similar for HUMALOG and regular human insulin treated patients (see Table 3).

Table 3: Catheter Occlusions and Infusion Site Reactions

	HUMALOG (n=38)	Regular human insulin (n=39)
Catheter occlusions/month	0.09	0.10
Infusion site reactions	2.6% (1/38)	2.6% (1/39)

In a randomized, 16-week, open-label, parallel design study of children and adolescents with type 1 diabetes, adverse event reports related to infusion-site reactions were similar for insulin lispro and insulin aspart (21% of 100 patients versus 17% of 198 patients, respectively). In both groups, the most frequently reported infusion site adverse events were infusion site erythema and infusion site reaction.

Allergic Reactions

Local Allergy — As with any insulin therapy, patients taking HUMALOG may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of HUMALOG. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy — Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including HUMALOG. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving HUMALOG (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in HUMALOG *[see Contraindications]*.

Antibody Production

In large clinical trials with patients with type 1 (n=509) and type 2 (n=262) diabetes mellitus, anti-insulin antibody (insulin lispro-specific antibodies, insulin-specific antibodies, cross-reactive antibodies) formation was evaluated in patients receiving both regular human insulin and HUMALOG (including patients previously treated with human insulin and naive patients). As expected, the largest increase in the antibody levels occurred in patients new to insulin therapy. The antibody levels peaked by 12 months and declined over the remaining years of the study. These antibodies do not appear to cause deterioration in glycemic control or necessitate an increase in insulin dose. There was no statistically significant relationship between the change in the total daily insulin dose and the change in percent antibody binding for any of the antibody types.

Postmarketing Experience—The following additional adverse reactions have been identified during post-approval use of HUMALOG. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Medication errors in which other insulins have been accidentally substituted for HUMALOG have been identified during postapproval use.

DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

Following are some of the examples:

- **Drugs That May Increase the Blood-Glucose-Lowering Effect of HUMALOG and Susceptibility to Hypoglycemia:** Oral antidiabetic agents, salicylates, sulfonamide antibiotics, monoamine oxidase inhibitors, fluoxetine, pramlintide, disopyramide, fibrates, propoxyphene, pentoxifylline, ACE inhibitors, angiotensin II receptor blocking agents, and somatostatin analogs (e.g., octreotide).
- **Drugs That May Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** corticosteroids, isoniazid, niacin, estrogens, oral contraceptives, phenothiazines, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), somatropin, atypical antipsychotics, glucagon, protease inhibitors, and thyroid hormones.
- **Drugs That May Increase or Reduce the Blood-Glucose-Lowering Effect of HUMALOG:** beta-blockers, clonidine, lithium salts, and alcohol. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
- **Drugs That May Reduce the Signs of Hypoglycemia:** beta-blockers, clonidine, guanethidine, and reserpine.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking HUMALOG.

Although there are limited clinical studies of the use of HUMALOG in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

In a combined fertility and embryo-fetal development study, female rats were given subcutaneous insulin lispro injections of 5 and 20 units/kg/day (0.8 and 3 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) from 2 weeks prior to cohabitation through Gestation Day 19. There were no adverse effects on female fertility, implantation, or fetal viability and morphology. However, fetal growth retardation was produced at the 20 units/kg/day-dose as indicated by decreased fetal weight and an increased incidence of fetal runts/litter.

In an embryo-fetal development study in pregnant rabbits, insulin lispro doses of 0.1, 0.25, and 0.75 unit/kg/day (0.03, 0.08, and 0.24 times the human subcutaneous dose of 1 unit/kg/day, based on units/body surface area, respectively) were injected subcutaneously on Gestation days 7 through 19. There were no adverse effects on fetal viability, weight, and morphology at any dose.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HUMALOG is administered to a nursing woman. Use of HUMALOG is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—HUMALOG is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. HUMALOG has not been studied in pediatric patients younger than 3 years of age. HUMALOG has not been studied in pediatric patients with type 2 diabetes.

As in adults, the dosage of HUMALOG must be individualized in pediatric patients based on metabolic needs and results of frequent monitoring of blood glucose.

Geriatric Use—Of the total number of subjects (n=2834) in eight clinical studies of HUMALOG, twelve percent (n=338) were 65 years of age or over. The majority of these had type 2 diabetes. HbA1c values and hypoglycemia rates did not differ by age. Pharmacokinetic/pharmacodynamic studies to assess the effect of age on the onset of HUMALOG action have not been performed.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

DOSAGE AND ADMINISTRATION

Dosage Considerations—When given subcutaneously, HUMALOG has a more rapid onset of action and a shorter duration of action than regular human insulin.

The dosage of HUMALOG must be individualized. Blood glucose monitoring is essential in all patients receiving insulin therapy.

The total daily insulin requirement may vary and is usually between 0.5 to 1 unit/kg/day. Insulin requirements may be altered during stress, major illness, or with changes in exercise, meal patterns, or coadministered drugs.

Subcutaneous Administration—HUMALOG should be given within 15 minutes before a meal or immediately after a meal.

HUMALOG given by subcutaneous injection should generally be used in regimens with an intermediate- or long-acting insulin.

HUMALOG administered by subcutaneous injection should be given in the abdominal wall, thigh, upper arm, or buttocks. Injection sites should be rotated within the same region (abdomen, thigh, upper arm, or buttocks) from one injection to the next to reduce the risk of lipodystrophy *[see Adverse Reactions]*.

Continuous Subcutaneous Infusion (Insulin Pump)—HUMALOG may be administered by continuous subcutaneous infusion by an external insulin pump. Do not use diluted or mixed insulins in external insulin pumps. Infusion sites should be rotated within the same region to reduce the risk of lipodystrophy *[see Adverse Reactions]*. Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days.

The initial programming of the external insulin infusion pump should be based on the total daily insulin dose of the previous regimen. Although there is significant variability among patients, approximately 50% of the total dose is usually given as meal-related boluses of HUMALOG and the remainder is given as a basal infusion. HUMALOG is recommended for use in pump systems suitable for insulin infusion such as MiniMed, Disetronic, and other equivalent pumps.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HUMALOG 100 units per mL (U-100) is available as:

10 mL vials	NDC 0002-7510-01 (VL-7510)
3 mL vials	NDC 0002-7510-17 (VL-7533)
5 x 3 mL cartridges[1]	NDC 0002-7516-59 (VL-7516)
5 x 3 mL prefilled pen	NDC 0002-8725-59 (HP-8725)
5 x 3 mL Humalog KwikPen (prefilled)	NDC 0002-8799-59 (HP-8799)

Storage

Do not use after the expiration date.

Unopened HUMALOG should be stored in a refrigerator (36° to 46°F [2° to 8°C]), but not in the freezer. Do not use HUMALOG if it has been frozen. In-use HUMALOG vials, cartridges, pens, and HUMALOG KwikPen® should be stored at room temperature,

below 86°F (30°C) and must be used within 28 days or be discarded, even if they still contain HUMALOG. Protect from direct heat and light. See table below:

	Not In-Use (Unopened) Room Temperature (Below 86°F [30°C])	**Not In-Use (Unopened) Refrigerated**	**In-Use (Opened) Room Temperature, (Below 86°F [30°C])**
10 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL vial	28 days	Until expiration date	28 days, refrigerated/ room temperature.
3 mL cartridge	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL prefilled pen	28 days	Until expiration date	28 days, **Do not refrigerate.**
3 mL Humalog KwikPen (prefilled)	28 days	Until expiration date	28 days, **Do not refrigerate.**

Use in an External Insulin Pump — Change the HUMALOG in the reservoir at least every 7 days, change the infusion sets and the infusion set insertion site at least every 3 days or after exposure to temperatures that exceed 98.6°F (37°C). A HUMALOG 3 mL cartridge used in the D-Tron® pumps should be discarded after 7 days, even if it still contains HUMALOG. However, as with other external insulin pumps, the infusion set should be replaced and a new infusion set insertion site should be selected at least every 3 days.

Diluted HUMALOG for Subcutaneous Injection — Diluted HUMALOG may remain in patient use for 28 days when stored at 41°F (5°C) and for 14 days when stored at 86°F (30°C). Do not dilute HUMALOG contained in a cartridge or HUMALOG used in an external insulin pump.

Preparation and Handling

Diluted HUMALOG for Subcutaneous Injection — HUMALOG may be diluted with Sterile Diluent for HUMALOG for subcutaneous injection. Diluting one part HUMALOG to nine parts diluent will yield a concentration one-tenth that of HUMALOG (equivalent to U-10). Diluting one part HUMALOG to one part diluent will yield a concentration one-half that of HUMALOG (equivalent to U-50).

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

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[1] 3 mL cartridge is for use in Eli Lilly and Company's HumaPen® Memoir™ and HumaPen® Luxura™ HD insulin delivery devices, Owen Mumford, Ltd.'s Autopen® 3-mL insulin delivery device and Disetronic D-TRON® and D-TRON® Plus pumps.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

Additional information can be found at www.humalog.com.

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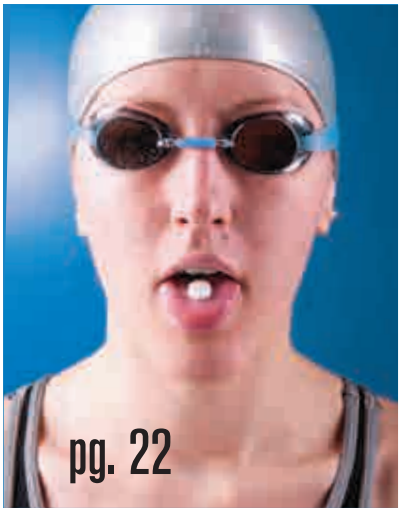
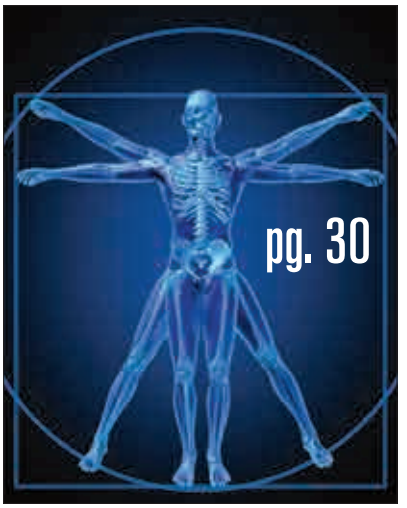
contents

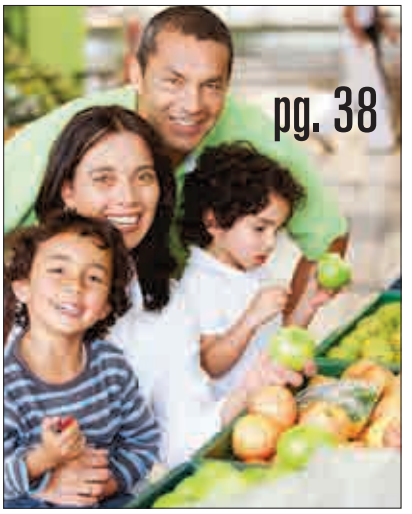
NEWS & INSIGHTS FOR THE ENDOCRINE COMMUNITY

THE ENDOCRINE SOCIETY®
WWW.ENDO-SOCIETY.ORG

Features







Departments

What is Diabetic Neuropathy?

Find out by reading the Hormone Health Network's fact sheet on Diabetic Neuropathy (pages 39, 40).

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Introducing the New President: William F. Young, Jr., M.D., M.Sc.

By Jacqueline Ruttimann

William F. Young, Jr. M.D., M.Sc.

The Endocrine Society welcomes its 2012–2013 president, William F. Young, Jr. M.D., M.Sc., who took office on June 26. A full-time clinician, he succeeds physician-scientist Janet E. Hall, M.D., in accordance with the Society's rotation of presidents who represent its primary constituencies: basic researchers, clinical researchers, and clinical practitioners. Young is a professor of medicine and chair of the Division of Endocrinology, Metabolism, and Nutrition at the Mayo Clinic College of Medicine in Rochester, Minnesota. Having delivered hundreds of oral presentations at national and international meetings and written 177 articles, 62 book chapters, and numerous abstracts, his presentation and publication record is extensive.

Young's involvement with the Society goes back to 1985, when he joined the membership after completing his clinical endocrinology fellowship at Mayo Clinic. He has served on numerous committees, co-chaired the Annual Meeting Steering Committee in 2002 to 2003, chaired the Self-Assessment Committee from 2007 to 2011, and was an associate editor of ***The Journal of Clinical Endocrinology & Metabolism*** from 2005 to 2009.

A Life-changing Experience

Endocrinology was not Young's first or even second calling. At Michigan State University, he majored in fisheries and wildlife and set his sights on "something outdoorsy" as a career. It was not until his sophomore year when a family member suffered a serious health crisis that he changed his major to pre-med and subsequently attended medical school at Michigan State University.

"It was a life-changing experience for me," he says. "I got an up-close-and-personal perspective on health care."

During a three-year residency in internal medicine, he initially wanted to pursue medical oncology, hoping to help patients at the most critical points in their lives. Such patients had already been diagnosed with an identifiable disease or condition, and he soon realized that the critical role for an oncologist would be providing effective treatment. During his endocrinology rotation, he encountered what he considered a perfect balance of clinical puzzle-solving and caring for patients with tumors.

"I like to solve puzzles," Young says. "Even after doing this for 28 years, it's still very challenging."

Young recalls a baffling case from 20 years ago that required creative medical sleuthing. The male patient exhibited dramatic "spells" of intense facial flushing, light-headedness, rapid heart rate, shortness of breath, and markedly low blood pressure. The unusual twist in this case was that the spells were triggered by sexual arousal. At baseline, measurements of all spell-associated hormones were normal. Young and his staff at Mayo designed a unique protocol to induce a spell and promptly measure blood and urine biomarkers. They found that the serum tryptase concentration rose more than six-fold with the provoked spell. The man was found to have systemic mastocytosis, an orphan disease that affects 200,000 or fewer people in the United States and is often misdiagnosed. The patient underwent treatment with histamine receptor blockers and a prostaglandin synthesis inhibitor and has remained spell-free.

"My Vocation is Also My Avocation"

These days, Young primarily sees patients with endocrine tumors (such as adrenal, pheochromocytomas, paragangliomas, and pituitary tumors), which are often associated with primary aldosteronism, Cushing syndrome, acromegaly, and multiple endocrine neoplasia.

"I see patients with unbelievably impossible clinical situations in which the Mayo Clinic is their last hope," he says, noting one recent patient who arrived with a cardiac paraganglioma twice as large as her heart.

"My vocation is also my avocation," says Young, who has traveled in North and South America, Africa, Asia, and Europe to participate in postgraduate educational meetings. He has won numerous teaching awards, including "Teacher of the Year" at the Mayo Clinic in 1997 and the Distinguished Physician Award from The Endocrine Society in 2011.

Young is married to a retired middle school science teacher he met while in college. They have two children, a daughter who is a genetic counselor and medical editor, and a son who is in a Ph.D. program in Japanese history. When he's not in the clinic or traveling for work, he spends time with his two granddaughters, ages 5 and 3. Although their attention span is rather short for Young's favorite fisheries and wildlife sport, fly-fishing, they love to go bobber fishing. ■

Ruttimann is the associate editor of ***Endocrine News****.*

Dear Readers,

In the last decade, many of our most admired athletes have been ignominiously brought down for using performance-enhancing drugs and subsequently stripped of their medals and awards. As the summer Olympics gets under way in London this month, officials will be working diligently to expose participants who use drugs to gain an edge on their competitors. Detecting who's doping, however, is not easy, experts told ***Endocrine News*** associate editor Jacqueline Ruttimann, who wrote this issue's cover story. Staying a step ahead of rogue chemists who concoct new ways to conceal banned substances presents a relentless challenge for Olympic officials (page 22).

Although women are very susceptible to osteoporosis, it is not a disease for women only. It strikes men as well and is frequently overlooked in this population. The older a man is, the more likely he is to suffer bone loss. Contributor Eric Seaborg examines the new Endocrine Society clinical guidelines and explains who's at risk and the best procedures for detecting, preventing, and treating the condition (page 30).

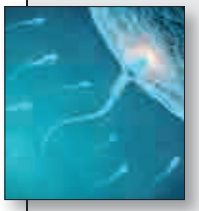
We launch a new feature this month called *Back Story,* which takes a behind-the-scenes look at surprising scientific and medical phenomena. Our first is about the ubiquitous HeLa cells used for decades by thousands of researchers. I hope you'll find the story of their origin as fascinating as I did (page 47). ■

Sincerely,

Marian Smith Holmes
Managing Editor
Endocrine News

ENDOCRINE NEWS ONLINE EXCLUSIVES

The following articles are housed online only. See ***Endocrine News*** *Online* to read them and find related links *(www.endo-society.org/endo_news).*



Birth Control Gel for Men?

A hormonal jelly applied daily to the skin can suppress sperm production and may lead to a reversible contraceptive for men.

Dessert with Breakfast

Adding a small piece of chocolate, a cookie or other treat to the morning meal was found to decrease cravings for sweets and help dieters stay on their regimen.

Bellies and Diabetes

Nearly half of the patients who underwent laparoscopic weight-loss surgery to reduce the size of their stomachs reversed their type 2 diabetes.

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Researchers Find Androgen Clues in Bird's Mating Dance

When a small Panamanian bird called a golden-collared manakin *(Manacus vitellinus)* goes courting, he performs an amazing acrobatic dance of rapid jumps and forceful wing snaps that pop like a firecracker to get a female's attention. A team of researchers led by Barney A. Schlinger, Ph.D., of the University of California, Los Angeles, wanted to find out if androgens fueled the bird's musculature for his rigorous athletic display.

Earlier work showed that manakins injected with radiolabeled testosterone accumulate radioactivity in the spinal cord, indicating the heightened presence of androgen receptors in this area, which is heavily used during copulation and courtship rituals. To follow up on this finding, the scientists compared the spinal cords of manakins and zebra finches for levels of androgen receptor, estrogen receptor α, and aromatase. The androgen receptor level was much higher throughout the manakin spinal cords, but levels of estrogen receptor and aromatase were not.

The researchers then injected fluorescent tracers into androgen receptor–sensitive wing muscles of manakins to map the distribution of their motor neurons. This showed abundant androgen-receptor mRNA in the cervical and lumbosacral spinal enlargements and the dorsal root ganglia attached to these enlargements.

In an article awaiting publication in ***Endocrinology,**** the researchers posit that androgens have widespread actions on motor and sensory circuits in the manakin spinal cord, including circuits that control three sexually dimorphic wing muscles. Their previous studies have found elevated androgen receptor expression in manakin skeletal muscles, suggesting that a unique androgen-sensitive neuromuscular phenotype facilitates these athletic courtship displays.

"There are few animal models to understand the complex coordinated neuromuscular systems simultaneously employed by most athletes," Schlinger told **Endocrine News.** Discovering that steroid hormones act not only on skeletal muscles but also on the spinal cord, sensory and motor neurons, and link back to the brain, lays the groundwork for understanding the homones' effects on humans. ■

* Fuxjager MJ, Schultz JD, Barske J, et al. Spinal motor and sensory neurons are androgen targets in an acrobatic bird. *Endocrinology*, doi:10.1210/en.2012-1313.

Vitamin D, a Defense Against Diabetes?

A new study presents more evidence that a person's vitamin D level may indicate whether or not he or she is at risk for type 2 diabetes mellitus (T2DM). Recent research shows that compared to people with high vitamin D levels, people with low vitamin D levels are more than 50 percent more likely to have high blood pressure, high triglycerides, high blood glucose, low HDL cholesterol, and a big waistline—all prime risk factors for this disease.

Using data from the Diabetes Prevention Program study, Joanna Mitri, M.D., M.S., of Tufts Medical Center, who presented the research at ***ENDO 2012,**** reports that participants with the highest risk of metabolic syndrome had a vitamin D blood concentration of approximately 12 ng/mL. The risks to those with a vitamin D concentration of 30 ng/mL were reduced by 48 percent. A vitamin D level of 20–30 ng/mL is considered healthy by the Institute of Medicine.

The association between Vitamin D and T2DM risk has been documented in the past, but this study includes people of diverse racial and ethnic backgrounds, Mitri said. "These include minority groups that are already at higher risk of diabetes."

If a causal relationship can be established with future studies, vitamin D's availability would be an easy and inexpensive therapy for defense against the disease. ■

* Mitri J, Nelson J, Garganta C, et al. Plasma 25-hydroxyvitamin D concentration and prevalence of metabolic syndrome in the diabetes prevention program randomized controlled trial. *ENDO* **2012**, Abstract # 993.

Progesterone Receptor Binding Could Be Key to Treating Endometrial Disease

➤ Dysfunctional progesterone signaling can contribute to the pathology of several gynecological diseases, but the role of progesterone has received much less attention than that of estrogen. Researchers from Baylor College of Medicine in Houston decided to correct this imbalance by examining the molecular mechanisms underlying progesterone signaling via the progesterone receptor.

Led by Francesco J. DeMayo, Ph.D., the team defined the genome-wide binding sites of progesterone receptor—its cistrome—in the murine uterus using chromatin immunoprecipitation, followed by massively parallel sequencing (ChIP-seq). This process first identified 6,327 progesterone receptor–binding sites in ovariectomized mice. However, after exposure to progesterone, the number of binding sites identified increased nearly three-fold.

Sequence analysis showed that 73 percent of these binding sites contain a progesterone response element or a half-site motif recognized by the progesterone receptor. The method identified progesterone receptor–binding sites in many progesterone-target genes known to regulate uterine function, which confirmed the validity of the researchers' approach.

The researchers identified an unexpected regulatory role for uterine progesterone in circadian rhythm gene expression, leading them to speculate that progesterone regulation of the circadian clock could be involved in the window of receptivity for embryo implantation.

The ChIP-seq data revealed an abundance of *Sox* (sex-determining region on the Y chromosome–related high mobility group box) motifs. In particular, the data revealed *Sox17* as a direct transcriptional progesterone-receptor target gene in the uterus, indicating that *Sox17* is a potential mediator of action.

In their upcoming ***Molecular Endocrinology**** article, the researchers say their upcoming analysis provides the first insights into these molecular mechanisms and will provide an important data set for future investigation of progesterone signaling through its receptor. The data will be useful in the identification of novel cooperating transactivating factors in normal uterine regulation, and could lead to the development of therapies to combat endometrial disease. ■

* Rubel CA, Lanz RB, Kommagani R, et al. Genome-wide profiling of progesterone receptor binding in the mouse uterus. *Mol Endocrinol*, doi:10.1210/me.2011-1355.

BAT Linked to Bigger Bones

➤ Once thought to exist only in infants, brown adipose tissue (BAT) is now known to be present in adults. Researchers have also found that it does more than regulate thermogenesis, its main role in infants, and conclude that brown fat influences musculoskeletal development in children and adolescents.

Positron emission tomography (PET) and computed tomography (CT) scans reveal that pediatric patients with more BAT also had more muscle than patients with less. During puberty, BAT and muscle increase at comparable rates and share structural and functional traits, suggesting a relationship. Animal studies show that the tissue may regulate mesenchymal stem cell differentiation into osteoblasts rather than adipocytes, thus building up bone and reducing fat. Finally, muscle is a primary source of anabolic mechanical stimuli for bone tissue. All of these clues suggest that BAT is involved in musculoskeletal integrity.

Scientists, led by Vicente Gilsanz, M.D., at Children's Hospital Los Angeles, California, explored the possible association between the amount of BAT and the development of leg bones and whether muscle contributes to this relationship, by reviewing PET and CT scans images of tissue in 40 children and teenagers who had been successfully treated for various cancers. In their paper, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism,**** the researchers report that the greater the volume of BAT the larger the femoral cross-sectional area and cortical bone area, even after accounting for height, weight, and gender. Factoring in muscle mass diminished BAT's role somewhat, which leaves the overall relationship unclear. Figuring out the dynamics of this interplay of bone, muscle, and BAT could lead to the development of therapies to mitigate bone loss. ■

* Ponrartana S, Aggabao PC, Hu HH, Aldrovandi GM, Wren TAL, Gilsanz V. Brown adipose tissue and its relationship to bone structure in pediatric patients. *J Clin Endocrinol Metab*, doi: 10.1210/jc.2012-1589.

Vitamin D Receptor Signals Healthy Cardiovascular System

➤ If vitamin D protects the cardiovascular system, what role does the vitamin D receptor (VDR) play?

Despite the strong correlation between cardiovascular disease and vitamin D deficiency, little is known about the underlying mechanism beyond the possibility that vitamin D regulates T lymphocytes and obstructs foam cell formation by macrophages. These, in turn, are important players in promoting atherosclerosis. Directly uncovering how the VDR fits in is a logical next step.

Scientists led by Yan Chun Li, Ph.D., at the University of Chicago, deleted the VDR from low-density lipoprotein receptor (LDLR)–null mice, and assessed the impact on atherosclerotic lesion formation at the innominate artery, ascending and descending aortas, and the aortic root of the heart. In their upcoming paper in ***Molecular Endocrinology,**** the researchers report that LDLR-null mice lacking VDR showed increased lesion formation at the innominate artery and the ascending aorta compared with controls, even after modifying the experiment to eliminate other potentially confounding factors such as differences in plasma cholesterol levels. Initially, the VDR-negative mice showed lower cholesterol levels, which is inconsistent with increased atherosclerosis. On deleting T and B lymphocytes through bone marrow transplantation, increased atherogenesis remained seen at the innominate artery and the ascending aorta in the experimental model, pointing to leukocytes/macrophages as the VDR signaling sites of action for the anti-atherosclerotic activity.

The researchers conclude that macrophage vitamin D–receptor signaling inhibits foam cell formation and, ultimately, atherogenesis in mice. In VDR-negative mice, significant up-regulation of the macrophage renin–angiotensin system (RAS), crucial for atherogenesis, suggests that the macrophage VDR signaling abrogates RAS locally. Thus, more potential for therapeutic and prophylactic use of vitamin D is put forward. ■

* Szeto FL, Reardon CA, Yoon D, et al. The vitamin D receptor signaling inhibits atherosclerosis in mice. *Mol Endocrinol,* 10.1210/me.2011-1329.

Prostate Not Damaged by Hormonal Contraception

➤ Male hormonal contraception (MHC) is on the advance. A number of studies show high rates of success in suppressing pituitary gonadotropin secretion through combined androgen-progestin therapy. However, the prostate normally uses androgen to stay in good health and the long-term effects of the extra androgens from MHC, such as the potential for an increase in prostate cancer risk, are poorly understood. In a three-month trial, researchers, primarily at the University of Washington and the Fred Hutchinson Cancer Research Center, found no increase in prostate androgen levels in 32 healthy men age 25–55 years.

Use of transdermal testosterone therapy (trans T) increased dihydrotestosterone (DHT) in the blood but not in the prostate. Trans T plus the progestin depomedroxyprogesterone acetate (DMPA) decreased prostate DHT by 40 percent. DMPA may account for this drop by inhibiting the conversion of testosterone to DHT in the prostate. Combining trans T with dutasteride, a 5α-reductase inhibitor, achieved decreases in both serum and prostate DHT for the same reason. In neither case was androgen-regulated gene expression reduced, possibly due to high testosterone levels in the prostate compensating for low DHT.

Despite changes in testosterone and DHT concentrations, the prostate proved able to maintain its own androgen levels. These results, to be published in ***The Journal of Clinical Endocrinology & Metabolism,**** are direct evidence that androgen therapy does not necessarily increase prostate androgens, and thus may not make prostate disease more likely. Instead, inhibiting DHT in the prostate might lower the risk of cancer. These results support a green light for MHC development. ■

* Mostaghel EA, Lin DW, Amory JK, et al. Impact of male hormonal contraception on prostate androgens and androgen action in healthy men: A randomized, controlled trial. *J Clin Endocrinol Metab* doi:10.1210/jc.2012-1536.

Thymulin Gene Therapy May Alleviate Reproductive Problems

➤ Researchers have found a potential gene therapy approach to the reproductive problems associated with thymus dysfunction.

During the perinatal period, a functioning thymus is necessary for proper maturation of the pituitary-gonadal axis. Congenitally athymic female mice show severe ovarian dysgenesis and a host of neuroendocrine derangements.

Because considerable evidence suggests that the peptide thymulin is important in thymus-pituitary communication, researchers led by Rodolfo G. Goya, Ph.D., of the University of La Plata in Argentina, examined the preventive action of neonatal thymulin gene therapy (NTGT) at the hypothalamic, pituitary, ovarian, and uterine levels in congenitally athymic female mice. Thymulin consists of a biologically inactive peptide called FTS coupled in an equimolecular ratio to the zinc ion, which activates it. The researchers injected the mice with an adenoviral vector containing a synthetic DNA sequence that encoded a biologically active analog of thymulin called metFTS.

This gene therapy approach restored the serum thymulin levels in the athymic mice. Morphometric analysis showed that the athymic mice had fewer brain gonadotropin-releasing hormone neurons and pituitary gonadotropic cells than heterozygous controls, but the NTGT brought these cells to normal levels and prevented the premature ovarian failure typically observed in athymic mice. Serum estrogen levels were low in the athymic mice but were partially raised by the NTGT. The NTGT also prevented the delay in the age of vaginal opening that occurs in athymic mice.

In a previous study, the researchers showed that NTGT therapy prevented the deficits in luteinizing hormone and follicle-stimulating hormone normally seen in these mice. They conclude in an upcoming ***Endocrinology**** article that their new results complement these previous findings and together support the hypothesis that thymulin is a key player in the thymus-reproductive axis. The researchers recommend thymulin gene therapy to treat reproductive pathologies associated with thymus dysfunction. ■

* Reggiani PC, Barbeito CG, Zuccolilli GO, et al. Neonatal thymulin gene therapy prevents ovarian dysgenesis and attenuates reproductive derangements in nude female mice. *Endocrinology*, doi:10.1210/en.2012-1183.

Poor Sleep Worsens Resting Energy Use

➤ A bad night's sleep can mean more than just morning crabbiness. Obesity is common with sleep deprivation and usually attributed to bad eating habits as compensation for the lack of rest. Researchers at the National Institute of Diabetes and Digestive and Kidney Diseases' Sleep Extension Study Group instead found a relationship between poor sleep quality and changes in a person's resting energy expenditure (REE).

In their cross-sectional study of 126 obese individuals, to be published soon in ***The Journal of Clinical Endocrinology & Metabolism,**** high degrees of sleep apnea directly associate with increased REE. Stress hormones might trigger the release of adrenaline and other catecholamines in a sympathetic response, raising heart rate and blood pressure. Hypoxia, a known result of sleep apnea, decreases REE, but any effect on the initial increase has not yet been seen.

Sleep apnea also associates strongly with a high respiratory quotient (RQ), indicating that carbohydrates are being oxidized instead of fat. Carbohydrate oxidation provides quicker energy but less of it, requiring more carbohydrate intake. Fat accumulates instead of being used, strongly predicted by a high RQ.

These changes appear more in men. Of the 126 participants, 30 were men and had higher morning levels of serum cortisol and catecholamines. They also slept 30 minutes less than their female counterparts and typically had a 70 percent increase in calorie intake per day as their sleep apnea worsened. With poor sleep quality a growing concern, the impact on weight control and stress response is enough to keep a person up at night. ■

* de Jonge L, Zhao X, Mattingly MS, et al. Poor sleep quality and sleep apnea are associated with higher resting energy expenditure in obese individuals with short sleep duration. *J Clin Endocrinol Metab*.doi:10.1210/jc.2011-2858.

BPA Linked to Transgenerational Behavioral Changes

➤ The once nearly ubiquitous commercial plasticizer bisphenol A (BPA) has received a lot of negative press in the past several years. Studies have implicated BPA in conditions from obesity to neurological impairment.

A new study adds an insidious twist to the damage BPA inflicts. Led by Emilie F. Rissman, Ph.D., at the University of Virginia, Charlottesville, scientists explored for the first time whether BPA's effects on behavior are transgenerational. They fed one group of mouse dams a chow supplemented with BPA in an amount correlating with what would typically be found in humans. A control group was fed a phytoestrogen-free chow. After mating the dams and establishing pregnancy, some embryos were removed for whole brain examination to determine gene expression.

In their paper, to be published soon in ***Endocrinology,**** the researchers report that BPA first-generation offspring exhibited less social investigation, such as side-by-side interactions, but had a greater tendency to display playful behaviors such as sniffing, digging, and jumping. They also noted that activity in BPA male and female mice was similar rather than dimorphic as in control mice. In second- through fourth-generation offspring, the two changes persisted but in reverse. They now exhibited more social investigation than controls and less play-seeking, but again, without a sex-related difference. The brains revealed lower transcript levels of estrogen receptors, vasopressin, and oxytocin, all of which are known behavior mediators. Two of these gene changes, vasopressin and oxytocin, persisted in the fourth generation, and of note at that time, oxytocin was only reduced in males whose great-great grandmothers had been exposed to BPA.

The researchers conclude that BPA alters social behaviors transgenerationally, possibly via DNA methylation. Because disruption occurred at BPA doses comparable to reported human levels, BPA's heritable effects may have implications for neurological disorders such as autism in humans. ■

* Wolstenholme J, Edwards M, Shetty S, et al. Gestational exposure to bisphenol A produces trans-generational changes in behaviors and gene expression. *Endocrinology,* 10.1210/en.2012-1195.

STATS

Sodas today are

6 times

larger than they were in the 1950s. And fast food burgers? Three times.

Source: Centers for Disease Control and Prevention. *http://makinghealtheasier.org/newabnormal.*

Plasticizer Possibly a Cause of Obesity in Children

➤ Bisphenol A may be getting all the press, but another common chemical used to soften plastic may be just as dangerous. Diethylhexyl phthalate (DEHP) is one in a long line of phthalates that might increase the risk of childhood obesity by as much as five times the norm. Many plastic and non-plastic products, from vinyl flooring to soap, use phthalates to retain flexibility. Because plasticizers are used in flooring and wall coverings, food containers, cosmetic products, and some medical devices (such as blood storage bags, intravenous medical tubing), phthalates are found in almost all categories of personal care products for infants, children, and adults, resulting in widespread non-occupational human exposure through multiple routes. Newborn babies are particularly vulnerable to phthalate exposure through medical devices, explained Mi-Jung Park, M.D., a pediatric endocrinologist at Inje University College of Medicine and Sanggye Paik Hospital in Seoul, who presented the findings at ***ENDO 2012.****

In recent research, DEHP levels were measured in 105 obese children compared to 99 non-obese children, all age 6–13 years. On average, the obese children showed DEHP blood levels of 107 ng/mL, compared to 53.8 ng/mL in their non-obese counterparts.

Park correlates high DEHP levels with the high percentages of fat mass and body mass index consistent with obesity. The increased risk of obesity according to the elevation of serum DEHP levels was independent of possible factors, such as physical activity and daily calorie intake.

Though DEHP does not conclusively cause childhood obesity, it is a suspected hormone-altering agent. ■

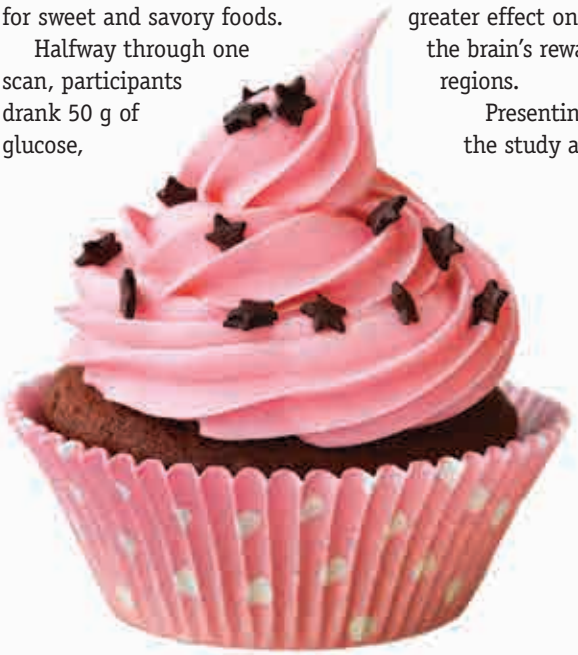
* Shin-Hye Kim, Mi-Jung Park. Serum di-ethylhexyl phthalate (DEHP) Levels in Obese Children. *ENDO* 2012, Abstract #525.

A Picture Worth a Thousand Calories

➤ As advertising knows, seeing is wanting. A new study demonstrates that images of high-calorie food significantly increase the desire for food.

Using functional magnetic resonance imaging sessions, researchers studied the brains of 13 obese Hispanic women age 20–25 years as they viewed images of high-calorie foods such as ice cream and cupcakes, and low-calorie foods such as fruits and vegetables. The participants also viewed non-food items. During scanning, each participant rated hunger and desire for food on a scale of 1 to 10, with 10 representing the greatest hunger and desire. Brain regions controlling appetite and reward processing lit up (indicating increased activity) when participants viewed the high-calorie images and ratings increased for sweet and savory foods.

Halfway through one scan, participants drank 50 g of glucose, equivalent to the amount of sugar in a can of soda, and 50 g of fructose halfway through the second scan. Both increased hunger and a desire for savory foods, but fructose had the greater effect on the brain's reward regions.



Presenting the study at ***ENDO 2012,**** Kathleen Page, M.D., of the University of Southern California, Los Angeles, chose the participants based on the high risk obese Hispanic women face for continued weight gain. Their reactions to dual stimulation by food images and sugar intake have immediate implications for appetite control. Food advertising is prevalent as are added sweeteners like high fructose corn syrup. In a society confronting overeating and obesity, they seem more than just a feast for the eyes. ■

* Page KA, Shan L, Romero A, et al. Fructose compared to glucose ingestion preferentially activates brain reward regions in response to high-calorie food cues in young, obese hispanic females. *ENDO* 2012, Abstract#1666.

Start a smart partnership

For patients not at goal on insulin glargine, adding BYETTA® can deliver a complementary approach to glycemic control

Indication and usage

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

- Not a substitute for insulin and should not be used in patients with type 1 diabetes or diabetic ketoacidosis.
- Concurrent use with prandial insulin cannot be recommended.
- Has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA; consider other antidiabetic therapies for these patients.

Important Safety Information

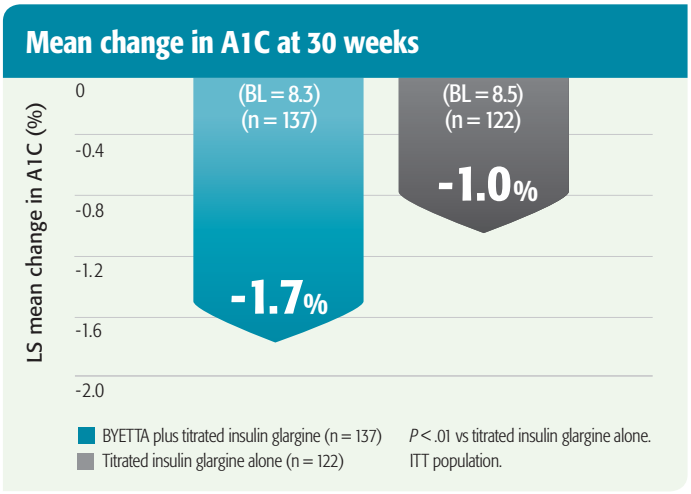
Contraindications

- BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

Warnings and precautions

- **Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation and dose increases of BYETTA, observe patients carefully for pancreatitis (persistent severe abdominal pain, sometimes radiating to the back, with or without vomiting). If pancreatitis is suspected, BYETTA should be discontinued promptly. BYETTA should not be restarted if pancreatitis is confirmed.**
- Increased risk of hypoglycemia when used in combination with glucose-independent insulin secretagogues (eg, sulfonylureas); reduction of the sulfonylurea dose may be needed. When used with insulin, evaluate and consider reducing the insulin dose in patients at increased risk of hypoglycemia.
- Postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis and kidney transplantation. BYETTA should not be used in patients with severe renal impairment or end-stage renal disease. Use with caution in patients with renal transplantation or when initiating or escalating the dose in patients with moderate renal failure.
- Not recommended in patients with severe gastrointestinal disease (eg, gastroparesis).
- Patients may develop antibodies to exenatide. In 3 registration trials, antibody levels were measured in 90% of patients, with up to 4% of patients having high-titer antibodies and attenuated glycemic response. If worsening of or failure to achieve adequate glycemic control occurs, consider alternative antidiabetic therapy.
- Postmarketing reports of serious hypersensitivity reactions (eg, anaphylaxis and angioedema). If this occurs, patients should discontinue BYETTA and other suspect medications and promptly seek medical advice.

BYETTA added to titrated insulin glargine achieved a significantly greater A1C reduction vs titrated insulin glargine alone



Abbreviations: LS, least squares; BL, baseline; ITT, intent to treat.

Patients with type 2 diabetes on insulin glargine alone or in combination with oral agents (metformin, thiazolidinedione, or both) were enrolled in a 30-week, randomized, double-blind, placebo-controlled clinical study to receive either BYETTA (5 mcg BID for 4 weeks then 10 mcg BID) or placebo in addition to titrated insulin glargine. In both arms, under investigator guidance, insulin was titrated to achieve a targeted fasting glucose level of <100 mg/dL using the Treat-to-Target algorithm.

- BYETTA did not increase the risk of hypoglycemia over that seen with insulin glargine alone and provided the potential benefit of weight loss (on average, 4.0 lb over 30 weeks).* Consider reducing the dose of insulin glargine in patients at increased risk for hypoglycemia.

***BYETTA is not indicated for the management of obesity, and weight change was a secondary endpoint.**

Warnings and precautions (cont'd)

- No clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

Adverse reactions

- Most common adverse reactions in registration trials associated with BYETTA vs placebo (PBO): nausea (44% vs 18%), vomiting (13% vs 4%), and diarrhea (13% vs 6%). Other adverse reactions ≥5% and more than PBO: feeling jittery, dizziness, headache, and dyspepsia. With a thiazolidinedione (TZD), adverse reactions were similar; as monotherapy, most common was nausea (8% vs 0%). With insulin glargine: nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%).
- Hypoglycemia incidence, BYETTA vs PBO, with metformin (MET): 5.3% (10 mcg) and 4.5% (5 mcg) vs 5.3%; with SFU, 35.7% (10 mcg) and 14.4% (5 mcg) vs 3.3%; with MET + SFU, 27.8% (10 mcg) and 19.2% (5 mcg) vs 12.6%; with TZD, 10.7% (10 mcg) vs 7.1%; as monotherapy, 3.8% (10 mcg) and 5.2% (5 mcg) vs 1.3%; with insulin glargine, 24.8% (10 mcg) vs 29.5%.
- Withdrawals: as monotherapy, 2 of 155 BYETTA patients withdrew due to headache and nausea vs 0 PBO; with MET and/or SFU vs PBO, nausea (3% vs <1%) and vomiting (1% vs 0); with TZD ± MET, nausea (9%) and vomiting (5%), with <1% of PBO patients withdrawing due to nausea; with insulin glargine vs PBO, nausea (5.1% vs 0), vomiting (2.9% vs 0).

Drug interactions

- BYETTA slows gastric emptying and can reduce the extent and rate of absorption of orally administered drugs. Use with caution with medications that have a narrow therapeutic index or require rapid gastrointestinal absorption. Medications dependent on threshold concentrations for efficacy should be taken at least 1 hour before BYETTA.
- Postmarketing reports of increased international normalized ratio (INR) sometimes associated with bleeding with concomitant use of warfarin. Monitor INR frequently until stable upon initiation or alteration of BYETTA.

Use in specific populations

- Based on animal data, BYETTA may cause fetal harm and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Caution should be exercised when administered to a nursing woman.
- Safety and effectiveness have not been established in pediatric patients.

To learn more, visit www.ByettaHCP.com.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

†SDI data, December 2009.

Byetta® exenatide injection

AMYLIN

BYETTA® (exenatide) injection

Brief Summary: For complete details, please see full Prescribing Information.

INDICATIONS AND USAGE

Type 2 Diabetes Mellitus

BYETTA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Important Limitations of Use

BYETTA is not a substitute for insulin. BYETTA should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended.

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYETTA has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYETTA. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Inject subcutaneously within 60 minutes prior to morning and evening meals (or before the two main meals of the day, approximately 6 hours or more apart). Initiate at 5 mcg per dose twice daily; increase to 10 mcg twice daily after 1 month based on clinical response. Do not mix with insulin. Do not transfer BYETTA from the pen to a syringe or vial.

CONTRAINDICATIONS

Hypersensitivity

BYETTA is contraindicated in patients with prior severe hypersensitivity reactions to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Acute Pancreatitis

Based on postmarketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis.

Use with Medications Known to Cause Hypoglycemia

The risk of hypoglycemia is increased when BYETTA is used in combination with a sulfonylurea. Therefore, patients receiving BYETTA and a sulfonylurea may require a lower dose of the sulfonylurea to reduce the risk of hypoglycemia.

When BYETTA is used in combination with insulin, the dose of insulin should be evaluated. In patients at increased risk of hypoglycemia consider reducing the dose of insulin. The concurrent use of BYETTA with prandial insulin has not been studied and cannot be recommended. It is also possible that the use of BYETTA with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYETTA should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well-tolerated due to gastrointestinal side effects. Because BYETTA may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Caution should be applied when initiating or escalating doses of BYETTA from 5 mcg to 10 mcg in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min).

There have been postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status, such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including BYETTA. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

BYETTA has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because BYETTA is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYETTA is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYETTA. Antibody levels were measured in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In 3%, 4% and 1% of these patients, respectively, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with BYETTA. If a hypersensitivity reaction occurs, the patient should discontinue BYETTA and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYETTA or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypoglycemia

Table 1: Incidence (%) and Rate of Hypoglycemia When BYETTA was Used as Monotherapy or With Concomitant Antidiabetic Therapy in Six Placebo-Controlled Clinical Trials*

	BYETTA		
	Placebo twice daily	**5 mcg twice daily**	**10 mcg twice daily**
Monotherapy (24 Weeks)			
N	77	77	78
% Overall	1.3%	5.2%	3.8%
Rate (episodes/patient-year)	0.03	0.21	0.52
% Severe	0.0%	0.0%	0.0%
With Metformin (30 Weeks)			
N	113	110	113
% Overall	5.3%	4.5%	5.3%
Rate (episodes/patient-year)	0.12	0.13	0.12
% Severe	0.0%	0.0%	0.0%
With a Sulfonylurea (30 Weeks)			
N	123	125	129
% Overall	3.3%	14.4%	35.7%
Rate (episodes/patient-year)	0.07	0.64	1.61
% Severe	0.0%	0.0%	0.0%
With Metformin and a Sulfonylurea (30 Weeks)			
N	247	245	241
% Overall	12.6%	19.2%	27.8%
Rate (episodes/patient-year)	0.58	0.78	1.71
% Severe	0.0%	0.4%	0.0%
With a Thiazolidinedione (16 Weeks)			
N	112	not evaluated	121
% Overall	7.1%	not evaluated	10.7%
Rate (episodes/patient-years)	0.56	not evaluated	0.98
% Severe	0.0%	not evaluated	0.0%
With Insulin Glargine (30 Weeks) †			
N	122	not evaluated	137
% Overall	29.5%	not evaluated	24.8%
Rate (episodes/patient-years)	1.58	not evaluated	1.61
% Severe	0.8%	not evaluated	0.0%

* A hypoglycemic episode was recorded if a patient reported symptoms of hypoglycemia with or without a blood glucose value consistent with hypoglycemia. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia requiring the assistance of another person and associated with either a blood glucose value consistent with hypoglycemia or prompt recovery after treatment for hypoglycemia.

† When BYETTA was initiated in combination with insulin glargine, the dose of insulin glargine was decreased by 20% in patients with an $HbA_{1c} \leq 8.0$ % to minimize the risk of hypoglycemia. See Table 9 for insulin dose titration algorithm.

N = The number of Intent-to-Treat subjects in each treatment group.

Immunogenicity

Antibodies were assessed in 90% of subjects in the 30-week, 24-week and 16-week studies of BYETTA. In the 30-week controlled trials of BYETTA add-on to metformin and/or sulfonylurea, antibodies were assessed at 2- to 6-week intervals. The mean antibody titer peaked at week 6 and was reduced by 55% by week 30. Three hundred and sixty patients (38%) had low titer antibodies (<625) to exenatide at 30 weeks. The level of glycemic control (HbA_{1c}) in these patients was generally comparable to that observed in the 534 patients (56%) without antibody titers. An additional 59 patients (6%) had higher titer antibodies (≥625) at 30 weeks. Of these patients, 32 (3% overall) had an attenuated glycemic response to BYETTA; the remaining 27 (3% overall) had a glycemic response comparable to that of patients without antibodies.

In the 16-week trial of BYETTA add-on to thiazolidinediones, with or without metformin, 36 patients (31%) had low titer antibodies to exenatide at 16 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 69 patients (60%) without antibody titer. An additional 10 patients (9%) had higher titer antibodies at 16 weeks. Of these patients, 4 (4% overall) had an attenuated glycemic response to BYETTA; the remaining 6 (5% overall) had a glycemic response comparable to that of patients without antibodies.

In the 24-week trial of BYETTA used as monotherapy, 40 patients (28%) had low titer antibodies to exenatide at 24 weeks. The level of glycemic control in these patients was generally comparable to that observed in the 101 patients (70%) without antibody titers. An additional 3 patients (2%) had higher titer antibodies at 24 weeks. Of these patients, 1 (1% overall) had an attenuated glycemic response to BYETTA; the remaining 2 (1% overall) had a glycemic response comparable to that of patients without antibodies.

Antibodies to exenatide were not assessed in the 30-week trial of BYETTA used in combination with insulin glargine.

Two hundred and ten patients with antibodies to exenatide in the BYETTA clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

Monotherapy

Adverse reactions (excluding hypoglycemia) for the 24-week placebo-controlled study of BYETTA BID (N = 155) when used as a monotherapy, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo BID-treated patients (N = 77): nausea (8% vs 0%), vomiting (4% vs 0%), and dyspepsia (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite, diarrhea, and dizziness. The most frequently reported adverse reaction associated with BYETTA, nausea, occurred in a dose-dependent fashion.

Two of the 155 patients treated with BYETTA withdrew due to adverse reactions of headache and nausea. No placebo-treated patients withdrew due to adverse reactions.

Combination Therapy

Add-on to metformin and/or sulfonylurea

Adverse reactions (excluding hypoglycemia) in the three 30-week controlled trials of BYETTA BID (N = 963) add-on to metformin and/or sulfonylurea, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 483): nausea (44% vs 18%), vomiting (13% vs 4%), diarrhea (13% vs 6%), feeling jittery (9% vs 4%), dizziness (9% vs 6%), headache (9% vs 6%), dyspepsia (6% vs 3%), asthenia (4% vs 2%), gastroesophageal reflux disease (3% vs 1%), and hyperhydrosis (3% vs 1%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Nausea was the most frequently reported adverse reaction and occurred in a dose-dependent fashion. With continued therapy, the frequency and severity decreased over time in most of the patients who initially experienced nausea. Patients in the long-term uncontrolled open-label extension studies at 52 weeks reported no new types of adverse reactions than those observed in the 30-week controlled trials.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (3% of patients) and vomiting (1%). For placebo-treated patients, <1% withdrew due to nausea and none due to vomiting.

Add-on to thiazolidinedione with or without metformin

Adverse reactions (excluding hypoglycemia) for the 16-week placebo-controlled study of BYETTA BID (N = 121) add-on to a thiazolidinedione, with or without metformin, with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 112): nausea (40% vs 15%), vomiting (13% vs 1%), dyspepsia (7% vs 1%), diarrhea (6% vs 3%), and gastroesophageal refiux disease (3% vs 0%).

Adverse reactions reported in ≥1.0 to <2.0% of patients receiving BYETTA and reported more frequently than with placebo included decreased appetite. Chills (n = 4) and injection-site reactions (n = 2) occurred only in BYETTA-treated patients. The two patients who reported an injection-site reaction had high titers of antibodies to exenatide. Two serious adverse events (chest pain and chronic hypersensitivity pneumonitis) were reported in the BYETTA arm. No serious adverse events were reported in the placebo arm.

The most common adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (9%) and vomiting (5%). For placebo-treated patients, <1% withdrew due to nausea.

Add-on to insulin glargine with or without metformin and/or thiazolidinedione

Adverse reactions (excluding hypoglycemia) for the 30-week placebo-controlled study of BYETTA BID (N = 137) as add-on to insulin glargine with or without oral antihyperglycemic medications with an incidence ≥2% and occurring more frequently in BYETTA-treated patients versus placebo-treated patients (N = 122): nausea (41% vs 8%), vomiting (18% vs 4%), diarrhea (18% vs 8%), headache (14% vs 4%), constipation (10% vs 2%), dyspepsia (7% vs 2%), asthenia (5% vs 1%), abdominal distension (4% vs 1%), decreased appetite (3% vs 0%), flatulence (2% vs 1%), gastroesophageal reflux disease (2% vs 1%).

The most frequently reported adverse reactions leading to withdrawal for BYETTA-treated patients were nausea (5.1%) and vomiting (2.9%). No placebo-treated patients withdrew due to nausea or vomiting.

Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema, anaphylactic reaction.

Drug Interactions: International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYETTA use in pregnant women. In animal studies, exenatide caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYETTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Female mice given SC doses of 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7 had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 390 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

In developmental toxicity studies, pregnant animals received exenatide subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given SC doses of 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 12 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC. Moreover, fetuses from pregnant mice given SC doses of 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Lactating mice given SC doses of 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure 3 times the human exposure resulting from the maximum recommended dose of 20 mcg/day, based on AUC.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling 1-800-633-9081.

Nursing Mothers

It is not known whether exenatide is excreted in human milk. However, exenatide is present at low concentrations (less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing) in the milk of lactating mice. Many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in nursing infants from exenatide, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account these potential risks against the glycemic benefits to the lactating woman. Caution should be exercised when BYETTA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of BYETTA have not been established in pediatric patients.

Geriatric Use

Population pharmacokinetic analysis of patients ranging from 22 to 73 years of age suggests that age does not influence the pharmacokinetic properties of exenatide. BYETTA was studied in 282 patients 65 years of age or older and in 16 patients 75 years of age or older. No differences in safety or effectiveness were observed between these patients and younger patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function.

OVERDOSAGE

In a clinical study of BYETTA, three patients with type 2 diabetes each experienced a single overdose of 100 mcg SC (10 times the maximum recommended dose). Effects of the overdoses included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations. One of the three patients experienced severe hypoglycemia requiring parenteral glucose administration. The three patients recovered without complication. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Manufactured for Amylin Pharmaceuticals, Inc., San Diego, CA 92121

1-800-868-1190

http://www.BYETTA.com

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DOPING FOR THE GOLD

By Jacqueline Ruttimann

In 1988, it was Canadian sprinter Ben Johnson. In 2000, American track star Marion Jones. In 2004, Russian shot putter Irina Korzhanenko. No doubt there will be at least one in the Olympic Games opening this month in London: a dazzling athlete who wins the gold only to be stripped of it later for using performance-enhancing drugs. The World Anti-Doping Agency (WADA), an international drug monitoring organization, estimates that 10 percent of the athletes in this year's games may be doping.

"The games will not be kept clean," says Alan Rogol, M.D., Ph.D., a pediatric endocrinologist and advisor to the U.S. Anti-Doping Association, "but there is not much more that can be legally done than testing." Rogol, who co-wrote *The Endocrine System in Sports and Exercise,* adds, "The new drugs that are used are not known until a test is made for them."

Doping is as old as the Olympics. Ancient Greek and Roman athletes pumped themselves up with herbs and animal extracts before competitions. Over the centuries, cocaine, caffeine, alcohol, and amphetamines have all been used to enhance performance. After World War II, a plethora of modern drugs emerged, including anabolic-androgenic steroids and peptide hormones such as growth hormone and erythropoietin. On the horizon lurk

designer drugs, among them selective androgen-receptor modulators (SARMs) and myostatin inhibitors, which can fly under the radar of current-day tests.

Trying to keep the Olympics clean is a daunting task for officials. More than 300 performance-enhancing substances are known, but as quickly as WADA, with its 33 testing laboratories, devises a method to detect one, the underground pharmacists and chemists develop new drugs to obscure the banned substance and thwart the tests. "It's a cat-and-mouse game between the pharmacists who make these things and the anti-doping agencies," says Rogol.

Officials will be gunning for anabolic-androgen steroids, growth hormone, and erythropoietin, the three primary endocrine system offenders in sports doping today. Altered versions of these substances, originally developed by pharmaceutical companies to treat various illnesses, are readily available online at such sites as *GetAnabolics.com* and *houseofmuscle.com*. The ethical aspects of the marketplace are fuzzy, and many countries ban the sales of these drugs without a prescription.

In their pure form, anabolic-androgen steroids are metabolic derivatives of testosterone, a major male sex hormone that is best known for building muscle. Bona fide therapeutic use of it includes treatment of male hypogonadism, helping AIDS patients gain weight, or treating anemia and muscle-wasting diseases. Human and veterinary anabolic-androgenic steroids are used by weightlifters and track stars because these drugs help them enhance their strength. Johnson and Korzhanenko were busted for the anabolic stanozolol.

Testing for steroids involves the use of liquid or gas chromatrography and mass spectrometry, which examines the "signatures" of the testosterone trunk and the chemical groups that make each anabolic steroid unique. The process is a lot like examining a fingerprint in a forensic case by scrutinizing the different parts of it. The problem with this detection strategy is that it's only as good as what it already knows. Rogue chemists can synthesize new anabolic substances with similar chemical structures that are not detected in the current anti-doping tests. A case in point is tetrahydrogestrinone (THG), which made headlines in the 2004 Olympics. Also known as "the clear" for its initial ability to go undetected, this anabolic steroid, manufactured by the Bay Area Laboratory Co-Operative, brought down numerous Olympians. Among them was Jones, who admitted in 2007 to using THG before competing in the 2000 Sydney Olympics, as well as Major League Baseball players Barry Bonds and Jeremy Giambi. Abuse of THG was widespread among athletes before the U.S. Anti-Doping Agency was able to identify and develop a specific test for it.

Growth hormone (GH), the pituitary peptide administered to under-statured children and adults, also increases muscle mass and decreases body fat. The word in gyms is that it increases muscle size in a shorter time than the usual training and allows a lifter to bench press more weight. In the scientific literature, however, the jury is still out as to whether GH actually brings any additional benefit to healthy adults. Only a handful of short-term studies indicate that it increases endurance and strength in older adults.

Olympic officials at this year's Games will try to detect the hormone by measuring and comparing the ratio of human recombinant GH, of which the majority of counterfeit drugs are made, to normal GH levels present in the body. The window of opportunity for detection of GH, however, is just 12–24 hours after the last GH dose. The pulsatile manner in which GH is secreted, with higher levels at night than in the day, also poses problems. A "high" GH could mean that the sample was taken during a peak, not that the athlete was doping.

A New Threat: Gene Doping

With all the promising medical advances that gene therapy may one day yield, the nascent technology is ripe for exploitation by the sports world. Instead of injecting DNA for therapeutic purposes, gene doping involves the manipulation of genes, via a virus or some other carrier, either in the entire body or specific tissues, such as muscle, solely to enhance athletic performance. In theory, the list of possible gene candidates for this approach include erythropoietin to bolster red blood cell mass and endurance, and insulin growth factor I and myostatin to increase muscle mass and strength. Some athletes may already be experimenting with the sinister side of gene therapy. At this time, no gene doping test exists and developing one will be a challenge. "It would be unlikely that there would be a single test for gene doping," Alan Rogol, M.D., Ph.D., told ***Endocrine News***. "It would depend upon which molecule was transferred (likely the same as the human form) and what vector was used. Perhaps finding components of the vector would be the strategy for doping detection."

Society Weighs in on Sports Doping

Two weeks before the London Games on July 12, The Endocrine Society will broadcast a Webinar on sports doping. See *www.endo-society.org/media/index.cfm* for more details.

Athletes have been known to add chemicals, such as soap detergent, to urine or blood samples to create a false negative.

The illicit drug of choice for cyclists and marathon runners is the kidney-based hormone, erythropoietin, which increases the number of circulating red blood cells, thereby boosting oxygen delivery to muscles and improving endurance. Both blood and urine tests can unmask abusers, but the drug is quickly eliminated from the body, generally within three days after initial injection, which makes detection very elusive.

"The effects of the drug often last longer than the drug can be detected in body fluids, thus an athlete may be enhanced and the test is negative," explains Don Catlin, M.D., founder of the first U.S. anti-doping lab and president and chief operating officer of Anti-Doping Research, an organization that strives to improve detection of performance-enhancing drugs.

Soon after Olympic medalists are lauded on the podium, they must give blood and urine samples, usually within two hours after the competition. The sample is divided and one part tested. If it comes back positive, the other portion is tested to confirm the results. If both are positive, the athlete loses the medals and is banned from competition for two years.

Is it possible that an athlete can get snared by innocently ingesting some nutraceutical, such as creatinine or "organic" powder? "The rules are strict," says Rogol. If a compound's in your body, you're responsible. It doesn't matter how it got there."

This zero-tolerance attitude led to the near-expulsion of MVP baseball player Ryan Braun in February after he received two positives for anabolic-androgenic steroid. When officials discovered that the test collector had taken Braun's sealed urine sample home for two days before sending it to an anti-doping laboratory, a 50-game suspension was averted, though Braun's reputation remains questionable. The case, however, underscores just how difficult it can be to sort out who's cheating and who's not.

Doping athletes have contrived a roster of ways to beat detection. Hiring a chemist to design a drug for which the anti-doping laboratories do not yet have a test is one of the latest trends. For example, androgens contain many metabolites, not all of which have been identified and will not be in anti-doping data banks. The new SARMS and myostatin inhibitors, which specifically target and increase muscle tissue, don't alter a person's endocrinology profile and cannot be picked up by the traditional blood or urine test. Anti-doping agencies are pursuing alternative methods to trace these new compounds.

Athletes have been known to add chemicals, such as soap detergent, to urine or blood samples to create a false negative. They sometimes try to dilute a banned drug in their urine or blood by drinking enormous amounts of fluids or taking diuretics. The dope busters fight back with sophisticated screening processes. Some athletes even connive to provide someone else's urine. Bradley Anawalt, M.D., professor of medicine at the University of Washington in Seattle and also a U.S. Anti-Doping Agency scientific advisor, says that athletes sometimes attempt to conceal a container or bag of clean urine in body cavities or clothing to provide as a sample.

"It's pretty impressive the lengths athletes have gone through to take an anabolic or prohibitive substance and hide it," says Anawalt.

Ultimately an athlete may pay a high price for the fame and fortune that comes with winning a medal through substance abuse. A lifetime of health problems can result, from acne and depression to infertility and cardiovascular disease. In a 1995 poll of 198 elite athletes, Chicago physician Bob Goldman discovered that more than half said they would take a banned drug if they were assured of not getting caught and could win their competitions for five years, even if they then died from the adverse effects of the drug. Says Anawalt, "We are talking about a group of people who are willing to do absolutely anything to win a medal." ■

Ruttimann is the associate editor of ***Endocrine News****.*

ENO LINKS For additional links related to this feature, please visit *Endocrine News Online* at *www.endo-society.org/endo_news*.

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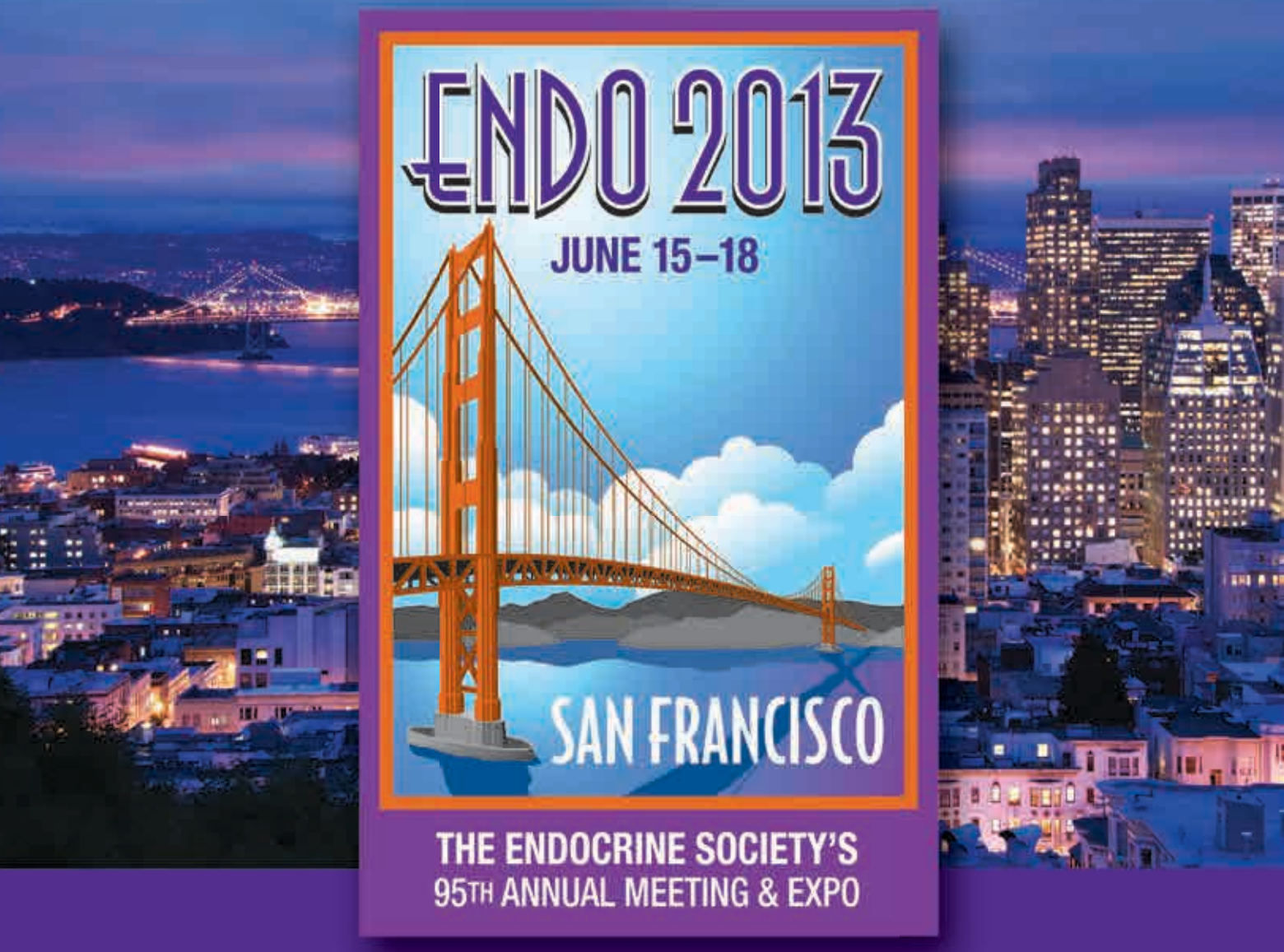

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The Endocrine Society®

Introducing BYDUREON

The first and only once-weekly treatment for type 2 diabetes

Indication and Usage

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

- Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe only to patients for whom potential benefits are considered to outweigh potential risk.
- Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.
- Not a substitute for insulin, should not be used in patients with type 1 diabetes or diabetic ketoacidosis, and cannot be recommended for use with insulin.
- BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and should not be used together.
- Exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, based on postmarketing data. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON; consider other antidiabetic therapies for these patients.

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

For additional safety profile and other important prescribing considerations, please see the adjacent pages for Brief Summary of Prescribing Information.

To learn more about once-weekly BYDUREON, visit www.BYDUREONHCP.com

Once-weekly

BYDUREON™

exenatide extended-release for injectable suspension

AMYLIN®

BYDUREON™ (exenatide extended-release for injectable suspension)

Initial U.S. Approval: 2012

Brief Summary: For complete details, please see full Prescribing Information

WARNING: RISK OF THYROID C-CELL TUMORS

Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether BYDUREON causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance could not be determined by clinical or nonclinical studies. BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with BYDUREON. Patients should be counseled regarding the risk and symptoms of thyroid tumors [see *Contraindications* and *Warnings and Precautions*].

INDICATIONS AND USAGE

BYDUREON is an extended-release formulation of exenatide, administered as an injection once every seven days (weekly).

Type 2 Diabetes Mellitus

BYDUREON is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in multiple clinical settings.

Important Limitations of Use

Because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans, prescribe BYDUREON only to patients for whom the potential benefits are considered to outweigh the potential risk.

BYDUREON is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

BYDUREON is not a substitute for insulin. BYDUREON should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings.

The concurrent use of BYDUREON with insulin has not been studied and cannot be recommended.

BYDUREON and BYETTA® (exenatide) injection both contain the same active ingredient, exenatide, and therefore should not be used together.

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. BYDUREON has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at increased risk for pancreatitis while using BYDUREON. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.

CONTRAINDICATIONS

Medullary Thyroid Carcinoma

BYDUREON is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Hypersensitivity

BYDUREON is contraindicated in patients with a prior serious hypersensitivity reaction to exenatide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors

In both genders of rats, exenatide extended-release caused a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and/or carcinomas) at clinically relevant exposures compared to controls. A statistically significant increase in malignant thyroid C-cell carcinomas was observed in female rats receiving exenatide extended-release at 25-times clinical exposure compared to controls and higher incidences were noted in males above controls in all treated groups at ≥2-times clinical exposure. The potential of exenatide extended-release to induce C-cell tumors in mice has not been evaluated. Other GLP-1 receptor agonists have also induced thyroid C-cell adenomas and carcinomas in male and female mice and rats at clinically relevant exposures. It is unknown whether BYDUREON will cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of exenatide extended-release-induced rodent thyroid C-cell tumors could not be determined by clinical or nonclinical studies. Serum calcitonin was not assessed in the clinical trials supporting the approval of BYDUREON [see *Boxed Warning*].

Serum calcitonin is a biological marker of MTC. Patients with MTC usually have calcitonin values >50 ng/L. Patients with thyroid nodules noted on physical examination or neck imaging should be referred to an endocrinologist for further evaluation. Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with BYDUREON. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. If serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

Acute Pancreatitis

Based on postmarketing data, exenatide has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYDUREON, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYDUREON should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYDUREON should not be restarted. Consider antidiabetic therapies other than BYDUREON in patients with a history of pancreatitis.

Hypoglycemia

The risk of hypoglycemia is increased when exenatide is used in combination with a sulfonylurea. Therefore, patients receiving BYDUREON and a sulfonylurea may require a lower dose of the sulfonylurea to minimize the risk of hypoglycemia. It is also possible that the use of BYDUREON with other glucose-independent insulin secretagogues (e.g. meglitinides) could increase the risk of hypoglycemia.

Renal Impairment

BYDUREON should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) or end-stage renal disease and should be used with caution in patients with renal transplantation. In patients with end-stage renal disease receiving dialysis, single doses of BYETTA 5 mcg were not well tolerated due to gastrointestinal side effects. Because BYDUREON may induce nausea and vomiting with transient hypovolemia, treatment may worsen renal function. Use BYDUREON with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). BYDUREON has not been studied in patients with end-stage renal disease or severe renal impairment.

There have been postmarketing reports of altered renal function with exenatide, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis or kidney transplantation. Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration. Reversibility of altered renal function has been observed in many cases with supportive treatment and discontinuation of potentially causative agents, including exenatide. Exenatide has not been found to be directly nephrotoxic in preclinical or clinical studies.

Gastrointestinal Disease

Exenatide has not been studied in patients with severe gastrointestinal disease, including gastroparesis. Because exenatide is commonly associated with gastrointestinal adverse reactions, including nausea, vomiting, and diarrhea, the use of BYDUREON is not recommended in patients with severe gastrointestinal disease.

Immunogenicity

Patients may develop antibodies to exenatide following treatment with BYDUREON. Anti-exenatide antibodies were measured in all BYDUREON-treated patients in the five comparator-controlled 24-30 week studies of BYDUREON. In 6% of BYDUREON-treated patients, antibody formation was associated with an attenuated glycemic response. If there is worsening glycemic control or failure to achieve targeted glycemic control, alternative antidiabetic therapy should be considered.

Hypersensitivity

There have been postmarketing reports of serious hypersensitivity reactions (e.g. anaphylaxis and angioedema) in patients treated with exenatide. If a hypersensitivity reaction occurs, the patient should discontinue BYDUREON and other suspect medications and promptly seek medical advice.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with BYDUREON or any other antidiabetic drug.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BYDUREON was assessed in five comparator-controlled trials, in patients who entered the studies not achieving adequate glycemic control on their current therapy. In a double-blind 26 week trial, patients on diet and exercise were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, pioglitazone 45 mg daily, or metformin 2000 mg daily. In a double-blind 26 week trial, patients on metformin were treated with BYDUREON 2 mg once every seven days (weekly), sitagliptin 100 mg daily, or pioglitazone 45 mg daily. In an open-label 26 week trial, patients on metformin or metformin plus sulfonylurea were treated with BYDUREON 2 mg once every seven days (weekly) or optimized insulin glargine. In two open-label 24 to 30 week studies, patients on diet and exercise or metformin, a sulfonylurea, a thiazolidinedione or combination of oral agents were treated with BYDUREON 2 mg once every seven days (weekly) or BYETTA 10 mcg twice daily.

Withdrawals

The incidence of withdrawal due to adverse events was 4.9% (N=45) for BYDUREON-treated patients, 4.9% (N=13) for BYETTA-treated patients and 2.0% (N=23) for other comparator-treated patients in the five comparator-controlled 24-30 week trials. The most common adverse reactions leading to withdrawal for BYDUREON-treated patients were nausea 0.5% (N=5) versus 1.5% (N=4) for BYETTA and 0.3% (N=3) for other comparators, injection site nodule 0.5% (N=5) versus 0.0% for BYETTA and 0.0% for other comparators, diarrhea 0.3% (N=3) versus 0.4% (N=1) for BYETTA and 0.3% (N=3) for other comparators, injection site reaction 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators and headache 0.2% (N=2) versus 0.0% for BYETTA and 0.0% for other comparators.

Hypoglycemia

The incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia in the five comparator-controlled 24-30 week trials of BYDUREON used as monotherapy or as add-on to metformin, a sulfonylurea, a thiazolidinedione or combination of these oral antidiabetic agents were as follows. In these trials, an event was classified as minor hypoglycemia if there were symptoms of hypoglycemia with a concomitant glucose <54 mg/dL and the patient was able to self-treat.

In the 26-week monotherapy trial: BYDUREON, 2.0% (0.05) [N = 248]; sitagliptin, 0.0% (0.00) [N = 163]; pioglitazone, 0.0% (0.00) [N = 163]; and metformin, 0.0% (0.00) [N = 246]. In the 26-week add-on to metformin trial: BYDUREON, 1.3% (0.03) [N = 160]; sitagliptin, 3.0% (0.12) [N = 166]; and pioglitazone, 1.2% (0.03) [N = 165]. In the 26-week add-on to metformin or metformin plus sulfonylurea trial: with concomitant sulfonylurea, BYDUREON, 20.0% (1.11) [N = 70] and titrated insulin glargine, 43.9% (2.87) [N = 66]; without concomitant sulfonylurea, BYDUREON, 3.7% (0.11) [N =163] and titrated insulin glargine, 19.1% (0.64) [N = 157]. Insulin glargine was dosed to a target fasting glucose concentration of 72 to 100 mg/dL. The mean dose of insulin glargine was 10 Units/day at baseline and 31 Units/day at endpoint.

In the 24-30 week trials of BYDUREON as monotherapy or add-on to metformin, sulfonylurea, thiazolidinedione or any combination of these oral agents, incidence (% of subjects) and rate (episodes/subject year) of minor hypoglycemia were as follows. In the 24-week trial: with concomitant sulfonylurea, BYDUREON, 12.5% (0.72) [N = 40] and BYETTA, 11.8% (0.31) [N = 34]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 89] and BYETTA, 0.0% (0.00) [N = 89]. In the 30-week trial: with concomitant sulfonylurea, BYDUREON, 14.5% (0.55) [N =55] and BYETTA, 15.4% (0.37) [N = 52]; without concomitant sulfonylurea, BYDUREON, 0.0% (0.00) [N = 93] and BYETTA, 1.1% (0.02) [N = 93].

There were no reported events of major hypoglycemia in these five comparator-controlled 24-30 week trials. Major hypoglycemia was defined as loss of consciousness, seizure or coma (or other mental status change consistent with neuroglycopenia in the judgment of the investigator or physician) which resolved after administration of glucagon or glucose or required third party assistance to resolve because of severe impairment in consciousness or behavior. Patients were to have a concomitant glucose <54 mg/dL.

Immunogenicity

Anti-exenatide antibodies were measured at prespecified intervals (4-14 weeks) in all BYDUREON-treated patients (N=918) in the five comparator-controlled studies of BYDUREON. In these five trials, 452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers. An additional 107 BYDUREON-treated patients (12%) had higher titer antibodies at endpoint. Of these patients, 50 (6% overall) had an attenuated glycemic response to BYDUREON (<0.7% reduction in HbA_{1c}); the remaining 57 (6% overall) had a glycemic response comparable to that of patients without antibodies. In the 30-week trial in which anti-exenatide antibody assessments were performed at baseline and at 4-week intervals from week 6 to week 30, the mean anti-exenatide antibody titer in the BYDUREON-treated patients peaked at week 6 then declined by 56% from this peak by week 30.

A total of 246 patients with antibodies to exenatide in the BYETTA and BYDUREON clinical trials were tested for the presence of cross-reactive antibodies to GLP-1 and/or glucagon. No treatment-emergent cross reactive antibodies were observed across the range of titers.

Other Adverse Reactions

Monotherapy

In a 26-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 248) vs sitagliptin (N = 163), pioglitazone (N = 163) and metformin (N = 246), respectively, were nausea (11.3% vs 3.7%, 4.3%, and 6.9%), diarrhea (10.9% vs 5.5%, 3.7%, and 12.6%), injection-site nodule (10.5% vs 6.7%, 3.7%, and 10.2%), constipation (8.5% vs 2.5%, 1.8%, and 3.3%), headache (8.1% vs 9.2%, 8.0%, and 12.2%), and dyspepsia (7.3% vs 1.8%, 4.9%, and 3.3%). Patients in the sitagliptin, pioglitazone, and metformin arms received weekly placebo injection.

Combination therapy

26-week add-on to metformin

Treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 160) vs sitagliptin (N = 166) and pioglitazone (N = 165), respectively, were nausea (24.4% vs. 9.6% and 4.8%), diarrhea (20.0% vs 9.6% and 7.3%), vomiting (11.3% vs 2.4% and 3.0%), headache (9.4% vs 9.0% and 5.5%), constipation (6.3% vs 3.6% and 1.2%), fatigue (5.6% vs 0.6% and 3.0%), dyspepsia (5.0% vs 3.6% and 2.4%), decreased appetite (5.0% vs 1.2% and 0.0%), and injection-site pruritus (5.0% vs 4.8% and 1.2%). Patients in the sitagliptin and pioglitazone arms received weekly placebo injection.

26-week add-on to metformin or metformin plus sulfonylurea

Treatment-emergent adverse reaction reported in ≥5% of BYDUREON-treated patients (N = 233) vs titrated insulin glargine (N = 223), respectively, were nausea (12.9 vs 1.3), headache (9.9 vs 7.6), diarrhea (9.4 vs 4.0), and injection-site nodule (6.0 vs 0.0).

24-30 week monotherapy or as add-on to metformin, sulfonylurea, thiazolidinedione or combination of oral agents

In the 24-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 129) vs BYETTA (N = 123), respectively, were nausea (14.0% vs 35.0%), diarrhea (9.3% vs 4.1%), and injection-site erythema (5.4% vs 2.4%). In the 30-week trial, treatment-emergent adverse reactions reported in ≥5% of BYDUREON-treated patients (N = 148) vs BYETTA (N = 145), respectively, were nausea (27.0% vs 33.8%), diarrhea (16.2% vs 12.4%), vomiting (10.8% vs 18.6%), injection-site pruritus (18.2% vs 1.4%), constipation (10.1% vs 6.2%), gastroenteritis viral (8.8% vs 5.5%), gastroesophageal reflux disease (7.4% vs 4.1%), dyspepsia (7.4% vs 2.1%), injection-site erythema (7.4% vs 0.0%), fatigue (6.1% vs 3.4%), headache (6.1% vs 4.8%), and injection-site hematoma (5.4% vs 11.0%).

Nausea was the most common adverse reaction associated with initiation of treatment with BYDUREON, and usually decreased over time.

Injection Site Reactions

In the five comparator-controlled 24-30 week trials, injection site reactions were observed more frequently in patients treated with BYDUREON (17.1%) than in patients treated with BYETTA (12.7%), titrated insulin glargine (1.8%) or those patients who received placebo injections (sitagliptin (10.6%), pioglitazone (6.4%), and metformin (13.0%) treatment groups). These reactions for patients treated with BYDUREON were more commonly observed in antibody-positive patients (14.2%) compared with antibody-negative patients (3.1%), with a greater incidence in those with higher titer antibodies. Incidence of injection site reactions for patients treated with BYETTA was similar for antibody positive patients (5.8%) and antibody negative patients (7.0%). One percent of patients treated with BYDUREON withdrew due to injection site adverse reactions (injection site mass, injection site nodule, injection site pruritus, and injection site reaction).

Small, asymptomatic subcutaneous injection site nodules are seen with the use of BYDUREON. In a separate 15-week study in which information on nodules were collected and analyzed, 24 out of 31 subjects (77%) experienced at least one injection site nodule during treatment; 2 subjects (6.5%) reported accompanying localized symptoms. The mean duration of events was 27 days. The formation of nodules is consistent with the known properties of the microspheres used in BYDUREON.

Post-Marketing Experience

BYETTA

The following additional adverse reactions have been reported during post-approval use of BYETTA. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergy/Hypersensitivity: injection-site reactions, generalized pruritus and/or urticaria, macular or papular rash, angioedema; anaphylactic reaction.

Drug Interactions: increased international normalized ratio (INR), sometimes associated with bleeding, with concomitant warfarin use.

Gastrointestinal: nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension, abdominal pain, eructation, constipation, flatulence, acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

Neurologic: dysgeusia; somnolence

Renal and Urinary Disorders: altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis), kidney transplant and kidney transplant dysfunction.

Skin and Subcutaneous Tissue Disorders: alopecia

DRUG INTERACTIONS

Orally Administered Drugs

Exenatide slows gastric emptying. Therefore, BYDUREON has the potential to reduce the rate of absorption of orally administered drugs. Use caution when administering oral medications with BYDUREON.

In patients with type 2 diabetes, BYDUREON did not affect the absorption of orally administered acetaminophen to any clinically relevant degree.

Warfarin

BYDUREON has not been studied with warfarin. However, in a drug interaction study, BYETTA did not have a significant effect on INR. There have been postmarketing reports for BYETTA of increased INR with concomitant use of warfarin, sometimes associated with bleeding. In patients taking warfarin, the INR should be monitored more frequently after initiating BYDUREON. Once a stable INR has been documented, the INR can be monitored at the intervals usually recommended for patients on warfarin.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of BYDUREON use in pregnant women. In rats, exenatide extended-release administered during the major period of organogenesis reduced fetal growth and produced skeletal ossification deficits in association with maternal effects; exenatide extended-release was not teratogenic in rats. In animal developmental studies, exenatide, the active ingredient of BYDUREON, caused cleft palate, irregular skeletal ossification and an increased number of neonatal deaths. BYDUREON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Fetuses from pregnant rats given subcutaneous doses of exenatide extended-release at 0.3, 1 or 3 mg/kg on gestation days 6, 9, 12 and 15 demonstrated reduced fetal growth at all doses and produced skeletal ossification deficits at 1 and 3 mg/kg in association with maternal effects (decreased food intake and decreased body weight gain). There was no evidence of malformations. Doses of 0.3, 1 and 3 mg/kg correspond to systemic exposures of 3, 7 and 17-times, respectively, the human exposure resulting from the recommended dose of 2 mg/week, based on area under the time-concentration curve (AUC).

Female mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day beginning 2 weeks prior to and throughout mating until gestation day 7, had no adverse fetal effects. At the maximal dose, 760 mcg/kg/day, systemic exposures were up to 148 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

In developmental toxicity studies, pregnant animals received exenatide, the active ingredient of BYDUREON, subcutaneously during organogenesis. Specifically, fetuses from pregnant rabbits given subcutaneous doses of exenatide at 0.2, 2, 22, 156, or 260 mcg/kg/day from gestation day 6 through 18 experienced irregular skeletal ossifications from exposures 4 times the human exposure resulting from the recommended dose of 2 mg/week, based on AUC. Fetuses from pregnant mice given subcutaneous doses of exenatide at 6, 68, 460, or 760 mcg/kg/day from gestation day 6 through 15 demonstrated reduced fetal and neonatal growth, cleft palate and skeletal effects at systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

Lactating mice given subcutaneous doses of exenatide, the active ingredient of BYDUREON, at 6, 68, or 760 mcg/kg/day from gestation day 6 through lactation day 20 (weaning), experienced an increased number of neonatal deaths. Deaths were observed on postpartum days 2-4 in dams given 6 mcg/kg/day, a systemic exposure that is equivalent to the human exposure resulting from the recommended dose of 2 mg/week, based on AUC.

Pregnancy Registry

Amylin Pharmaceuticals, Inc. maintains a Pregnancy Registry to monitor pregnancy outcomes of women exposed to exenatide during pregnancy. Physicians are encouraged to register patients by calling (800) 633-9081.

Nursing Mothers

Exenatide is present in the milk of lactating mice at concentrations less than or equal to 2.5% of the concentration in maternal plasma following subcutaneous dosing. It is not known whether exenatide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for exenatide extended-release in animal studies, a decision should be made whether to discontinue nursing or to discontinue BYDUREON, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of BYDUREON have not been established in pediatric patients. BYDUREON is not recommended for use in pediatric patients.

Geriatric Use

In the five comparator-controlled 24-30 week trials, BYDUREON was studied in 132 patients (16.6%) who were at least 65 years old and 20 patients who were at least 75 years old. No differences in safety (N = 152) and efficacy (N = 52) were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

In separate trials, BYETTA was studied in 282 patients at least 65 years old and in 16 patients at least 75 years old. No differences in safety and efficacy were observed between these patients and younger patients, but the small sample size for patients ≥75 years old limits conclusions.

Because elderly patients are more likely to have decreased renal function, use caution when initiating BYDUREON in the elderly.

Hepatic Impairment

No pharmacokinetic study has been performed in patients with a diagnosis of acute or chronic hepatic impairment. Because exenatide is cleared primarily by the kidney, hepatic impairment is not expected to affect blood concentrations of exenatide.

OVERDOSAGE

There were no reports of overdose in the five comparator-controlled 24-30 week trials of BYDUREON. Effects of overdoses with BYETTA in clinical studies included severe nausea, severe vomiting, and rapidly declining blood glucose concentrations, including severe hypoglycemia requiring parenteral glucose administration. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

Manufactured by Amylin Pharmaceuticals, Inc., San Diego, CA 92121
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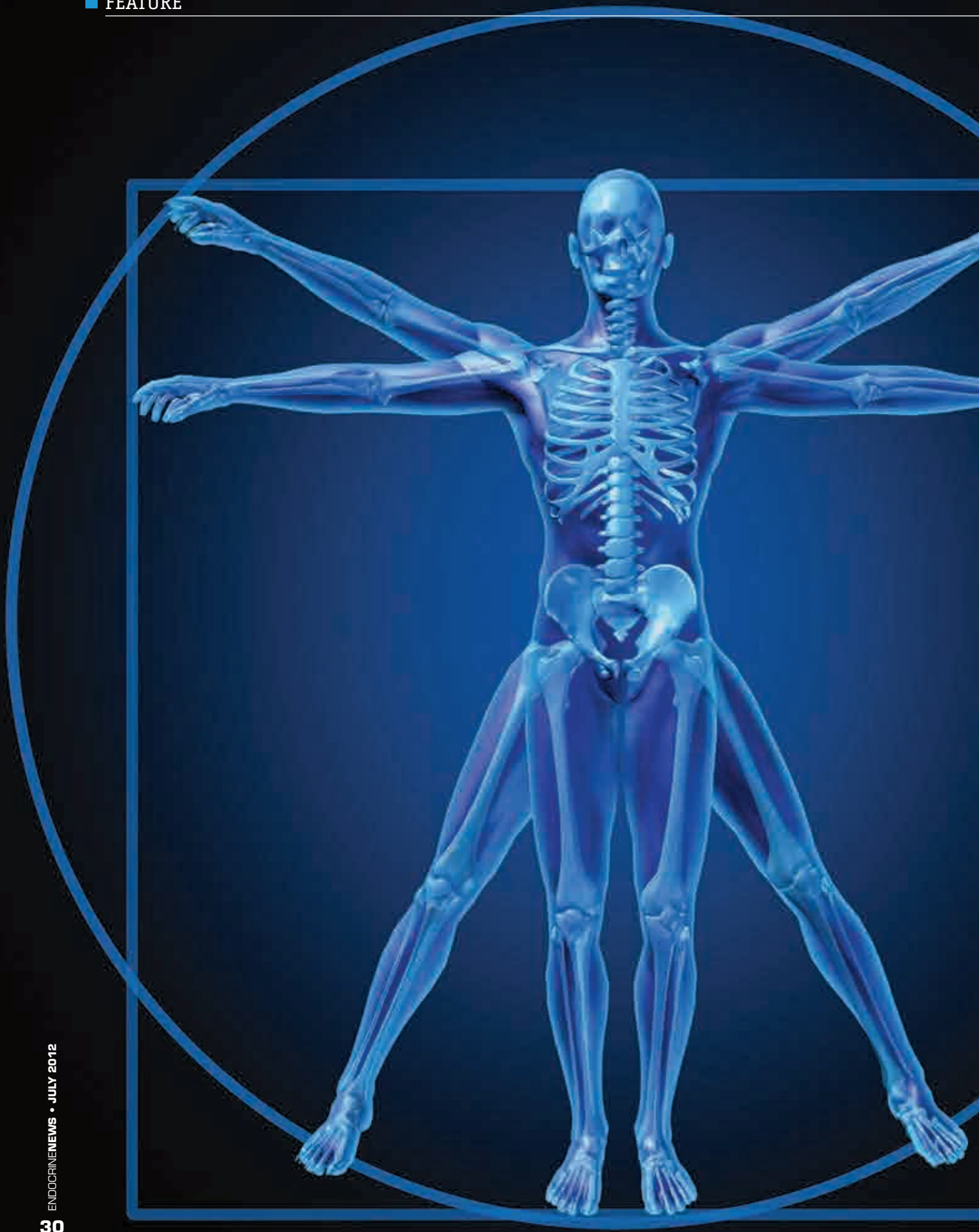


BREAKING NEWS: MEN at RISK for OSTEOPOROSIS

By Eric Seaborg

"What do you mean I should be tested for osteoporosis? Isn't that a woman's disease?!" your patient asks incredulously. But he really gets upset when you send him to the women's health center to get a bone scan.

This scenario could play out often in coming years if physicians heed a recommendation of a new Endocrine Society clinical guideline: All men age 70 and over should have a bone mineral density (BMD) test to check for osteoporosis.

Make no bones about it, osteoporosis is a serious problem for older men.

"Based on low bone density, there are about 10 million Americans with osteoporosis, and about 20 percent of those are men," said Nelson Watts, M.D., who chaired the guideline committee. Watts is director of Mercy Health Osteoporosis and Bone Health Services in Cincinnati. "Of the two million fractures each year due to osteoporosis, about 600,000 are in men."

Perhaps because their bone loss lacks the accelerator of menopause and their larger stature endows them with greater strength than women, men's bones typically become brittle a decade later than women's. The medical problems that increase with aging may also explain why mortality after a hip fracture is two to three times higher in men than in women.

The aging population, with more men living long enough to develop weakness in their bones, highlights the need for "Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline," which was published in the June issue of *The Journal of Clinical Endocrinology & Metabolism.*

In addition to those over 70, the guideline says that men age 50–69 should be tested if they have other risk factors, the most important of these being a history of

fracture after age 50. Additional reasons for testing men in this age range include diseases and conditions such as delayed puberty, hypogonadism, hyperparathyroidism, hyperthyroidism, chronic obstructive pulmonary disease, long-term use of synthetic hormones, and life choices such as alcohol abuse or smoking.

The preferred test is dual-energy x-ray absorptiometry (DXA) of the spine and hip, although in cases of men who have hyperparathyroidism or are receiving androgen-deprivation therapy (ADT) for prostate cancer, the guideline suggests measuring the forearm DXA. In both instances, the evidence indicates that the forearm is a better indicator of the patient's osteoporosis risk.

The guideline recommends that men being evaluated for osteoporosis receive a complete physical examination, including history. Laboratory tests should include serum calcium, phosphate, creatinine, alkaline phosphatase, liver function, 25-hydroxyvitamin D (25[OH]D), total testosterone, complete blood count, and 24-hour urinary calcium.

These lab results, the history, and physical examination may indicate the need for further testing, such as thyroid function tests, to home in on specific causes.

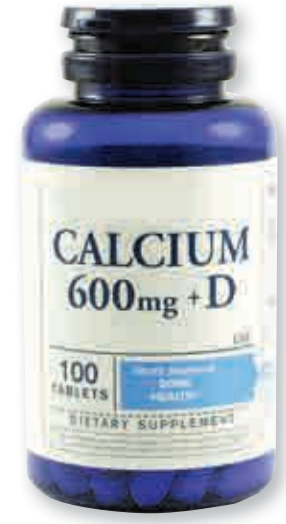
Who Needs Treatment

The question of which male patients should be treated with drugs is controversial among doctors and other experts. Because osteoporosis is widely seen as a woman's disease, women have been the focus of most of the studies, and there have been many large clinical trials using women to test the efficacy of various drugs in reducing fractures. In contrast, the studies in men have generally been small, with change in BMD as the primary end point, so "the experts have to shift the evidence for nuggets" in their approach to treating men, Watts said.

Complicating the treatment decision is that there is no single controlling indicator, such as a T-score. "In selecting men or women for treatment, the emphasis has moved from just looking at a T-score to including other clinical risk factors such as age, prior fracture history, family history of osteoporosis, glucocorticoid use, cigarette smoking, low body weight, and the FRAX tool or other fracture risk–assessment tools that allow us to objectively put those things together and make better treatment decisions," Watts said.

For example, a BMD T-score of –2.5 or less indicates a need for treatment but leaves out many men who might benefit from treatment because most men who suffer fractures have a T-score above this level. The guideline states that "FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk," but even these algorithms do not incorporate some of the known risk factors.

Given these caveats, the guideline recommends pharmacological treatment "for men age 50 or older who have had spine or hip fractures, those with T-scores of –2.5 or below, and men at high risk of fracture based on low bone mineral density and/or clinical risk factors."



The guideline recommends that therapeutic drugs should be chosen only from the list currently approved by U.S. and European regulatory agents for general use—alendronate, risedronate, zoledronic acid, and teriparatide. Denosumab is the only drug specifically indicated for use in men receiving ADT for nonmetastatic prostate cancer.

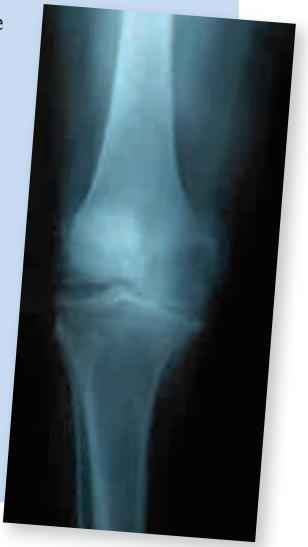
The drug selection can be individualized based on considerations such as fracture history, T-score, co-morbid conditions, and parts of the body at highest risk. Generic alendronate is generally the first choice because of its low cost and extensive track record. But men with upper or lower gastrointestinal problems may be better off with non-oral therapies, such as zoledronic acid and teriparatide. Some drugs appear to target certain areas. For example, men with a recent hip fracture may benefit from zoledronic acid.

Although some osteoporosis medications have received negative coverage in the lay press, in general they are well tolerated, safe with long-term use, and effective at reducing fracture risk, Watts said.

Healthy Choices, Healthy Bones

The first line of defense is, of course, a healthy lifestyle, and the guideline recommends several approaches that men with or at risk for osteoporosis should incorporate:

- A daily dietary calcium intake of 1000–1200 mg, with supplements added if dietary sources can't meet the target.
- Vitamin D supplements aimed at achieving agency-recommended vitamin D levels, preferably a 25(OH)D level of at least 30 ng/mL. This level is higher than the 20 ng/mL recommended by the Institute of Medicine guideline and in line with the target of The Endocrine Society's recent clinical guideline on vitamin D deficiency.
- Three to four sessions per week of weight-bearing activities for 30 to 40 minutes.
- Smoking cessation and a daily alcohol intake of less than three drinks a day.



The Role of Testosterone

Another controversial area in bone health concerns the role of testosterone. "Because testosterone and estradiol levels decline as men age, it has been suggested that this decline may be responsible, at least in part, for the decrease in BMD that occurs in aging men," the guideline notes. "Skeletal health may be compromised when serum testosterone levels fall below 200–250 ng/dL." For example, one study found that baseline testosterone levels below 200 ng/dL tripled the odds of having osteoporosis at the hip and rapid hip bone loss compared with levels above 200 ng/dL.

"Osteoporosis in men is a significant public health problem," Watts concluded. "It carries with it a potentially devastating, life-changing toll in patients who have fractures."

Managing hypogonadism and low BMD with a single agent is a possibility, and the guideline, therefore, recommends that some patients try testosterone therapy alone before going on a bone drug. Because the benefits and risks of testosterone therapy are not well established, the committee recommends using a "conservative level" of 200 mg/mL as the cut-off for intervention pending the availability of more data. For men with a borderline high risk for fracture, low testosterone, and symptoms of androgen deficiency or a known cause of androgen deficiency such as a pituitary disorder, the guideline suggests trying testosterone therapy three to six months to see if it alleviates the symptoms.

Testosterone therapy can also be tried in patients who have a high risk of fracture and low testosterone levels but contraindications for osteoporosis drugs. For patients already receiving testosterone therapy who are at high risk of fracture, the guideline suggests adding an agent with proven antifracture efficacy, such as bisphosphonate or teriparatide.

Monitor BMD with Scans

Once a patient is on a drug, the guideline suggests monitoring BMD by DXA at the spine and hip every year or two to assess the response to treatment. If the patient's BMD appears to reach a plateau, this frequency can be reduced. Physicians should also consider measuring a bone turnover marker three to six months after the start of treatment using a bone resorption marker for antiresorbtive therapy and a bone formation marker for anabolic therapy.

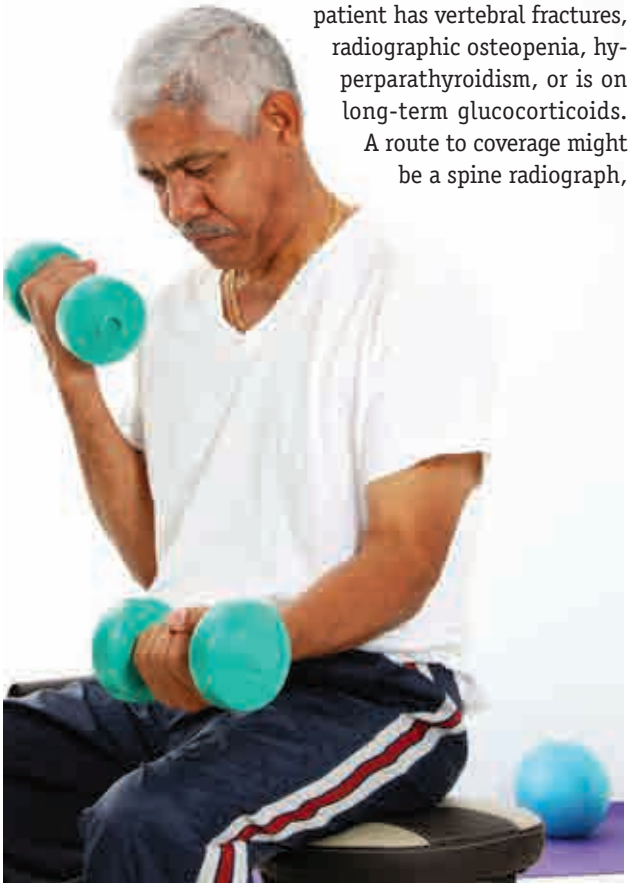
"There is uncertainty over what constitutes an adequate BMD response to treatment. Stable or increasing BMD appears to indicate a good response," the guideline states. The drugs increase BMD modestly. For example, one study found that two years of alendronate increased BMD of the spine by 7 percent and the femoral neck by 2.5 percent. That response at least reverses the trend of loss.

As with all Endocrine Society clinical guidelines, the committee included members with a wide range of expertise and experience. Their work included a meta-analysis of the literature and systematic discussions via email, telephone, and in-person meetings. The guideline was reviewed by Endocrine Society committees and members, and representatives of organizations such as the American Society for Bone and Mineral Research and the European Society of Endocrinology. The committee rated the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to give the reader an idea of the strength of a recommendation or suggestion.

Reimbursement Issues

Watts said that one source of resistance to implementation of the guideline could be men themselves, who may need to be convinced that this is not just a woman's disease.

But an even bigger obstacle could be insurance coverage, especially when it comes to the recommendation for 70-year-old men to get their BMD tested. Medicare generally covers BMD screening for women, but it covers an initial DXA in men only if the patient has vertebral fractures, radiographic osteopenia, hyperparathyroidism, or is on long-term glucocorticoids. A route to coverage might be a spine radiograph,



Candidates for Drug Therapy

- Men who have had a"fragility" hip or vertebral fracture, that is, one without major trauma.
- Men who have not experienced a spine or hip fracture but who have a T-score in the spine, femoral neck, or total hip below –2.5, using the young male reference range.
- Men who have a T-score between –1.0 and –2.5 should be evaluated using the FRAX risk calculator. In the United States, men with a 10-year fracture risk of 20 percent for any fracture or 3 percent for the hip should receive therapy.
- Men receiving high doses of long-term glucocorticoid therapy, such as prednisone at 7.5 mg/dL or higher.
- Hypogonadal men at high risk of fracture.
- Men with prostate cancer receiving ADT who have a high risk of fracture.

and if that test shows osteopenia or a vertebral fracture, a subsequent DXA would be covered by Medicare.

As more men live long enough for their bones to deteriorate—from 30 to 40 percent of fractures due to osteoporosis occur in men already—the importance of having older men tested routinely could become more apparent. "Osteoporosis in men is a significant public health problem," Watts concluded. "It carries with it a potentially devastating, life-changing toll in patients who have fractures. We now have a pretty good sense of men who are at sufficiently high risk to warrant bone density testing, and we have a number of therapeutic agents that are available to reduce fracture risk."

The only thing left is for physicians to teach their male patients that osteoporosis is an equal opportunity disease. ■

Seaborg is a freelance writer in Charlottesville, Virginia.

ENO LINKS For additional links related to this feature, please visit *Endocrine News Online* at *www.endo-society.org/endo_news*.

RESEARCH BRIEFS

➤ The following studies will be published in Endocrine Society journals. Before print, they are edited and posted online in each journal's Early Release section. You can access the journals via *www.endo-society.org*.

Endocrinology

➤ **Synthetic progestins already used for contraception may promote recovery after a stroke.**
Liu A, Margaill I, Zhang S, et al. *Progesterone receptors: A key for neuroprotection in experimental stroke.*

➤ **Resveratrol regulates steroidogenesis by deacetylating and activating mitochondrial P450s via SIRT proteins.**
Li D, Dammer EB, Sewer MB. *Resveratrol stimulates cortisol biosynthesis by activating SIRT-dependent deacetylation of P450scc.*

➤ **Orexin A inhibits firing frequency of GnRH neurons in ovariectomized mice by suppressing spike initiation and burst maintenance.**
Gaskins GT, Moenter SM. *Orexin A suppresses gonadotropin-releasing hormone (GnRH) neuron activity in the mouse.*

➤ **Lowered plasma FFA levels activates the HPA axis to increase adrenocorticoptropic hormone and corticosterone, which help restore these levels to normal.**
Oh YT, Oh K-S, Kang I, Youn JH. *A fall in plasma free fatty acid (FFA) level activates the hypothalamic-pituitary-adrenal axis independent of plasma glucose: Evidence for brain sensing of circulating FFA.*

The Journal of Clinical Endocrinology & Metabolism

➤ **Patients with serum 25(OH)D levels less than 50 nmol/L are at increased risk for mortality.**
Saliba W, Barnett O, Rennert HS, Rennert G. *The risk of all-cause mortality is inversely related to serum 25(OH)D levels.*

➤ **Compared to normal premenopausal women, premenopausal women with IOP or idiopathic low bone mineral density have greater marrow adiposity.**
Cohen A, Dempster DW, Stein EM, et al. *Increased marrow adiposity in premenopausal women with idiopathic osteoporosis.*

➤ **"Conditional HD:SDS" is an appropriate proxy marker for pubertal timing in males.**
Ong KK, Bann D, Wills AK, et al. *Timing of voice breaking in males is associated with growth and weight gain across the life course.*

➤ **High E2 and high-sensitive C-reactive protein levels are associated with frailty in postmenopausal women not taking hormonal therapy.**
Carcaillon L, Garcia-García FJ, Tresguerres JAF, Gutierrez Avila G, Kireev R, Rodriguez-Mañas L. *Higher levels of endogenous estradiol are associated with frailty in postmenopausal women from the Toledo Study for Healthy Aging.*

Molecular Endocrinology

➤ **CNP secreted by growing ovarian follicles is capable of stimulating preantral and antral follicle growth and could one day be used to avoid ovarian hyper-stimulation syndrome.**
Sato Y, Cheng Y, Kawamura K, Takae S, Hsueh AJW. *C-type natriuretic peptide stimulates ovarian follicle development.*

➤ **Oxytocin maintains the undifferentiated state of mouse ESCs via the gap junction protein connexin43 and NF-κB/CREB1/CBP signaling.**
Yun SP, Park SS, Ryu JM, et al. *Oxytocin stimulates connexin43 expression through NF-κB/CREB1/CBP complex via lipid-raft-independent oxytocin receptor-mediated cAMP/PKA in mouse embryonic stem cells.*

➤ **Genomic studies indicate 121 potential direct target genes for the pituitary transcription factor POU1F1.**
Herman J-P, Jullien N, Guillen S, Enjalbert A, Pellegrini I, Franc J-L. *Research resource: A genome-wide study identifies potential new target genes for POU1F1.*

➤ **SST/SSTR5 signaling is linked to PDX-1, a β-cell–specific transcription factor essential for insulin expression/secretion and cell proliferation.**
Zhou G, Liu S-H, Shahi KM, et al. *Negative regulation of pancreatic and duodenal homeobox-1 by somatostatin receptor subtype 5.*

Hormones and Cancer

➤ **Insulin use in diabetes patients is linked to an increased risk of overall, pancreatic, and colorectal cancer.**
Janghorbani M, Dehghani M, Salehi-Marzijarani M. *Systematic review and meta-analysis of insulin therapy and risk of cancer.*

➤ **Apigenin, a low molecular weight anti-carcinogenic flavonoid found in fruits, vegetables, nuts, and plant-derived beverages, inhibits the proliferation of aggressive Her2/neu-positive BT-474 xenograft tumors in nude mice exposed to MPA, a commonly used progestin in the United States.**
Mafuvadze B, Liang Y, Besch-Williford C, Zhang X, Hyder SM. *Apigenin induces apoptosis and blocks growth of medroxyprogesterone acetate-dependent BT-474 xenograft tumors.* ■

The Society Lobbies Congress to Fix Pay Discrepancies

By Meredith Dyer

In the last year, The Endocrine Society has advocated diligently on Capitol Hill for improved payments for endocrinologists. Halting potential payment cuts resulting from the Sustainable Growth Rate (SGR) and the expiration of a fee-fix for dual-energy X-ray absorptiometry (DXA) tests have been a key focus in these efforts.

Repealing the Flawed SGR

Congressional delay in repealing the Sustainable Growth Rate (SGR) formula, a methodology originally intended to control the growth of Medicare fees for physician services, creates cliffhanger anxiety among doctors year after year. Although legislators were able to agree on a temporary fix in February to avert a 27.4 percent payment cut, doctors may now face a 35 percent reduction come January 2013. The Society has been an advocate for the permanent repeal of SGR a formula that results in dramatically reduced Medicare reimbursements to doctors. The Society recommends replacing the flawed formula with five years of stable payments to allow for the testing of new payment models. In addition to a fee-for-service system, physicians should have the option of being reimbursed through a menu of payment models. With that goal in sight, the Society's Clinical Affairs Core Committee has met with payment experts to help identify which model could be most beneficial to endocrinologists.

In anticipation of the 2013 expiration of the temporary SGR fix, Congress has been evaluating payment options that could replace the impaired system while addressing current workforce shortages that have impeded patient access to care. Congress has used incentive payments in the last several years, but the bonus payment plans stipulate that a physician must be one of several specialty designations (such as an internist, geriatrist, or pediatrician) and bill at least 60 percent primary care services. Cognitive specialists, such as endocrinologists or rheumatologists, however, have been excluded from the bonuses, even though they provide a significant amount of primary care services and face many of the same hurdles as primary care in attracting medical students. The Society has been actively lobbying legislators and regulators to address this discrepancy.

Establishing New Payment Plans

On May 9, 2012, Representatives Allyson Schwartz (D-PA) and Joe Heck (R-NV) introduced the Medicare Physician Payment Innovation Act that would eliminate the SGR and establish the framework for new payment models. A provision included in the legislation would implement temporary, four-year differential updates to payments for physician services. For years 2014 to 2017, the bill provides an annual increase of 2.5 percent to physicians who bill at least 60 percent of Medicare allowable charges for primary care, preventive care, and care coordination services, while all other physicians receive a 0.5 percent update. The differential increases are designed to address the undervaluation of primary and preventive care and care coordination services.

The Society has endorsed the legislation and will work with Rep-

resentatives Schwartz and Heck to build support in the House of Representatives. The Society will continue to remain active in the Cognitive Specialties Coalition, which works to bring awareness of the importance of and value that cognitive specialists bring to the care of their patients. To that end, the Society and coalition members have met with more than 200 congressional offices to discuss these issues and will continue to work to ensure improved payments for the cognitive specialties.

Payments for Bone Scans

On March 1, 2012, payments for DXA services in a physician's office dropped nearly 50 percent due to the expiration of an Affordable Care Act provision that had bolstered rates for these services for two years. The Society has been actively lobbying Congress to pass the Preservation of Access to Osteoporosis Testing for Medicare Beneficiaries Act of 2011, which would improve payments for these services. The bill, which is sponsored by Representatives Michael Burgess (R-TX) and Shelley Berkley (D-NV) and Senators Olympia Snowe (R-ME) and Debbie Stabenow (D-MI), would set DXA rates at 70 percent of the 2006 level (approximately $98) for an additional two years.

On March 1, 2012, payments for DXA services in a physician's office dropped nearly 50 percent due to the expiration of an Affordable Care Act provision that had bolstered rates for these services for two years.

During the debate on the Middle Class Tax Relief and Job Creation Act of 2012, Capitol Hill supporters attempted to include the DXA provision. The Society mobilized key grassroots members and initiated a letter-writing campaign, and the DXA Coalition also rallied support. Despite the massive effort, the osteoporosis bill was excluded from the legislation.

The Endocrine Society, along with the members of the DXA coalition, will continue to work with Congressional sponsors to identify a legislative route for a solution to the payment decreases while addressing concerns of a lack of data regarding the impact of the cuts. ■

Dyer is the manager of health policy at The Endocrine Society.

Rx for Reducing Health Disparities in Type 2 Diabetes

By Melissa Mapes

Over the past 30 years, the U.S. population living in poverty has become increasingly obese while wealthier income brackets have maintained lower body mass indexes (BMIs). This trend is a reversal of the global correlation of BMI and income. Why are the poor seemingly overfed in America and starving elsewhere? An excess of food may be preferable to a shortage, but the social issues behind this and other health disparities provide some of the most challenging obstacles in medicine today. Physicians, researchers, and politicians are working together on innovative interventions to overcome these barriers to health.

No drug can cure a lack of health care access and nutritious foods. It is easy to point out the basic causes of increasing rates of type 2 diabetes and obesity—poor diet and little to no exercise—but recommending a higher dosage of physical activity and vegetables is often inadequate. The actions required to reverse these trends should target social systems rather than focusing solely on the individual.

Changes must also occur in the household, such as limiting television time, Garg said. "Part of it is the school's responsibility, but part is the parents' responsibility too."

Abhimanyu Garg, M.D., professor of internal medicine and chief of the Division of Nutrition and Metabolic Diseases, University of Texas Southwestern Medical Center, Dallas, who recently led a symposium on "Reasons for Increased Diabetes Risk in Southeast Asians" at **ENDO 2012,** suggested a multi-level approach that begins with education: "We have to reduce risk by lifestyle intervention, and we have to introduce the intervention early in life." He emphasized the importance of healthy meals and beverages in schools, in addition to including physical activity in the curriculum. Changes must also occur in the household, such as limiting television time, Garg said. "Part of it is the school's responsibility, but part is the parents' responsibility too."

Good Policy vs. Bad Policy

Responsibility also falls on the shoulders of policy makers. Good policy, such as bicycle lanes, can drive positive changes in health disparities, whereas bad policy, like the subsidization of high fructose corn syrup, may exacerbate the issue. Garg described the planning of new communities as one potential way to reduce the disparity of obesity and type 2 diabetes among varying populations. By designing cities and residential areas that are conducive to walking, people may naturally increase their daily activity. "Not jogging or running for exercise," he said, "but walking, like to the grocery store." Some European cities are providing free bicycles, Garg said, as a way increase citizen health, decrease traffic congestion, and reduce greenhouse gas emissions from vehicles.

Sherita Hill Golden, M.D., M.H.S., associate professor in the Division of Endocrinology and Metabolism, core faculty in the Johns Hopkins Center to Eliminate Cardiovascular Health Disparities, and Chairperson of the Writing Group for The Endocrine Society's ***Scientific Statement on Health Disparities in Endocrine Disorders,*** agreed that infrastructure influences health disparities. Many urban environments promote obesity because they lack access to bike paths, walking and play areas, and stores that sell healthy foods.

Urban design is an important factor in closing the gap, and like Garg, she said change can be achieved on several levels. "Health care can implement disparity interventions at one or more levels of

FACT SHEET

Hormone Health NETWORK
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Diabetic Neuropathy

WHAT IS DIABETIC NEUROPATHY?

Diabetic neuropathy is nerve damage from high blood glucose (sugar) levels in people with diabetes. Nerves throughout the body can suffer damage. People with poor glucose control and who have had diabetes for a long time are at highest risk for nerve damage.

DID YOU KNOW?

About 60 to 70 percent of people who have had diabetes for many years have some form of nerve damage, but not everyone has symptoms.

WHAT ARE THE TYPES AND SYMPTOMS OF DIABETIC NEUROPATHY?

The most common types of diabetic neuropathy are those that affect the limbs and those that affect organs and muscles inside the body.

The first type (called distal polyneuropathy or DPN) affects the sensitivity of your feet, legs, hands, and arms. It also can affect the movement of your limbs. Symptoms of DPN include

- Pain, tingling, and burning
- Numbness and loss of feeling
- Muscle weakness
- Skin ulcers (open sores)

About half of people who have DPN might not have symptoms, except for losing feeling in their feet. Because of this feeling loss, they could injure their feet and not know it. Untreated foot injuries can lead to ulcers and infection and, sometimes, amputation.

The second type (called autonomic neuropathy) affects your urinary tract, digestive system, sex organs, sweat glands, eyes, and heart. Symptoms of autonomic neuropathy include

- Bladder problems (loss of bladder control, not being able to fully empty the bladder, frequent urinary tract infections)
- Digestive system problems (bloating, nausea, vomiting, diarrhea, constipation)
- Erectile dysfunction in men and sexual problems in women
- Too much or too little sweating
- Dizziness when you stand up

HOW IS DIABETIC NEUROPATHY DIAGNOSED?

Your doctor will do a physical exam and ask about your symptoms. You should be checked once a year for DPN, or more often if you have foot problems. The doctor will check for loss of feeling in your feet by seeing whether you can feel light touch, pinpricks, and vibrations from a tuning fork. You might have tests to see how well your nerves are working. Your doctor will also make sure you don't have other conditions, such as blood flow problems or a vitamin deficiency.

WHEN TO SEE YOUR DOCTOR

See your doctor as soon as possible if you have

- Frequent numbness or pain in your feet, legs, hands, or arms
- An ulcer (sore) on your foot or leg that isn't healing
- A foot or leg infection
- Digestive problems
- Problems with urination or sexual function
- Dizziness when you stand

WHAT TREATMENTS ARE AVAILABLE FOR DIABETIC NEUROPATHY?

Good blood glucose control (keeping blood glucose from being too high or too low) may prevent further nerve damage but usually can't reverse damage that's already happened. Your doctor may prescribe medicines for pain that occurs with some types of nerve damage, and suggest certain vitamins if needed.

HOW CAN YOU PREVENT PROBLEMS FROM DIABETIC NEUROPATHY?

The best way to prevent damage is to keep your blood glucose level under good control. You can do so by eating a healthy diet, exercising regularly, and reaching a healthy weight. Avoiding smoking and limiting alcoholic beverages can also help. Your doctor or diabetes educator can help you plan your healthy lifestyle.

You also can do a lot to prevent leg ulcers and amputations. Protect your feet by

- Checking them every day
- Always wearing shoes (or slippers) and clean, dry socks
- Choosing shoes that are comfortable and fit well
- Seeing a podiatrist (foot doctor) for foot care if you need help

TIPS FOR GOOD FOOT CARE

Wash and dry your feet and check them **every day**.

- Look for blisters, calluses, bruises, redness, swelling, cracked skin, sores, or cuts
- Cut your nails once a week or as needed.
- Put lotion on dry skin but not between your toes.

Questions to ask your doctor

- **Do I have nerve damage from diabetes?**
- **What kind of nerve damage do I have?**
- **Is the nerve damage permanent or temporary?**
- **Do I need treatment for my nerve damage?**
- **Should I see a podiatrist?**
- **Should I see a diabetes educator?**

RESOURCES

- Find-an-Endocrinologist: *www.hormone.org* or call *1-800-HORMONE (1-800-467-6663)*
- Find a diabetes educator (American Association of Diabetes Educators): *www.diabeteseducator.org/DiabetesEducation/Find.html*
- Find a podiatrist (American Podiatric Medical Association): *http://iweb.apma.org/buyersguide/professionalsearch.aspx*
- Hormone Health Network diabetes information: *www.hormone.org/diabetes*
- National Diabetes Information Clearinghouse (National Institutes of Health-NIH):
  — *http://diabetes.niddk.nih.gov/dm/pubs/neuropathies*
  — *http://diabetes.niddk.nih.gov/dm/pubs/complications_nerves/index.aspx*
- National Diabetes Education Program (NIH): *http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=67&redirect=true*
- MedlinePlus (NIH): *www.nlm.nih.gov/medlineplus/diabeticnerveproblems.html*
- The American Diabetes Association: *www.diabetes.org/living-with-diabetes/complications/neuropathy/*
- Mayo Clinic: *www.mayoclinic.com/health/diabetic-neuropathy/DS01045*

EDITORS

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May 2012

The Hormone Health Network offers free, online resources based on the most advanced clinical and scientific knowledge from The Endocrine Society (*www.endo-society.org*). The Network's goal is to move patients from educated to engaged, from informed to active partners in their health care. This fact sheet is also available in Spanish at *www.hormone.org/Spanish*.

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influence: patients, providers, microsystems, health care organization, community, and policy." She recommended a review conducted by the Robert Wood Johnson Foundation Diabetes Initiative as a resource to learn more about the different techniques for reducing health disparities. Successful strategies include sensitivity to cultural differences and involving family and community.

Poverty a Marker of Diabetes

Although much discussion of diabetes and obesity incidence has revolved around ethnicity, evidence indicates that these issues are more than skin deep.

"Socioeconomic status is an indicator of diabetes independent of race," Golden said.

Though cultural factors like language barriers can lead to health disparities, race correlations within type 2 diabetes and obesity appear to be more incidental than causal. Studies show that although some groups may be predisposed to metabolic diseases such as diabetes, poverty is likely to be a stronger driver than genetics, Garg noted. "What we have learned so far from the genome-wide association studies is that the genetic variants that cause susceptibility to diabetes among white Europeans are the same in Asian Indians."

So how can providers diminish these disparities? The complex social issues at play can make treatment difficult, but there are instruments available that may help. Telemedicine can be a useful option. Studies have shown that patients respond well to remote care through the Internet and other mobile technologies. Such software can remind patients to take medication, get daily exercise, track glucose levels, and answer questions about food choices. Cheap, effective tools like the American Diabetes Association's *MyFoodAdvisor* and the Hormone Health Network's *Patient Resources* are one route to help level the health care playing field. By encouraging patients to take advantage of such resources and becoming involved in policy decisions, providers can help close these prevalent health gaps. ■

Mapes is a freelance writer in Washington, D.C.

ENDOCRINE Society update

Vitamin D Story Wins Society Journalism Award

The winner of The Endocrine Society's 2012 Award for Excellence in Science and Medical Journalism is biomedical writer Nathan Seppa for his article in *Science News* magazine, "The Power of D." Society President Janet Hall presented the award to Seppa at **ENDO 2012**.

The benefits of vitamin D from the sun for healthy bones are well known, and recently researchers are discovering that vitamin D might also be advantageous against other conditions such as cancer, hypertension, and diabetes. Yet these new findings face the same opposition that connecting smoking to cancer once did—the lack of evidence from randomized controlled trials. As such, scientists and doctors are at odds on the daily doses to recommend to their patients. Seppa's article chronicles the latest studies in the vitamin D field and the discord between the recommendations of the Institute of Medicine and those of The Endocrine Society. The winning article appeared in the July 16, 2011, issue of *Science News,* and is available at *www.sciencenews.org/view/feature/id/332009/title/The_power_of_D_*.

This annual award includes travel and hotel expenses to ENDO and a plaque. Established in 2008, it recognizes outstanding reporting that enhances public understanding of health issues pertaining to endocrinology. It is also intended to promote greater Society visibility among medical and science writers and to foster media relationships.

Find out more information about the award at *www.endo-society.org/media/Journalism-Award Requirements.cfm*.

Healthy Cooking Demo Is Now Online

If you missed The Hormone Health Network's three-day program series at **ENDO 2012,** visit *www.hormone.org* for a virtual tour of *Cooking for Pleasure, Healthy for Life*. The Web site features videos of patient panel discussions, moderated by Hormone Health Network Chair Bradley D. Anawalt, and live cooking demonstrations by awarding-winning chefs Amy Riolo and Norene Gilletz. View and download free patient education resources from the event, including therapeutic area-focused recipe booklets, diet tip recommendations, and a portion placemat.

2012 Trainee Awards Winners

This year The Endocrine Society provided over $500,000 in funding to support more than 450 award winners. The wide range of awards recognizes young endocrinologists who have demonstrated exceptional accomplishments in endocrinology. Many awards supported travel to **ENDO 2012,** allowing young scientists to present their research at the meeting. Additional awards will support research training and fellowships for the next generation of leaders in endocrinology.

Check out the Society's Awards & Grants Web page to access the complete list of the 2012 trainee award winners, *www.endo-society.org/awards/index.cfm,* and get a jump on preparing yourself for the 2013 awards season.

Society Honored For Online Programs

Two of The Endocrine Society's online educational programs were winners of the 14th Annual Web Health Awards announced in May. The iPhone app *Diagnosis and Treatment of Male Hypogonadism* won a silver award in the category of Mobile Application: Medical Education/Small Mobile Device. The Society's online resource for primary care physicians, *Betacellsindiabetes.org* also won a bronze award in the category of Web-Based Research/Tool.

The goal of the Web Health Awards is to recognize high-quality electronic health information. The awards program is organized by the Health Information Resource Center (HIRC), a national clearinghouse for professionals who work in consumer health fields. A panel of judges selected winners from 542 entries this year.

Hormone Health Network Launches Menopause Web Site

A new Web site is designed to help the thousands of menopausal women suffering hot flushes, night sweats, mood swings, and other symptoms. With all the confusion surrounding hormone therapy, women often suffer in silence rather than discuss other options with their doctors. To help clarify some of the problems and remedies associated with menopause, the Hormone Health Network recently released the "Menopause Map," a Web-based tool to facilitate the conversation between women and their doctors about the choices available to them when they reach menopause. Patients can go online to *www.hormone.org/MenopauseMap* and answer a series of questions about their personal health history and menopausal symptoms. The tool will then calculate their personal risks of developing breast cancer and heart disease should they decide to undergo hormone or non-hormonal therapy. Additionally, the Web site provides a list of focused questions that women can raise with their doctors.

An accompanying survey conducted by the Hormone Health Network of 810 women age 45–60 years reveals that 7 out of 10 women suffering from menopausal symptoms are not treated. Other findings show that nearly half of all women have a negative impression of hormone therapy. More Caucasian women than African American and Latinas talked to their health care provider about hormone therapy, non-hormonal options, or lifestyle changes.

The Web site is also available in Spanish.

Update Your Member Profile

Guarantee that you receive the latest news about opportunities to present research, new Clinical Practice Guidelines, new Scientific Statements, and more, when you update your member profile online.

Go to *www.Endo-Society.org/Profile* and login with your Member ID and password. Review the information we have on file for you and make changes where necessary.

If you have any questions, please contact Society Services at *SocietyServices@endo-society.org* or via phone at +1-301-941-0210 (toll-free in the U.S. at 1-888-363-6762), Monday-Friday, 8:30 a.m. – 5:00 p.m. ET.

Building a Better ENDO

The Endocrine Society is already planning **ENDO 2013**. If you have any suggestions for sessions that you'd like included or ways to improve the conference, please submit these at *www.call4abstracts.com/endo_suggest*. Your ideas make a difference. For instance, in 2009, the landmark forum on the emerging field of endocrine-disrupting chemicals that brought together regulators, policy makers, and researchers, and placed the Society in the forefront of this field, came about from a member's suggestion.

Legacy Archives at Your Fingertips

The Endocrine Legacy archive is a compilation of nearly a century of developments and groundbreaking achievements in endocrinology and is free to all Society members. The online source includes past issues of our four seminal Society journals from 1917–1996: ***The Journal of Clinical Endocrinology & Metabolism, Molecular Endocrinology, Endocrinology,*** and ***Endocrine Reviews.***

For more information on this essential member benefit, visit *www.endo-society.org/legacy*. ■

SMART MOVES

developments in the endocrinology world

Dick Allen, M.B.A., became the chairman of the board for the Juvenile Diabetes Research Foundation International Inc. Allen has a 40-year career in the health care industry, including positions as an operating executive and a capital investor. As a grandparent of a child with type 1 diabetes, he has also been involved with the JDRFI for more than 10 years on both the local and international levels. Allen will replace Frank Ingrassia, president and chief executive officer of Clever Devices, Ltd.

*** Tracy L. Bale, Ph.D.,** received the 2012 Society for Women's Health Research Medtronic Prize for Scientific Contributions to Women's Health. An associate professor of neuroscience at the University of Pennsylvania's School of Veterinary Medicine's Department of Animal Biology and in the Perelman School of Medicine's Department of Psychiatry, Bale's research focuses on how and why certain individuals are predisposed to developing neuropsychiatric diseases such as autism and affective and eating disorders.

Gary Hall, Jr., an Olympic swimmer and patient with type 1 diabetes, has been elected to the U.S. Olympic Hall of Fame. The 37-year-old professional swimmer has won 10 Olympic medals, including five gold medals three silver medals, and two bronze medals.

Franmarie Kennedy, Joan M. Lappe, Ph.D., R.N., F.A.A.N., C. Berdon Lawrence, Meryl S. LeBoff, M.D., * and **C. Michael Lewiecki, M.D., F.A.C.P., F.A.C.E., F.A.C.P.,** joined the National Osteoporosis Foundation's Board of Trustees.

Mingyu Liang, Ph.D., was honored with the American Physiological Society's 2012 Henry Pickering Bowditch Lecture Award for his "novel and exceptional work on the mechanisms behind hypertension and kidney disease." A physiology professor at the Medical College of Wisconsin in Milwaukee, Dr. Liang's laboratory focuses on the cellular metabolism of hypertension and tissue disease, incorporating both microRNAs and stem cells into the work. The award is one of the highest offered by the society and is given to scientists younger than 42 years of age whose accomplishments are original and outstanding.

** Member of The Endocrine Society*

Share Your News
If you or others you know change jobs, receive a promotion, are granted an award, or otherwise make endocrinology-related career news, please don't hesitate to let us know at *endocrinenews@endo-society.org*.

calendar

AUG 8-9: SANTA FE, NEW MEXICO
The 10th Annual Osteoporosis Update conference.
www.endo-society.org/meetings/symposia/osteoupdate.cfm

SEPT 11–15: MIAMI, FLORIDA.
Endocrine Board Review and Clinical Endocrinology Update.
www.endo-society.org/ceu.

SEPT 19–23: QUEBEC CITY, CANADA
American Thyroid Association
82st Annual Meeting.
www.thyroid.org/ann_mtg/index.html

SEPT 20–24: SAN ANTONIO, TEXAS
The Obesity Society's 30th Annual Scientific Meeting.
www.obesity.org/meetings-and-events/annual-meeting.htm

OCT 13–17: NEW ORLEANS, LOUISIANA
Society for Neuroscience 42nd Annual Meeting.
www.sfn.org/am2012

OCT 17–19: PHILADELPHIA, PENNSYLVANIA
American Academy of Family Physicians (AAFP).
www.aafp.org/online/en/home/cme/aafpcourses/conferences/assembly.html

DEC 15–19: SAN FRANCISCO, CALIFORNIA
American Society for Cell Biology Annual Meeting.
www.ascb.org/meetings

See more events at *www.endosociety.org*, on the **Worldwide Endocrine Events Calendar.**

In Memoriam

Angelika Bierhaus, Ph.D.
Heidelberg, Germany
1962–2012

J. Harold Brown, M.D.
Seattle, Washington
1934–2012

Thomas G. Dunn, Ph.D.
Laramie, Wyoming
1935–2012

Classifieds

If you are interested in submitting classified advertising to **Endocrine News**, *please contact Christine Whorton at* endocareers@endo-society.org *or 800-361-3906.*

Attractive Pediatric Endocrinology Position in the Midwest — Toledo, Ohio

Endocrine and Diabetes Care Center (EDCC), located in Toledo, Ohio, is recruiting a BC/BE Pediatric Endocrinologist. EDCC is the premier Endocrine group in the region of northwest Ohio and southeast Michigan that has been experiencing nonstop growth. This enables a new physician to rapidly build a successful practice in the community. EDCC is comprised of seven endocrinologists: five adult and two pediatric specialists. Due to future retirement, EDCC is seeking a Pediatric Endocrinologist. Advantages: the first comprehensive diabetes and endocrine care center in northwest Ohio; the only care center in northwest Ohio that provides complete care for both adults and children; a comprehensive diagnostic, treatment, education, and support center for metabolic bone health and patients with diabetes, endocrine-related disorders, and thyroid disease; an American Diabetes Association (ADA)–recognized provider since 2000; large referral base—27 counties throughout northwest Ohio and southeast Michigan (population base of 1.8 million); affiliated with ProMedica Health System, ranked the nation's top most integrated health system; competitive compensation, signing bonus, and excellent benefits package; and assistance with relocation. Please visit: *www.edcc.net and www.promedica.org/doctors.* For more information, please contact: Denise Johnston, In-House, Physician Recruiter, ProMedica Health System, Toll Free: 800-427-2755; Office: 419-824-7445; Email: *denise.johnston@promedica.org.*

Academic Endocrinologist/ Diabetologist

The University of Nebraska Medical Center (UNMC) is seeking a BC/BE Endocrinologist to be a Clinician Educator. Duties to include inpatient and outpatient care, supervision of fellows, residents, and students. Full-time position with rank and salary dependent upon qualifications. Campus includes a Diabetes Center, NIH-funded Cancer Research Center, and a Clinical Research Center. Send CV to email: *Christine.nystrom@unmc.edu,* phone 402-559-6276. Individuals from diverse backgrounds are encouraged to apply.

Medical Director Clinical Trials

Diabetes/endocrinology openings for remote employees, and in NC and MA. Join an industry leader where you will provide medical leadership and guidance/consulting to assist in the development of new drugs. Provide medical and scientific support to manage clinical trials, assess medical drug safety, and act as the physician lead on projects. PAREXEL International—apply at: *www.parexel.com.*

Endocrinologist Needed in Growing Philadelphia Suburb

Gateway Medical Endocrinology Associates is seeking a

Classifieds Cont.

BC/BE Endocrinologist to join well-established group. Join three endocrinologists, one diabetologist, two nurse practitioners, and a diabetes educator. This respected practice is located in West Chester PA, an outstanding place to live and work. Allscripts EMR. Competitive Salary! Email CV to *mdyson@gatewaydoctors.com.*

Florida

Join an Endocrinologist in a busy practice. Walk into an existing patient base. Compensation is upwards of $230,000 with an inclusive benefits package. Light phone call only. Located in Tampa, one of the cleanest cities in the USA! Gorgeous area provides all of the shopping and entertainment you could ask for. Contact Angela Albright, Alpha Medical Group, 800-584-5001, *aalbright@alphamg.org.* Visit *www.alphamg.org.*

New Jersey

Endocrinologist to join a hospital-supported practice. 100 percent Endocrinology—minimal call. Spanish language skills a plus. Complete financial package with excellent benefits. Desirable locale just outside of Manhattan; perfect for commuting spouses. Choose from numerous fine suburban communities or live in NYC. Contact Angela Albright, Alpha Medical Group, 800-584-5001, *aalbright@alphamg.org.* Visit *www.alphamg.org.*

California Endocrinologist

St. Jude Heritage Medical Group, a premier multi-specialty practice of 170 physicians in Fullerton, California, seeks well-trained Endocrinologist to join busy department of four. Fully integrated with St. Jude Med Center, group is ranked amongst the best in Southern California. Opportunity includes generous compensation structure and comprehensive benefit package. Candidates submit CV to Paul Martyr- Director Physician Services at *paul.martyr@stjoe.org.*

Pennsylvania Endocrinologist

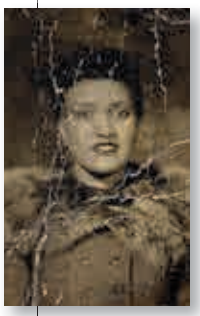
Well-respected endocrinology group with offices in upscale suburban Philadelphia seeks BE/BC endocrinologist for their successful practice. The group has two office locations and one of the offices will be expanding. The group is involved in both inpatient and outpatient care, and the patient mix is heavily weighted toward diabetes and thyroid management. The practice has approximately 50–60 new patients weekly. A nurse educator is being added to the practice in the near future. Call will be l:5. Local residents in training rotate through the practice. The group is employed by a local hospital which will be moving to a new facility in October of this year. The offices are very near to the new facility. A competitive compensation package will be available to appropriate candidates along with excellent benefits. For further information please contact Malinda D. Hale, CMSR, President, Physician Options, Inc., 800-208-6088, *malinda@VONL.com.*

Endocrinologist—North of Boston

Hallmark Health, a Joslin Diabetes Center Affiliate, seeks BC Endocrinologist for clinical outpatient practice. 1–3 years experience and MA professional preferred. Competitive comp and benefits package. Please contact Gina Mariona, 781-338-7517 or *gmariona@hallmarkhealth.org.* ■

HeLa Cells: 'Spreading like Crabgrass'

By Marian Smith Holmes

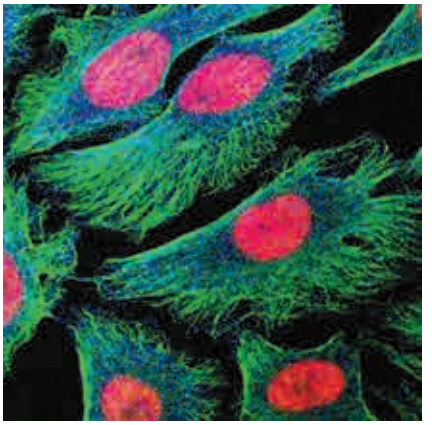


In February 1951, in the Johns Hopkins Hospital ward for "colored" patients, a 30-year-old woman underwent radium treatment for an aggressive strain of cervical cancer. Just before the surgeon sewed tubes of radium to her cervix, he excised a sliver of the tumor, a biopsy that the unconscious patient, Henrietta Lacks, was unaware of. Eight months later, Lacks, a poor tobacco farmer and mother of five, died and was buried in a pine box in an unmarked grave.

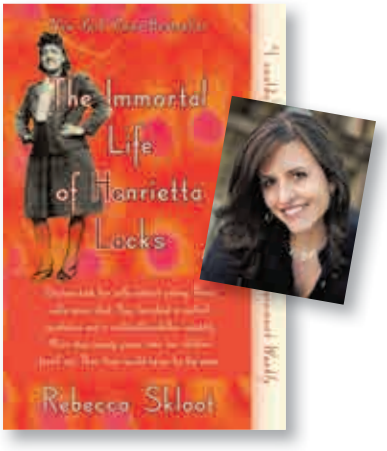
More than 60 years later, a journalist cogently summed up Lacks' impact on the scientific world with this comment: "No dead woman has done more for the living." In the decades since the tissue sample was taken, the cells would become vital to countless medical breakthroughs and usher in a new era of laboratory research and modern medicine. Lacks was soon forgotten, but her cells, known as "HeLa" from the first two letters of her first and last name, are propagated by the trillions and still live on in hundreds of laboratories.

Award-winning science writer Rebecca Skloot puts a face on the woman who unwittingly gave the world HeLa cells in the bestselling book *The Immortal life of Henrietta Lacks*. Skloot's non-fiction reads like a gripping detective novel as she deftly explores the Lacks family's tragic personal story; the thorny issues of race, poverty, and medical ethics; and the stunning medical achievements wrought with HeLa.

While Lacks' body struggled to fight the virulent cancer in the days following her first radium treatment, the slice of malignant tissue was sent to the laboratory of George Otto Gey, M.D., head of tissue culture research at Johns Hopkins. For many years Gey had tried to grow human cells outside the body but all died within a few days. Lacks' cancerous cells, however, started "spreading like crabgrass" according to Gey's wife, Margaret, a nurse and his research assistant. As the cells doubled in number every day, accumulating into the millions, Gey realized that he had at last cultured the first immortal human cells.



Hungry for human cells for all kinds of experiments, the scientific world came calling and Gey obliged, dispensing HeLa cells to researchers far and wide. HeLa cells were the first-ever living cells to be shipped via mail. As polio swept the globe in the early 1950s, they were used to test the Salk vaccine. Activist-educator Charles Bynum lobbied to establish a HeLa production and distribution center at Tuskegee Institute, a historically black college in Alabama, thus creating valuable training and opportunities for African American scientists.



HeLa cells soon became the workhorse of the modern laboratory. They were exposed to myriad viruses and toxic substances, including massive radiation, so that researchers could assess the damage to human cells. They were sent on space missions and to the bottom of the ocean in efforts to learn more about how the human cells might fare in alien environments. They've been vital to numerous cancer studies testing the effects of estrogen and estradiol. Medicines developed to fight influenza, Parkinson's, herpes, and many other diseases are indebted to HeLa, as are studies of cutting-edge science such as gene mapping, in vitro fertilization, and cloning.

As essential as HeLa cells have been to scientific research, people today often question the ethics of taking and using the cells without Lacks' consent. In the 1950s no law required physicians to tell patients how their excised tissue would be used or if they would be compensated. As Skloot points out in her book, such issues are even more complicated and controversial today. But even as courts shift through lawsuits over patients' rights, the story of Henrietta Lacks' unintentional gift of her miraculous cells remains compelling and important. ■

Holmes is managing editor of **Endocrine News**.

Matthew Daniels, Wellcome Images

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