PLUS

Breast Cancer and Stress

Obesity Rates Plateau

Benefit in Thyroid Autoimmunity?

DOWN WITH LDL CHOLESTEROL
When it comes to selecting a company to meet your specialized diagnostic test kit needs, the decision is quite simple...

For more than twenty years, KRONUS has provided specialized ELISA and RIA immunoassay test kits to medical professionals at the world’s most respected commercial, university, research, and testing hospital laboratory facilities.

To obtain additional information on KRONUS’ unique and progressive product line, please call us toll-free at 800 4 KRONUS* or visit us at our web site at www.kronus.com.

*For calls originating outside of USA and Canada, please contact KRONUS at +208 377 4800.
FEVERUARY 2010
Vol. 35 No.2

NEWS & INSIGHTS FOR THE ENDOCRINE COMMUNITY

Features

COVER STORY
14 Down with LDL Cholesterol
Research increasingly shows that the lower this blood-clogging compound goes, the better.

18 Can Thyroid Autoimmunity Be Good?
The elderly might be less frail if they have thyroid autoantibodies, new research suggests.

23 Worldwide Obesity Rates Stabilizing
The global obesity epidemic seems to be leveling out in places, but the battle is far from over.

24 Breast Cancer and Stress
Why, we don’t know, but African American women with breast cancer face a worse outcome, especially under high stress.

26 Advocating for You
The Endocrine Society is working to ensure policy makers know what’s important to endocrinologists.

31 Fat Fighters
Some unconventional treatments might help in obesity and diabetes.

Departments

02 Viewpoint
03 Editor’s Page
04 Trends & Insights
11 Smart Moves
17 CME Connections
26 Spotlight on Policy
28 Research Briefs
29 Practice Resources
32 Society Update
33 Calendar
34 Classifieds
36 Countdown to ENDO
Dear Colleagues:

This month I want to provide you with an update on The Endocrine Society’s 2009 financial performance and how we plan to deal with the economic uncertainties in 2010.

2009 Financial Performance

As with many organizations, the Society has been affected by the global economic downturn. However, I am pleased to report that our organization has successfully navigated these difficult financial times and will end the year with a surplus from operations. This was accomplished by using the same businesslike approach to operations that has served the Society so well over the years, resulting in an organization that is financially sound and well positioned for the future.

Our staff identified a significant revenue shortfall early in 2009, primarily due to reduced support from the pharmaceutical industry, which is adapting to a lower U.S. Food and Drug Administration approval rate for new products and increased restrictions on expenditures. This decrease has translated into significantly lower commercial advertising and reprint sales revenue. The Society has also had less revenue from new Continuing Medical Education Services (CMES) programs and subscriptions. As a result, staff monitored income vigilantly and developed a detailed plan to reduce expenses, which was phased in strategically during 2009 after consultation with the Society’s volunteer leadership. Society programs and services were trimmed instead of eliminated, conference calls were used for the fall committee meetings, and hiring was selectively deferred. We not only kept the Society fiscally healthy, but our staff remained intact and morale is high.

2010 Operations Budget

Council approved a balanced operations budget of $22.5 million for 2010. However, based on our recent experiences and the economic outlook, 2010 looks as though it will be as challenging as 2009. We are projecting that revenue streams will continue to be weak and have budgeted accordingly. To be less reliant on pharmaceutical industry support in the future, we have taken several steps to diversify our revenue sources with new programs and products that you will see soon. To stimulate sales of our existing products, we have added new international sales representatives and have reevaluated vendor relationships. Finally, we will make an investment in the new ENDOExpo exhibit hall at ENDO 2010: The 92nd Annual Meeting & Expo. ENDOExpo’s enhancements are designed to make the attendees and exhibitors’ meeting experience more productive and enjoyable.

Many of the expense reductions implemented in 2009 will continue in 2010, although the fall in-person committee meetings have been reinstated. Should revenue be improved in 2010, we may be able to restore some other expenditures. Alternatively, if there is a shortfall in 2010, we are ready to use the same proactive and effective financial management employed in 2009.

Reserve and Renewal Funds

The Society’s Reserve Fund is essentially a quasi-endowment and like many institutions’ endowments, it suffered in 2008 and early 2009. However, much of the loss has been recovered and the Fund’s value is well above the minimum 50% of the operating budget required by Council. In addition to assuring the financial security of the Society, the Reserve Fund feeds the Renewal Fund, from which Strategic Plan Initiatives (SPIs) are financed. The committee-generated SPIs are critical to the Society, because they permit innovative ideas to be tried for up to 3 years before either being incorporated into the operating budget or phased out. Since 2003, the Renewal Fund has provided approximately $7 million for such initiatives. I encourage our committee members to continue developing creative initiatives consistent with the 2006 Strategic Plan, so that our Society can successfully meet future challenges.

If you have any questions or comments, please do not hesitate to contact me at president@endo-society.org.

Sincerely,

Robert A. Vigersky, M.D.
President
Dear Readers,

By this time of year, many people are giving up on their New Year’s resolutions, not least dieters aiming to avoid delicious cheeses, desserts, hamburgers, and other foods high in saturated fat. But they might find renewed vim by reading the main article in this month’s *Endocrine News* that suggests no level of LDL cholesterol—low-density lipoproteins rife in this fat—is too low in battling the world’s biggest killer, cardiovascular disease (page 14).

Thyroid disorders are common in the elderly and typically need treatment. However, a new study links higher levels of thyroid autoantibodies with less frailty in the elderly, contrary to the trend seen with other types of autoimmunity (page 18).

Happily, the burgeoning obesity rate in some nations has stabilized, but whether this change is but a pause is unclear (page 23).

Breast cancer rates are higher in African American women than in other groups, but the reasons are still unclear. A recent study suggests that the environment and stress may be bigger culprits than previously suspected (page 24).

This is also a time of year when many endocrinologists receive awards and promotions, so we hope you’ll let us know about them at endocrinenews@endo-society.org.

Sincerely,

Cathy Kristiansen
Editor
Endocrine News
Triiodothyronine Treatment in Brain Stem–Dead Donors

About 77 people in the United States receive organ transplants each day—those are the lucky few. More than 100,000 patients are on the waiting list for transplants, and only 1 in 4 will receive them in time to save their lives.

Most organ donors have died recently or are considered “brain stem dead” (BSD). In BSD, a low triiodothyronine (T₃) state is common, possibly compounded by hypothalamic–pituitary–thyroid axis failure. T₃ supplementation is advocated to help heart function and yield for transplantation, but whether this treatment offers true benefit has been unknown.

Robert S. Bonser, M.D., at the University of Birmingham, United Kingdom, and his colleagues, set out to assess T₃ effects on T₃–responsive genes in the BSD human heart. In a prospective, double-blind trial, they submitted potential BSD cardiac donors undergoing hemodynamic optimization to either T₃ (0.8 μg/kg bolus; infusion 0.113 μg/kg/h) or a dextrose placebo, for up to 6 hours. The team then obtained left ventricular biopsies from 30 donors, submitting the samples to real-time PCR to determine the mRNA expression of voltage-gated potassium channel Kv1.5, beta-one adrenergic receptor (ADRB1), sarcoplasmic reticulum calcium ATPase type 2a (SERCA2a), and phospholamban (PLB). They also measured various hemodynamic parameters such as cardiac input and heart rate.

The researchers found that acute administration of T₃ reversed the low T₃ state. The treatment increased expression of Kv1.5 and SERCA2a mRNAs. But it did not improve expression of ADRB1 or PLB, or hemodynamic performance.

“The role of T₃ in donor management remains a subject of debate,” the researchers summarize in their upcoming article in The Journal of Clinical Endocrinology & Metabolism.*

Caloric Restriction in Lactation and Offspring Obesity

Instead of combating obesity in adulthood, some physicians and researchers advocate starting as early as infancy. Epidemiological and animal studies have shown a link between perinatal nutritional environment and the susceptibility to obesity and metabolic alterations in adult life. For instance, malnutrition in lactating dams on protein-restricted diets has been associated with reduced adult body weight, whereas overnutrition during lactation produced heavier adult offspring.

Weighing in on the proper caloric level for nursing mothers, a research team led by Andreu Palou, Ph.D., at the University of the Balearic Islands, Palma, Spain, examined in rats the effects of moderate caloric restriction during lactation. They fed dams either a standard diet ad libitum or a 30% calorie–restricted (CR) diet, and then gave the weaned offspring either a normal or a high-fat (HF) diet. The team also measured weight and leptin concentrations.

In an upcoming article in Endocrinology, the researchers report that CR dams had higher breast leptin levels than controls, without parallel reductions in their milk. The offspring of CR mothers ate fewer calories and showed less body weight gain and fat accumulation under the HF diet; they also maintained unchanged circulating leptin levels under the HF diet, whereas levels increased in control offspring on the same diet. Additionally, CR male offspring were shielded against increasing triglycerides and insulin resistance, and CR female offspring were protected against the higher preference for fat food, both changes that normally occur with a HF diet.

“Moderate caloric restriction during lactation protects from obesity development in offspring in adult life and from the related metabolic alterations, particularly dyslipidemia, insulin resistance, and hyperleptinemia associated with HF diet feeding,” the authors write.*

Estrogen Preserves Cancellous Bone via Receptor

Bones weaken at menopause when a population explosion of bone-resorbing osteoclasts bore deep pockets in cancellous bone and give cortical bone’s inner portion a cancellous-like structure. The bone-forming osteoblasts are unable to completely refill these cavities. Although estrogen controls the birth and death rates of both cell types, the molecular mechanisms by which the hormone prevents osteoporosis remain controversial. However, new research soon to be published in Molecular Endocrinology,* suggests that estrogen’s actions on different bone tissue cell types are involved in cancellous versus cortical bone mass preservation.

Stavros C. Manolagas, M.D., Ph.D., and his coworkers at the University of Arkansas for Medical Sciences in Little Rock, investigated the importance of estrogen receptor α (ERα) in estrogen’s actions on osteoclasts and in bone maintenance.

They found that compared with controls, mice lacking ERα in their monocytes/macrophage cell lineage (ERα<sub>myel-/-</sub>) had twice as many osteoclast progenitors in the marrow and osteoclasts in cancellous bone, along with lower cancellous bone mass. Surprisingly, after ovariectomy, the progenitor and mature osteoclast numbers in the ERα<sub>myel-/-</sub> animals did not increase and the animals did not lose more cancellous bone. However, following estrogen loss, cortical bone loss in control and ERα<sub>myel-/-</sub> mice was similar.

The researchers discovered that estrogen in the forms of 17β-estradiol (E2) and a polymeric estrogen incapable of stimulating nuclear ERα actions were equally effective in causing osteoclast apoptosis. Preventing ERα DNA binding did not protect the cells from E<sub>2</sub>. However, ERα<sub>myel-/-</sub> osteoclasts resisted E<sub>2</sub>-induced apoptosis.

The researchers conclude that estrogens hinder production and shorten the life-span of osteoclasts through effects that are cell-autonomous and independent of ERα DNA binding. They say that although these effects account for cancellous bone loss due to low estrogen, the hormone’s preservation of cortical bone, which makes up 80% of the skeleton, appears to involve actions on osteoblasts, osteocytes, or other cell types. ■

Impact of Grandpa’s Bones

Bone health may be passed down not just by one generation but by two, a recent study shows. Family fracture history, particularly of a parent, is a known risk factor for osteoporosis, but whether the grandparents’ history could be linked has been unclear.

Mattias Lorentzon, M.D., Ph.D., and his group at Sahlgrenska University Hospital in Sweden, examined 1,015 grandsons and 3,688 grandparental pairs to see if hip fracture prevalence in the older generation was associated with lower areal bone mineral density (aBMD) and reduced cortical bone size in their progeny. They measured aBMD in the 19-year-old grandsons, who were at peak bone mass, by dual X-ray absorptiometry and peripheral quantitative computerized tomography.

In an upcoming article in The Journal of Clinical Endocrinology & Metabolism,* the researchers report that compared with grandsons of grandparents without hip fractures, those whose grandparents had hip fractures (n = 269) had lower aBMD at the total body, radius, and lumbar spine, as well as a reduced cortical cross-sectional area at the radius. More specifically, these bone parameters in the grandsons were linked solely to the grandfathers, because those with only an afflicted grandmother did not have lower aBMD.

These results, the authors surmise, indicate that “patient history of hip fracture in a grandfather could be of value when evaluating the risk of low bone mass in men.” ■


Less Prednisone Still Curbs RAI-Linked Orbitopathy

➤ Treatment with radioiodine (RAI) for Graves’ disease can be a double-edged sword. Although such therapy may heal the hyperthyroidism caused by the disease, it risks triggering or encouraging orbitopathy, primarily in patients who smoke. Steroid prophylaxis with prednisone is widely used in hyperthyroidism, but its optimal treatment schedule is undefined.

To clarify, Luigi Bartalena, M.D., at the University of Insubria, Italy, and his team, compared the effectiveness of standard (starting dose, >0.3 mg/kg body weight [bw]) and lower (<0.3 mg/kg bw) doses of oral prednisone. Among 111 RAI-treated Graves’ patients, 35 received no steroid prophylaxis, 28 took low-dose prednisone (starting dose, 0.16–0.27 mg/kg bw, group 1), and 48 had higher doses (starting dose, 0.32–0.56 mg/kg bw, group 2). Those on prednisone started 1 day after RAI and stopped after 6 weeks. At 1, 3, and 6 months, the researchers assessed the patients’ thyroid function and ocular changes, and noted any side effects.

The team reports in an upcoming article in The Journal of Clinical Endocrinology & Metabolism* that 2 of the 35 patients not receiving steroid prophylaxis (6%) developed mild-to-moderate Graves’ orbitopathy after RAI. Conversely, no patients in groups 1 or 2 had orbitopathy progression. The main side effect in those two groups was weight gain, which was less in those taking the smaller prednisone dose.

The authors conclude that lower doses of prednisone (about 0.2 mg/kg bw) are as effective as the commonly used doses in the 0.3–0.5 mg/kg bw range. They also state that the shorter treatment period is as sufficient as the currently recommended 2–3 month period.

GH Alters Progression of Prader-Willi Syndrome

➤ Like fertilizer to a plant, growth hormone (GH) can spur a child’s stature, but it also has other impacts just beginning to be unearthed, such as in metabolism. And knowing when to apply it is an unresolved question.

Among potential patients are children with Prader-Willi syndrome (PWS), commonly manifested by hypotonia, obesity, delayed motor skill acquisition, mental retardation, and impaired linear growth. Giving recombinant human GH (hGH) therapy to these children for up to 4 years during childhood slightly improves body composition, energy expenditure, strength, and agility.

In their study, the researchers report that the GH-treated PWS children had lower body fat (8.5% reduction), greater height (16-cm increase), and better motor strength (nearly double, measured by standing broad jumps and sit-ups). Their metabolic make-up improved, with 14 mg/dl higher HDL cholesterol and 31 mg/dl lower LDL cholesterol.

The authors say, “long-term hGH therapy favorably alters the natural history of PWS to an extent that exceeds risks and justifies consideration for initiation during infancy.”

Endocrinology & Metabolism*, the researchers report that the GH-treated PWS children had lower body fat (8.5% reduction), greater height (16-cm increase), and better motor strength (nearly double, measured by standing broad jumps and sit-ups). Their metabolic make-up improved, with 14 mg/dl higher HDL cholesterol and 31 mg/dl lower LDL cholesterol.

The authors say, “long-term hGH therapy favorably alters the natural history of PWS to an extent that exceeds risks and justifies consideration for initiation during infancy.”


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

Important safety information

NovoLog® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® or one of its excipients. NovoLog® has a more rapid onset and shorter duration of action than regular human insulin. An injection of NovoLog® should be immediately followed by a meal within 5 to 10 minutes. Because of the short duration of action of NovoLog®, a longer-acting insulin also should be used in patients with type 1 diabetes and may be needed in patients with type 2 diabetes. When used in an external subcutaneous insulin infusion pump, NovoLog® should not be mixed with any other insulin or diluent. Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulins. Any change of insulin dose should be made cautiously and only under medical supervision. Glucose monitoring is recommended for all patients with diabetes and is particularly important for patients using external pump infusion therapy. As with all insulin preparations, the time course of action of NovoLog® may vary in different individuals or at different times in the same individual and is dependent on many conditions, including injection site, local blood supply, temperature, and level of physical activity. Severe, life-threatening generalized allergy, including anaphylactic reaction, may occur with any insulin product, including NovoLog®. Adverse reactions observed with NovoLog® include hypoglycemia, allergic reactions, local injection site reactions, lipodystrophy, rash, and pruritus. Insulin, particularly when given intravenously or in settings of poor glycemic control, may cause hypokalemia. Like all insulins, NovoLog® requirements may be reduced in patients with renal impairment or hepatic impairment. 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.

To access complimentary e-learning programs, visit novomedlink.com/NovoLog.
NovoLog® (insulin aspart [rDNA origin] injection)

Rx only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

INDICATIONS AND USAGE: NovoLog® is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

CONTRAINDICATIONS: NovoLog® is contraindicated during episodes of hypoglycemia and in patients hypersensitive to NovoLog® or one of its excipients.

WARNINGs AND PRECAUTIONS: Administration: NovoLog® has a more rapid onset of action and shorter duration of action than regular human insulin. An injection of NovoLog® should be immediately followed by a meal within 5-10 minutes. Because of NovoLog’s short duration of action, a longer-acting insulin should also be used in patients with type 1 diabetes and may also be needed in patients with type 2 diabetes who require additional monotherapy or intensified therapy for patients with diabetes is particularly important for patients using external pump infusion therapy. Any change of insulin close should be made cautiously and only under medical supervision. Changing from one insulin product to another or changing the insulin in strength may result in the need for a change in dosage. As with all insulin preparations, the time course of NovoLog® action 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, temperature, and physical activity. Patients who change their diet of physical activity or measurements may require adjustment of insulin dosage. In addition, changes in insulin requirements may be altered during illness, emotional disturbances, or other stresses. 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.

Hypoglycemia: Hypoglycemia is the most common adverse effect of all insulin therapies, including NovoLog®. Severe hypoglycemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or death. Severe hypoglycemia requiring the assistance of another person and/or spontaneous glucose infusion or glucose administration has been observed in clinical trials with insulin, including trials with NovoLog®. The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations (see Clinical Pharmacology). Other factors that may change the time of insulin onset (e.g., amount of food or timing of meal), injection site, exercise, and concomitant medications also may affect 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., patients who are fasting or have erratic food intake). The patient’s ability to concentrate and perform as a result of hypoglycemia may be impaired in situations where these abilities are especially important, such as driving or operating other machinery. Rapid changes in serum glucose levels may induce symptoms of hypoglycemia in persons with diabetes, regardless of the glaubergen as a determinant of hypoglycemia or concern that persons with diabetes may be a low in insulin, exercise, and/or stress levels of patients with diabetes, as well as in patients with chronic conditions, such as emaciation, diet, and other conditions, such as emaciation. In the setting of hypoglycemia, hyperglycemia: 1:5 insulin products, including NovoLog® cause a shift in potassium from the extracellular space to the intracellularly, possibly leading to hypokalemia that, if untreated, may cause respiratory paralysis, ventricular arrhythmias, and death. Use caution in patients who may be at risk for hypoglycemia (e.g., patients using potassium-sparing medications, patients taking medications that potentiate potassium-sparing medications, patients receiving inhaled beta-agonists) (see Clinical Pharmacology). Renal Impairment: As with all insulins, the dose requirement for NovoLog® may be reduced in patients with renal impairment (see Clinical Pharmacology). Hepatic Impairment: As with other insulins, the dose requirements for NovoLog® may be reduced in patients with hepatic impairment (see Clinical Pharmacology). Hypersensitivity and Allergic Reactions: Local Reactions: As with other insulin therapy, patients may experience redness, swelling, or itching at the site of injection. These reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of NovoLog®. In some instances, these reactions may be related to factors other than insulin, such as insulin causing a skin abnormality may occur. In contrast, in the case of other insulins, major reactions reported have been reported with insulin reactions and localized reactions are generally mild to moderate. The occurrence of severe reactions (see Clinical Pharmacology) and local irritation may be reduced by using the insulin containing a low concentration of epinephrine. Antibody Production: In rare cases, patients receiving NovoLog® have been reported post-approval. Insulin antibody formation may occur in a subset of patients receiving insulin therapy. Patients receiving insulin therapy should be monitored for the development of antibodies. The efficacy and safety of mixing NovoLog® with insulin preparations produced by other manufacturers have not been studied. Insulin mixtures should not be administered immediately after mixing. Subcutaneous continuous insulin infusion by external pump: When using NovoLog® in an external insulin pump, the NovoLog®-specific information should be followed (e.g., insulin dose, time of discovery). Additional information specific to NovoLog®-specific information may differ from general pump manual instructions. Pump or infusion set malfunctions or insulin delivery can lead to a rapid onset of hypoglycemia and ketosis because of the small subcutaneous depot of insulin. NovoLog® for external insulin pump therapy is intended for use in novodisc-shaped pump sets, which are internally fluid and skin have a slower absorption rate. Prompt identification and correction of the cause of hypoglycemia or ketosis is necessary. Intravenous therapy with subcutaneous injection may be required (see Dosage and Administration, Warnings and Precautions, How Supplied/Storage and Handling, and Patient Counseling Information). NovoLog® is recommended for use in patients using insulin pump therapy as listed below. Patients using NovoLog®-specific information should be involved in the decision-making process. More detailed information is available on request.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NovoLog® + NPH N=596</th>
<th>Human Regular Insulin + NPH N=528</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia*</td>
<td>448 (75%)</td>
<td>205 (72%)</td>
</tr>
<tr>
<td>Headache</td>
<td>70 (12%)</td>
<td>28 (10%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65 (11%)</td>
<td>29 (10%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (7%)</td>
<td>13 (5%)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>24 (4%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>
| Hypoglycemia* is defined as an episode of blood glucose concentration <55 mg/dL, with or without symptoms. See Clinical Studies for the incidence of severe hypoglycemia in the individual clinical trial.

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (except for hypoglycemia, adverse events with frequency > 5% and occurring more frequently with NovoLog® compared to human regular insulin are listed)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>NovoLog® + NPH N=591</th>
<th>Human Regular Insulin + NPH N=581</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia*</td>
<td>25 (27%)</td>
<td>33 (36%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (11%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>8 (9%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (8%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Skin rash</td>
<td>5 (5%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Shingles</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (8%)</td>
<td>8 (9%)</td>
</tr>
</tbody>
</table>

*Hypoglycemia is defined as an episode of blood glucose concentration <55 mg/dL, with or without symptoms. See Clinical Studies for the incidence of severe hypoglycemia in the individual clinical trial.

Postmarketing Data: The following additional adverse reactions have been identified during postapproval use of NovoLog®. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency, and determine whether they are caused by the use of insulin products

OVERDOSAGE: Excess insulin administration may cause hypoglycemia, and particularly when given intravenously. Hypokalemia, MI episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in diet, meals, or exercise may be needed. More severe episodes with coma, seizures, or neurological impairment may require treatment with intravenous/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may occur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

More detailed information is available on request.

Date of Issue: March 14, 2008

Version 14

Manufactured by Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

Manufactured for Novo Nordisk Inc., Princeton, New Jersey 08540

www.novonordisk-us.com

NovoLog® is a registered trademark of Novo Nordisk A/S

NovoLog® is covered by U.S. Patent Nos 5,619,913; 5,866,539; and other patents pending.

© 2008 Novo Nordisk Inc. 13460 - 408

novodisc®

Insulin aspart [rDNA origin] injection
Scheduled Feeding Prevents Obesity

When you eat may be just as important as what you eat, according to the latest research in an upcoming *Endocrinology* article. Night work or shift work forces people to be active in a phase of the light/dark cycle usually devoted to sleeping, causing them to eat more food—usually laden with carbohydrates—during the normal resting phase. This eating pattern desynchronizes the body’s metabolic processes, and this lifestyle has been linked to hypertension, metabolic syndrome, cancer, and other diseases.

While considering these previous observations, Carolina Escobar, Ph.D., at the Universidad Nacional Autónoma de México, and her colleagues, sought to find out whether feeding habits prevent or induce internal desynchrony and obesity. They created “night working” rats by altering their activity patterns.

Originally nocturnal in nature, the rats were kept awake and alert during the light phase by staying on a rotating wheel for 8 hours. Like their human counterparts, the animals started eating more during the day and gaining weight—similar to developments seen in the group’s previously published work. In the present study, the researchers allowed exercising rats and control rats to feed ad libitum, some during the day and some at night, and measured their weight, temperature, and triglyceride levels.

When food was restricted to the day, independent of exercising conditions, the triglyceride and temperature rhythms shifted toward the day and abdominal fat increased. In contrast, offering food only at night prevented increased body and fat weight gain.

“The findings support the notion that uncoupling feeding-related processes from the light cycle is deleterious for health,” the researchers write.

---

Testosterone Could Fuel Athletic Avian Displays

Animal courtship displays can feature spectacular athleticism, but little is known about the relationship between androgens and the skeletal muscles that control such displays. The male Golden-collared Manakin (Manacus vitellinus), a bird of the lowland rainforests of Central and South America, puts on an acrobatic courtship display featuring a series of loud firecracker-like wingsnaps that depend on sexually dimorphic wing muscles.

A research team led by Barney A. Schlinger, Ph.D., of the University of California, Los Angeles, explored androgen’s role in these muscles, testing the hypothesis that androgen sensitivity, reflected in androgen receptor (AR) mRNA expression levels, is an adaptation supporting these courtship displays. They compared muscles involved in the display with non-sexually dimorphic muscles not used in the wingsnaps, and male and female manakin wing muscles, with those of species that do not perform these courtship displays.

Contrary to their expectations, they found comparable AR expression in all manakin limb muscles examined in both sexes—including a leg muscle that (unlike manakin wing muscles) exhibits no sexually dimorphic or intra-species differences in mass, fiber size, or myosin expression.

However, they found a large difference between species, with more AR mRNA expression in all limb muscles of male and female manakins than in two other avian species that do not perform athletic courtship displays, Zebra Finches (*Taeniopygia guttata*) and Ochr-bellied Flycatchers (*Mionectes oleaginous*).

Compared with Zebra Finches, the male manakin also had greater activity of the testosterone-activating enzyme, 5α-reductase, in a wing-lifting muscle.

In an article soon to be published in *Endocrinology*, the researchers say their results confirm that manakin limb muscles are important androgen targets, where testosterone may act to promote the speed, force, and endurance required for the display. Androgen-dependent muscular phenotypes adapt the males of many species to perform impressive athletic displays, they posit.

---


Vasotocin-Dependent Aquaporin in Lungfish Kidney

To move from water to land, fish had to adapt, so legs and lungs formed. The latter development was crucial for adapting to terra firma, because body fluid homeostasis is regulated in opposite ways in aquatic and terrestrial habitats. In freshwater, animals excrete excess water from the body, whereas on land they retain water. To aid landlubbing fish, the neurohypophysial hormones vasopressin and its non-mammalian counterpart vasotocin exert an antidiuretic action in the kidney. These hormones bind to special receptors in the kidney (V2R) that regulate a water channel called aquaporin 2 (AQP2). In mammals, lacking any part of the vasopressin/vasotocin–V2-type receptor–AQP2 axis causes diabetes insipidus.

Although V2R and AQP2 are found in all tetrapods, including amphibians, neither has been demonstrated in fish. Thus, it has been thought that this axis emerged with the arrival of terrestrial tetrapods.

Now in an upcoming Endocrinology* article, a Japanese team led by Minoru Uchiyama, D.Sc., at the University of Toyama, reports that lungfish, the closest living relative of tetrapods, already possess a system similar to the VT–V2R–AQP2 axis, but it is functional only when these organisms live on land. In a series of molecular studies, they identified a novel AQP protein called AQP0p. This protein is expressed only when the fish lives on land during estivation.

These findings, the authors conclude, suggest that this axis contributed to the evolutionary transition from aquatic to terrestrial environments in early tetrapods. “Since the tetrapod AQP2/AQP5 lineage is considered to be evolved from duplication of an AQP0 gene, the paralogous AQP0 in the lungfish probably represents [an] ancestral molecule for tetrapod AQP2,” they write.


Androgens Tied to Abdominal Aortic Aneurysms

Not only do our waistlines expand as we get older but so do our blood vessels. Men are more affected than women and are five times more likely to develop an abdominal aortic aneurysm (AAA).

Why this sex bias occurs is unclear, so Bu Beng Yap, M.B.B.S., Ph.D., and his team at Fremantle Hospital in Australia, investigated whether male sex hormones contribute to AAA independently or are linked with increased abdominal aortic diameter, the main indicator for this condition. In a cross-sectional analysis soon to be published in The Journal of Clinical Endocrinology & Metabolism, they examined 3,620 community-dwelling men aged 70–88 years, measuring abdominal aortic diameters by ultrasound and assessing early morning sera for total testosterone, sex hormone–binding globulin, and luteinizing hormone (LH).

They report that men with AAA, versus those without, had lower serum total and free testosterone and higher LH levels. After adjusting for other variables, lower free testosterone and higher LH were associated with both AAA and increasing aortic diameter. Men with both low total testosterone and elevated LH consistent with primary gonadal failure had an approximately 3-fold greater risk of having AAA than other men. However, different categories of impaired gonadal function, such as hypogonadotrophic hypogonadism and Leydig cell impairment, were also associated with AAA, with affected men showing a 2-fold greater incidence.

Testosterone therapy is currently given to men diagnosed with androgen deficiency who have symptoms of hypogonadism and confirmed low early morning serum testosterone levels. The team concludes that the relationship between lower testosterone and AAA needs further clarification, not least to investigate a causal link and to assess the feasibility of interventional studies with aortic diameter as an end point.

**Smart Moves**

developments in the endocrinology world

* Richard M. Bergenstal, M.D., Nash M. Childs, P.E., and Christine T. Tobin, R.N., M.B.A., C.D.E., were named board members of the American Diabetes Association. Ms. Childs will be board chair, Ms. Tobin president of Health Care & Education, and Dr. Bergenstal president of Medicine & Science.

* John S. Bevan, F.R.C.P., M.B.Ch.B., M.D., was awarded a personal chair of endocrinology at the University of Aberdeen, Scotland.

* Steven C. Elbein, M.D., has joined the Wake Forest University Baptist Medical Center as a professor of internal medicine and chief of the Section on Endocrinology and Metabolism. Dr. Elbein is internationally recognized for his research on type 2 diabetes genetics.

* Claude J. Migeon, M.D., at the Johns Hopkins Children’s Center in Baltimore, Md., received the 2009 Judson J. Van Wyk Prize for career achievement in pediatric endocrinology from the Lawson Wilkins Pediatric Endocrine Society.

Amy McGuire Porter became executive director and CEO of the National Osteoporosis Foundation. She was previously executive director of the Foundation for the National Institutes of Health.

* David W. Russell, Ph.D., will be awarded the 2010 Avanti Award in Lipids for his outstanding research contributions. His laboratory has isolated more than a dozen genes that encode enzymes involved in cholesterol breakdown, and has identified the molecular bases of six human genetic diseases characterized by abnormal cholesterol and lipid metabolism. He is the Eugene McDermott Distinguished Chair in Molecular Genetics at the University of Texas Southwest Medical Center at Dallas.

Nora D. Volkow, M.D., director of the National Institute on Drug Abuse, was awarded the International Prize from the French Institute of Health and Medical Research (Inserm) for her pioneering work in brain imaging and addiction science. Her work has made important contributions to the neurobiology of obesity, drug addiction, ADHD, and aging.

* Member of The Endocrine Society

---

**Dopamine’s Role in Diabetes**

- Treating psychotic patients is not all about getting into their heads. The pancreas, too, is often involved, with hyperinsulinemia and diabetes common side effects of chronic treatment with neuroleptic drugs. Because many of these drugs target the neurotransmitter dopamine, a group of researchers set out to study how the dopamine D2 receptor (D2R), a possible culprit, affects pancreatic function.

  In a series of pharmacological studies, Damasia Becu-Villalobos, Ph.D., and her team at the Instituto de Biología y Medicina Experimental-CONICET, Argentina, examined glucose homeostasis in D2R knockout mice (Drd2−/−). Their results will be published in an upcoming issue of *Endocrinology.*

  The researchers found that Drd2−/− mice gradually developed glucose intolerance and impaired insulin response to glucose.

  In vitro studies revealed that pancreatic islets from Drd2−/− mice displayed blunted glucose-stimulated insulin secretion (GSIS); only in wild-type islets did dopamine inhibit GSIS, an effect that was blocked by a D2R but not a D1R antagonist. Immunohistochemistry showed that Drd2−/− mice displayed diminished pancreatic β-cell masses and had decreased β-cell replication starting at 2 months. The 7-month-old Drd2−/− mice showed a complete lack of islet responsiveness to glucose. Furthermore, in wild-type animals but not Drd2−/− mice, treatment with cabergoline, a dopamine agonist, induced glucose intolerance and decreased insulin response to glucose, an effect that was partially prevented by haloperidol, a D2R antagonist. Therefore, pancreatic D2Rs participate in the inhibition of glucose stimulated insulin release.

  The authors point out, the “lack of dopaminergic inhibition throughout development may exert a gradual deteriorating effect on insulin homeostasis so that eventually glucose intolerance develops.” These effects, they said, might be mimicked in patients on longterm antipsychotic medications.


---

ENDOCRINE NEWS • FEBRUARY 2010

11
SAVE UP TO $500 ON ENDO REGISTRATION

Become a member of The Endocrine Society and you can save up to $500 off the cost of registration for the premier endocrinology event — ENDO 2010 in San Diego, June 19–22.

Network with your colleagues from around the world. Learn about the latest advancements in research and treatment trends. And utilize all the benefits that membership has to offer you and 14,000 of your professional colleagues.

To join The Endocrine Society, go to www.EndoSociety.org/Join.

www.Endo-Society.org/ENDO

© 2010 The Endocrine Society

THE ENDOCRINE SOCIETY’S 2010 ELECTION

Time is running out to vote.

Electronic ballots were sent to members with voting privileges in early January 2010. Information for online voting can be accessed by visiting http://www.endo-society.org/membership/election.cfm.

Questions should be directed to Elizabeth Kan at 301.941.0206 or ekan@endo-society.org.

Electronic votes must be received by midnight EST on March 8, 2010.

Deadline March 8, 2010
Providing the highest caliber of evaluation and management of thyroid, parathyroid, adrenal and pancreatic disease requires a combination of scientific research, sophisticated diagnostics and clinical expertise.

At Yale-New Haven Hospital, we treat endocrine disease with the latest advances in medical management, a full range of traditional surgical procedures and state-of-the-art minimally invasive operations, such as minimal access thyroidectomy, minimally invasive parathyroidectomy and laparoscopic adrenalectomy. Our emphasis is on the safest, most successful surgery with the least pain and trauma, resulting in optimized healing and fastest recovery time.
THE LOWDOWN ON LIPIDS:

DRIVE THEM DOWN

EXPERT SEES NO LOWER LIMIT TO LDL CHOLESTEROL

BY ERIC SEABORG*
The science of lipid management is undergoing a paradigm shift, with the emphasis now on driving low-density lipoproteins (LDL) cholesterol levels as far down as possible, particularly in high-risk patients with levels in the traditional danger range. Lowering LDL levels reduces the risk of cardiovascular events, and some research suggests there’s no limit on how low to aim.

Steps Down
Clinicians should start treatment with a statin, then consider adding another agent, even in patients whose LDL levels appear to conform to official targets, such as those from the National Cholesterol Education Program (NCEP) in the United States (see sidebar). Treatment should be aggressive, because even when high-risk patients attain lower LDL levels and seem to have factors such as blood pressure under control, they are still more likely to experience serious adverse cardiovascular events.

This was the core message of a “Controversies in Lipid Management” presentation by Lisa R. Tannock, M.D., chief of the division of endocrinology and molecular medicine at the University of Kentucky College of Medicine in Lexington. She spoke at The Endocrine Society’s most recent Clinical Endocrinology Update meeting, held in October, and in a recent interview with Endocrine News.

Dr. Tannock’s three main points were that there is no floor for LDL target levels; that adding an agent such as ezetimibe to statin treatment can diminish LDL further; and that clinicians need to seriously consider steps in addition to standard drug regimens to counter the residual risk in patients with conditions such as metabolic syndrome and diabetes.

The Shift
Times have changed in lipid treatment, Dr. Tannock said: “When we went through our training, we were taught to measure lipid levels. If high, put that person on treatment. Start with a low dose of statins, and titrate them up until you get to your target LDL. And that’s really passé now. Where we are now is treating the disease. We know that there is a continual relationship between lipid levels and atherosclerosis. Now what we are being asked to do is to identify patients who have the disease or are at very high risk. We know from analysis of statin trials that all these patients benefit regardless of what their entry LDL levels were. Just because they have an LDL of 90 [mg/dl] doesn’t mean they won’t benefit from lowering it further. So don’t be reassured by the level.”

Low doses and titration have gone by the wayside as physicians more toward attaining an effective dose quickly.

Evidence is mounting that very low LDL cholesterol levels pose no health risks to patients. Dr. Tannock said that people who achieve an LDL of 40 mg/dl exhibit no higher incidence of other adverse conditions. The genetic condition hypobetalipoproteinemia results in LDL cholesterol levels between 30 and 50 mg/dl, and these patients have fewer cardiovascular events than the general population over the course of their lifetimes—with no raised risk of other diseases.

How To Get There
If a physician’s goal is to drive down LDL levels, the question becomes how to do so. Dr. Tannock said the clinician has a choice of many statins for the first-line treatment, but in general each has the characteristic that patients plateau at a certain level. Doubling the dose of a statin generally leads to an additional 5%–6% lowering of LDL, but one obviously can’t raise the statin dose indefinitely without influencing effectiveness and side effects such as muscle pain and liver damage.

A more potent option is to prescribe ezetimibe on top of the statin, which can reduce LDL levels an additional 20%–25%. In contrast to the statins’ mechanism of action of decreasing cholesterol production in the liver, ezetimibe prevents cholesterol absorption in the intestine. It can be added to a prescription for any statin, Dr. Tannock said, or can be used in the combination drug Vytorin, which contains simvastatin and ezetimibe.

Testing Vytorin
In 2008, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial raised the question of a possible association of Vytorin and an increased incidence of cancer. However, since that time, much larger, ongoing studies have released data showing no increased cancer incidence in the Vytorin groups compared with groups receiving statins alone, and “the overall effect of statins on cancer is neutral,” Dr. Tannock said.

Studies comparing Vytorin with simvastatin alone have demonstrated Vytorin’s ability to lower LDL cholesterol, total cholesterol, and triglycerides, with no significant effects on high-density lipoprotein (HDL) cholesterol. However, several recent imaging trials have not found an added benefit for statin plus ezetimibe compared with statin alone or statin plus niacin. Its efficacy has yet to be proven by outcome studies, but several in process could yield definitive answers. “I expect it to be proven in outcome studies, but we are a few years out from getting that data,” Dr. Tannock said.

Dr. Tannock said she is satisfied with the safety data on ezetimibe with statins, and based on the preliminary efficacy results, does not consider that now is too early to prescribe it.
Residual Risk

Research has shown that statins can reduce LDL and curb cardiovascular events by 20%–40%. But that still leaves patients vulnerable to a significant number of myocardial infarctions and other serious threats. “You take a high-risk individual, somebody who has already had a heart attack. You have them on a potent statin, you’ve got their LDL less than 70, you’ve got their blood pressure controlled; you’ve got them on an aspirin, a beta blocker, and an ACE inhibitor—all these standard drugs. They are still going to have another heart attack,” Dr. Tannock told Endocrine News.

That residual risk must be reduced, and this appears to involve looking beyond LDL cholesterol levels to the roles of low HDL cholesterol, high triglycerides, and small, dense LDL cholesterol. Increasingly, data suggest that the small, dense LDL particles—the smallest LDL cholesterol particle sizes—are more atherogenic than the larger, buoyant particles. The triad of (low) HDL cholesterol, high triglycerides, and a predominance of small, dense LDL particles is characteristic of diabetes and metabolic syndrome patients, Dr. Tannock said, and gives a clue about other attributes that could be targeted to improve the residual hazard in these high-risk patients. “For any level of LDL, HDL is inversely correlated to risk, and actually has a greater relative impact than the LDL,” she said.

Treatment strategies for HDL and triglycerides include niacin, fibrates, and thiazolidinediones (TZDs).

Not Nixing Niacin

“Every time I talk about niacin, I find probably 10% of the audience is niacin enthusiasts, and 90% hates it,” Dr. Tannock said. She said that niacin is a misunderstood drug, which, used properly, is a valid alternative to statins in statin-intolerant patients. “Niacin affects all components of dyslipidemia, and is actually the best drug we have for raising HDL,” Dr. Tannock said. Its effects on LDL cholesterol can be modest, but it can raise HDL 20%–30%.

Because it causes severe flushing, careful patient education and titration of the dose are critical. “If you don’t tell them they’ll flush, and you don’t titrate, they will take one dose, and will never see you again. They feel like they are dying. They turn bright red and look really uncomfortable. They will be on the phone to your office, thinking you are the worst doctor ever,” Dr. Tannock said.

She takes several weeks to reach a daily dose of 1,000 mg, starting at 250 mg a day for a week, and stepping up 250 mg/week. Patients need to take it in the middle of a meal, with no hot beverages, soup, or alcohol. No-flush preparations are useless, because they pass through the gut unabsorbed.

Definitive data showing that niacin in combination with statins reduces residual risk are not yet in, but preliminary findings are positive. Dr. Tannock noted two studies with designs that did not ask this question directly but did provide relevant side data. A trial comparing various combinations of potential cholesterol-lowering approaches showed an almost 90% reduction in cardiovascular events with simvastatin plus niacin compared with placebo. And the ARBITER 2 imaging study, comparing statin plus placebo with statin plus extended-release niacin, showed that adding niacin had no effect on total or LDL cholesterol, but caused a significant increase in HDL cholesterol and a significant decrease in triglycerides.

“Niacin is reasonable to use as monotherapy in statin-intolerant patients, and I suspect there is going to be a benefit from statin in combination with niacin in high-risk people,” Dr. Tannock said.

Figuring Fibrates

The fibrates, fenofibrate and gemfibrozil, have been suggested for reducing residual risk, especially because they deal more directly with triglycerides and low HDL cholesterol.

Studies investigating the efficacy of adding fibrates to statins are ongoing, so some answers may emerge in a year or two. Extrapolating from monotherapy studies, Dr. Tannock noted, one can conclude that fibrates will have the most benefit in metabolic syndrome and diabetes patients—those with the gravest risks from high triglycerides and low HDL cholesterol.

Many clinicians are concerned about the safety of combining a statin and a fibrate, but Dr. Tannock said large analyses of all published data have identified no increased risk of rhabdomyolysis or renal failure in trials with subjects receiving a statin–fibrate combination compared with those on a statin or fibrate alone. Even singly, fibrates can cause rhabdomyolysis at a very low rate, so prescribers should keep...
in mind that the highest risk patients are small, elderly, frail, and taking multiple drugs.

Dr. Tannock noted that all statin product inserts favor fenofibrate, because gemfibrozil affects statin glucuronidation, raising statin plasma levels. “But you can put patients on gemfibrozil and get away with a lower dose,” Dr. Tannock said. “You can go down in the statin dose for the same biological effect.”

The Drugs Not Taken

Dr. Tannock noted that many of the data she presented are preliminary. With the results of numerous clinical trials of new drug uses and new drug combinations expected in the next couple of years, large areas in lipid management will be clarified. Also, the NCEP is expected to publish much-anticipated updated guidelines in March 2010.

But Dr. Tannock emphasized that, whatever the drug regime, the biggest challenge in any lipid-lowering scheme is getting the patient to take the drugs. Six months after receiving a statin prescription, fewer than half the patients still take them. “One of the big issues to work on is education to increase adherence to therapy,” she said.

Trying Thiazolidinediones

In common use among diabetes patients, TZDs counter insulin resistance, but also have lipid-lowering effects. The lipid impact of pioglitazone (Actos) is greater than that of rosiglitazone (Avandia). Both drugs actually increase total LDL cholesterol, but appear to shift its make-up from small, dense particles to the larger, more buoyant ones.

“When you are considering adding further medications to your patient with diabetes, you might want to consider adding pioglitazone, which can affect both the glucose and the lipid control. It probably has benefits and effects in combination with statins, but we need prospective cardiovascular event–driven trials to confirm this,” Dr. Tannock said.

CME connections

Incretin-Based Therapies Webcast

Based on content presented at the live Clinical Endocrinology Update (CEU) 2009 satellite symposium titled, The Evolving Landscape of Incretin-Based Therapies: Evaluating Recent Data and Its Clinical Applications, this online webcast discusses incretin-based therapies in depth and offers interactive questions to help you evaluate your answers against those of your colleagues, along with a concluding faculty panel discussion. The most cutting-edge information available on these therapeutic agents will be highlighted, along with a concluding faculty panel discussion. Earn up to 2.0 AMA PRA Category 1 Credits™. To view, please visit www.endo-society.org/education/CME/diabetes.cfm.

CEU 2009 Session Library

Now you can access core content from the 2009 CEU and have the latest developments in clinical endocrinology at your fingertips! The CEU 2009 Session Library includes a compilation of digital audio recordings and synchronized speaker slides from live CEU 2009 presentations and is available for purchase online only or online plus CD-ROM. Earn up to 29 AMA PRA Category 1 Credits™. For more information, visit www.softconference.com/endocrine/am.asp.

LDL Cholesterol Recommendations

United States

The National Cholesterol Education Program (NCEP) specifies a plasma LDL cholesterol target of 1.8 mmol/L (70 mg/dl) for the highest risk patients, 3.4 mmol/L (130 mg/dl) for those at moderate risk, and 4.1 mmol/L (159 mg/dl) or less, otherwise. See the NCEP site at www.nhlbi.nih.gov/about/ncep/index.htm and the American Heart Association site at www.americanheart.org.

United Kingdom

The National Institute for Health and Clinical Excellence and Department of Health cholesterol guidelines, followed by physicians, recommend LDL at < 3.0 mmol/L (116 mg/dl), see www.nice.org.uk.

The Joint British Societies (a group of the main UK professional societies involved in cardiovascular disease) recommend a target for those at risk of < 2.0 mmol/L (77 mg/dl).

Europe

2003 European guidelines recommended LDL at < 3.0 mmol/L, or < 2.5 mmol/L (< 97 mg/dl) for patients at risk. Individual countries range in their national targets from 1.8 mmol/L in Austria to 3.4 mmol/L in Italy. See “European Cholesterol Guidelines Report” by Tony Hockley and Marin Gemmill at the London School of Economics and Political Science: www.policy-centre.com/downloads/European-Cholesterol-Guidelines07.pdf.

* Eric Seaborg is an award-winning free-lance writer living in Charlottesville, Va.

To view Dr. Tannock’s CEU presentation in its entirety or talks by other experts on various topics, please visit www.softconference.com/endocrine/am.asp. There is a fee for this service. To register for The Endocrine Society’s CEU 2010, to be held in September in Los Angeles, Calif., visit www.endo-society.org/meetings/CEU/index.cfm.
ANNOUNCING: The Nurse Home Injection Program
For eligibility, call 1-888-LAR-4759

For the long-term treatment of acromegaly, Sandostatin LAR<sup>®</sup> provides...

**POWERFUL EFFICACY, UNPARALLELED EVIDENCE**

Proven long-term efficacy in acromegaly.<sup>1</sup>
Backed by over 600,000 patient-years of experience<sup>2,3</sup>:
- 57%-68% of patients experienced both GH <2.5 ng/mL + IGF-1 normalization<sup>1,3</sup>

Now the only somatostatin analogue proven to shrink tumors in acromegaly.<sup>1</sup>
- 36% median tumor shrinkage achieved in previously untreated acromegalic patients at Week 48 (n=94)<sup>1,2</sup>
  - Greater than 20% median tumor shrinkage at Week 24 (N=143)<sup>4</sup>
- No patient experienced an increase in tumor volume while on treatment with Sandostatin LAR<sup>®</sup><sup>4</sup>

Sandostatin LAR<sup>®</sup> Depot (octreotide acetate for injectable suspension) is indicated for long-term maintenance therapy in acromegalic patients for whom medical treatment is appropriate and who have been shown to respond to and can tolerate immediate release Sandostatin<sup>®</sup> (octreotide acetate) Injection. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Sandostatin LAR<sup>®</sup> Depot can be used in patients who have had an inadequate response to surgery or in those for whom surgical resection is not an option. It may also be used in patients who have received radiation and have had an inadequate therapeutic response.

**Important Safety Information**:<sup>1</sup>
As with immediate release Sandostatin<sup>®</sup> Injection, the most frequently reported drug-related adverse events were biliary disorders (52%), gastrointestinal disorders (7% to 36%), and injection-site pain (2% to 11%). Hypoglycemia (2%), hyperglycemia (15%), and hypothyroidism (2%) have been reported. While not measured in acromegalic patients receiving Sandostatin LAR<sup>®</sup> Depot, ECG changes have been reported in patients receiving immediate release Sandostatin<sup>®</sup> Injection; the degree to which these abnormalities are related to octreotide acetate is not clear, as many acromegalics have cardiovascular disease.

*Please see brief summary of Prescribing Information on adjacent page.*


*Combined use of immediate release Sandostatin<sup>®</sup> Injection and Sandostatin LAR<sup>®</sup> Depot from all approved indications.
† Includes both ongoing and completed trials from all approved indications.
‡ Range reflects results derived from pivotal trials and long-term follow-up data.
§ Reduction in tumor size was demonstrated in 2 open-label studies (N=143).
Initial U.S. Approval: 1988

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

Sandostatin LAR Depot 10 mg, 20 mg and 30 mg is indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerable.

1.1 Acromegaly

Long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal [see Clinical Studies (14) and Dosage and Administration (2) in the full prescribing information.]

1.2 Carcinoid Tumors

Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

1.3 Vasovagal Intestinal Peptide Tumors (VIPomas)

Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

1.4 Important Limitations of Use

In patients with carcinoid syndrome and VIPomas, the effect of Sandostatin Injection and Sandostatin LAR Depot on tumor size, rate of growth and development of metastases, has not been determined.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Cholelithiasis and Gallbladder Sludge

Sandostatin may inhibit gallbladder contractility and decrease bile secretion, which may lead to gallbladder abnormalities or sludge. Patients should be monitored periodically [see Adverse Reactions (6)].

5.2 Hyperglycemia and Hypoglycemia

Octreotide alters the balance between the counter-regulatory hormones, insulin, glucagon, and growth hormone, which may result in hyperglycemia or hypoglycemia. Blood glucose levels should be monitored when Sandostatin LAR treatment is initiated, or when the dose is altered. Anti-diabetic treatment should be adjusted accordingly [see Adverse Reactions (6)].

5.3 Thyroid Function Abnormalities

Octreotide suppresses the secretion of thyroid stimulatory hormone, which may result in hypothyroidism. Baseline and periodic assessment of thyroid function (TSH, total and/or free T4) is recommended during chronic octreotide therapy [see Adverse Reactions (6)].

5.4 Cardiac Function Abnormalities

In both acromegalic and carcinoid syndrome patients, bradycardia, arrhythmias and conduction abnormalities have been reported during octreotide therapy. Other EKG changes were observed such as QT prolongation, axis shifts, early repolarization, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease. Dose adjustments in drugs such as beta blockers that have bradycardia effects may be necessary. In one acromegalic patient with severe congestive heart failure, initiation of Sandostatin Injection therapy resulted in worsening of CHF with improvement when drug was discontinued. Confirmation of a drug effect was obtained with a positive rechallenge [see Adverse Reactions (6)].

5.5 Nutrition

Octreotide may alter absorption of dietary fats. Depressed vitamin B12 levels and abnormal Schilling’s tests have been observed in some patients receiving octreotide therapy, and monitoring of vitamin B12 levels is recommended during therapy with Sandostatin LAR Depot.

Octreotide has been investigated for the reduction of excessive fluid loss from the G.I. tract in patients with conditions producing such a loss. If such patients are receiving total parenteral nutrition (TPN), serum zinc levels may rise excessively when the fluid loss is reversed. Patients on TPN and octreotide should have periodic monitoring of zinc levels.

5.6 Monitoring: Laboratory Tests

Laboratory tests that may be helpful as biochemical markers in determining and following patient response depend on the specific tumor. Based on diagnosis, measurement of the following substances may be useful in monitoring the progress of therapy [see Dosage and Administration (2.0) in the full prescribing information].

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)

Carcinoid: 5-HIAA (urinary 5-hydroxyindole acetic acid), plasma serotonin, plasma Substance P

VIPoma: VIP (plasma vasovagal intestinal peptide) baseline and periodic total and/or free T4 measurements should be performed during chronic therapy

5.7 Drug Interactions

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine [see Drug Interactions (7.2)].

6 ADVERSE REACTIONS

6.1 Clinical Studies 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 trial of another drug and may not reflect the rates observed in practice.

6.1.1 Acromegaly

The safety of Sandostatin LAR in the treatment of acromegaly has been evaluated in 3 phase 3 studies in 261 patients, including 209 exposed for 48 weeks and 96 exposed for greater than 108 weeks. Sandostatin LAR was studied primarily in a double-blind, cross-over manner. Patients on subcutaneous Sandostatin Injection were switched to the LAR formulation followed by an open-label extension. The population age range was 14-81 years old and 53% were female. Approximately 35% of these acromegaly patients had not been treated with surgery and/or radiation. Most patients received a starting dose of 20 mg every 4 weeks intramuscularly. Dose was up or down titrated based on efficacy and tolerability to a final dose between 10-60 mg every 4 weeks. Table 1 below reflects adverse events from these studies regardless of presumed causality to study drug.

Table 1. Adverse Events Occurring in ≥10% of Acromegalic Patients in the Phase 3 Studies

<table>
<thead>
<tr>
<th>WHO Preferred Term</th>
<th>Phase 3 Studies (Pooled)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of Subjects with AE’s</td>
<td></td>
</tr>
<tr>
<td>10 mg/20 mg/30 mg</td>
<td>(n=261)</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>93 (35.6)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>75 (28.7)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>66 (25.3)</td>
</tr>
<tr>
<td>Influenza-Like Symptoms</td>
<td>52 (19.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>46 (17.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>40 (15.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>40 (15.3)</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>36 (13.8)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>35 (13.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (12.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (11.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (11.1)</td>
</tr>
</tbody>
</table>

The safety of Sandostatin LAR in the treatment of acromegaly was also evaluated in a post-marketing randomized phase 4 study. 104 patients were randomized to either pituitary surgery or 20 mg of Sandostatin LAR. All the patients were treatment naïve (‘de novo’). Cross over was allowed according to treatment response and a total of 76 patients were exposed to Sandostatin LAR. Approximately half of the patients initially randomized to Sandostatin LAR were exposed to Sandostatin LAR up to 1 year. The population age range was between 20-76 years old and 45% were female, 95% were Caucasian, and 1% Black. The majority of these patients were exposed to 30 mg every 4 weeks. Table 2 below reflects the adverse events occurring in this study regardless of presumed causality to study drug.

Table 2. Adverse Events Occurring in ≥10% of Acromegalic Patients in Phase 4 Study

<table>
<thead>
<tr>
<th>WHO Preferred Term</th>
<th>Phase 4 Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAS LAR Surgery</td>
<td></td>
</tr>
<tr>
<td>N=76 n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (47.4)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>29 (38.2)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>19 (25.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (15.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
</tbody>
</table>

Acromegaly: Growth Hormone, IGF-1 (somatomedin C)
Galbladder Abnormalities
Single doses of Sandostatin Injection have been shown to inhibit galbladder contractility and decrease bile secretion in normal volunteers. In clinical trials with Sandostatin Injection (primarily patients with acromegaly or psoriasis) in patients who had not previously received octreotide, the incidence of biliary tract abnormalities was 65% (27% gallstones, 24% sludge without stones, 12% biliary duct dilatation). The incidence of stones or sludge in patients who received Sandostatin Injection for 12 months or longer was 52%. The incidence of galbladder abnormalities did not appear to be related to age, sex or dose but was related to duration of exposure.

In clinical trials 52% of acromegalic patients, most of whom received Sandostatin LAR Depot for 12 months or longer, developed new biliary abnormalities including gallstones, microlithiasis, sludge and dilatation. The incidence of new cholelithiasis was 22%, of which 7% were microstones.

Across all trials, a few patients developed acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, or pancreatitis during octreotide therapy or following its withdrawal. One patient developed ascending cholangitis during Sandostatin Injection therapy and died.

Despite the high incidence of new gallstones in patients receiving octreotide, 1% of patients developed acute symptoms requiring cholecystectomy.

Glucose Metabolism - Hypoglycemia/Hyperglycemia
In acromegalic patients treated with either Sandostatin Injection or Sandostatin LAR Depot, hypoglycemia occurred in approximately 2% and hyperglycemia in approximately 15% of patients [see Warnings and Precautions (5)].

Hypothyroidism
In acromegaly patients, Sandostatin Injection, 12% developed biochemical hypothyroidism, 8% developed goiter, and 4% required initiation of thyroid replacement therapy while receiving Sandostatin Injection. In acromegalic patients treated with Sandostatin LAR Depot hypothyroidism was reported as an adverse event in 2% and goiter in 2%. Two patients receiving Sandostatin LAR Depot required initiation of thyroid hormone replacement therapy [see Warnings and Precautions (5)].

Cardiac
In acromegalic, sinus bradycardia (<50 bpm) developed in 25%; conduction abnormalities occurred in 10% and arrhythmias developed in 9% of patients during Sandostatin injection therapy. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see Warnings and Precautions (5)].

Gastrointestinal
The most common symptoms are gastrointestinal. The overall incidence of the most frequent of these symptoms in clinical trials of acromegalic patients treated for approximately 1 to 4 years is shown in Table 3.

Table 3. Number (%) of Acromegalic Patients with Common G.I. Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Sandostatin Injection S.C. Three Times Daily n=114</th>
<th>Sandostatin LAR Depot Every 28 Days n=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>66 (57.9)</td>
<td>95 (36.4)</td>
</tr>
<tr>
<td>Abdominal Pain or Discomfort</td>
<td>50 (43.9)</td>
<td>76 (29.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (29.8)</td>
<td>27 (10.3)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>15 (13.2)</td>
<td>67 (25.7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (8.8)</td>
<td>49 (18.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (4.4)</td>
<td>17 (6.5)</td>
</tr>
</tbody>
</table>

Only 2.6% of the patients on Sandostatin Injection in U.S. clinical trials discontinued therapy due to these symptoms. No acromegalic patient receiving Sandostatin LAR Depot discontinued therapy for a G.I. event.

In patients receiving Sandostatin LAR Depot the incidence of diarrhea was dose related. Diarrhea, abdominal pain, and nausea developed primarily during the first month of treatment with Sandostatin LAR Depot. Thereafter, new cases of these events were uncommon. The vast majority of these events were mild-to-moderate in severity.

In rare instances gastrointestinal adverse effects may resemble acute intestinal obstruction, with progressive abdominal distention, severe epigastric pain, abdominal tenderness, and guarding. Dyspepsia, steatorrhea, discoloration of feces, and tenesmus were reported in 4%-6% of patients.

In a clinical trial of carcinoid syndrome, nausea, abdominal pain, and flatulence were reported in 27%-38% and constipation or vomiting in 15%-21% of patients treated with Sandostatin LAR Depot. Diarrhea was reported as an adverse event in 14% of patients but since most of the patients had diarrhea as a symptom of carcinoid syndrome, it is difficult to assess the actual incidence of drug-related diarrhea.

Pain at the Injection Site
Pain at injection, which is generally mild-to-moderate, and short-lived (usually about 1 hour) is dose related, being reported by 2%, 9%, and 11% of acromegalic patients receiving doses of 10 mg, 20 mg, and 30 mg, respectively, of Sandostatin LAR Depot. In carcinoid patients, where a diary was kept, pain at the injection site was reported by about 20%-25% at a 10-mg dose and about 30%-50% at the 20- and 30-mg dose.

Antibodies to Octreotide
Studies to date have shown that antibodies to octreotide develop in up to 25% of patients treated with octreotide acetate. These antibodies do not influence the degree of efficacy response to octreotide; however, in two acromegalic patients who received Sandostatin Injection, the duration of GH suppression following each injection was about twice as long as in patients without antibodies. It has not been determined whether octreotide antibodies will also prolong the duration of GH suppression in patients being treated with Sandostatin LAR Depot.

6.1.2 Carcinoid and VIPomas
The safety of Sandostatin LAR in the treatment of carcinoid tumors and VIPomas has been evaluated in one phase 3 study. Study 1 randomized 93 patients with carcinoid syndrome to Sandostatin LAR 10 mg, 20 mg or 30 mg in a blind fashion or to open label Sandostatin Injection subcutaneously. The population age range was between 25-78 years old and 44% were female, 95% were Caucasian and 5% Black. All the patients had symptom control on their previous Sandostatin subcutaneous treatment. Eighty patients finished the initial 24 weeks of Sandostatin exposure in study 1. In study 1, comparable numbers of patients were randomized to each dose. Table 4 below reflects the adverse events occurring in >15% of patients regardless of presumed causality to study drug.

Table 4. Adverse Events Occurring in ≥15% of Carcinoid Tumor and VIPoma Patients in Study 1

<table>
<thead>
<tr>
<th>WHO Preferred Term</th>
<th>Study 1</th>
<th>Number (%) of Subjects with AE’s (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>Sc N=29</td>
<td>10 mg N=22</td>
</tr>
<tr>
<td>Arthrophy</td>
<td>8 (28.6)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>7 (24.1)</td>
<td>6 (27.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (13.8)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (10.3)</td>
<td>1 (4.4)</td>
</tr>
<tr>
<td>Generalized Pain</td>
<td>1 (3.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (28.6)</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (3.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0 (0.0)</td>
<td>1 (4.4)</td>
</tr>
<tr>
<td>URTI</td>
<td>6 (21.4)</td>
<td>4 (18.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11.5)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Galbladder Abnormalities
In clinical trials 62% of malignant carcinoid patients who received Sandostatin LAR Depot for up to 18 months developed new biliary abnormalities including jaundice, gallstones, sludge and dilatation. New gallstones occurred in a total of 24% of patients.

Glucose Metabolism - Hypoglycemia/Hyperglycemia
In carcinoid patients, hypoglycemia occurred in 4% and hyperglycemia in 27% of patients treated with Sandostatin LAR Depot [see Warnings and Precautions (5)].

Hypothyroidism
In carcinoid patients, hypothyroidism has only been reported in isolated patients and goiter has not been reported [see Warnings and Precautions (5)].

Cardiac
Electrocardiograms were performed only in carcinoid patients receiving Sandostatin LAR Depot. In carcinoid syndrome patients sinus bradycardia developed in 19%, conduction abnormalities occurred in 9%, and arrhythmias developed in 3%. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac disease [see Warnings and Precautions (5)].

Other Clinical Studies Adverse Events
Other clinically significant adverse events (relationship to drug not established) in acromegalics and/or carcinoid syndrome patients receiving...
Sandostatin LAR Depot were malignant hyperpyrexia, cerebral vascular disorder, rectal bleeding, ascites, pulmonary embolism, pneumonia and pleural effusion.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during the post-marketing setting, mainly in patients with cardiovascular risk factors. Hypoadrenalism has been reported in some reports in patients 18 months of age and under.

Additional events reported in the post-marketing setting include anaphylactic reactions, including anaphylactic shock, cardiac arrest, renal failure, renal insufficiency, convulsions, atrial fibrillation, aneurysm, hepatitis, increased liver enzymes, gastrointestinal hemorrhage, pancreatitis, pancytopenia, thrombocytopenia, arterial thrombosis of the arm, retinal vein thrombosis, intracranial hemorrhage, hemiparesis, paralytic ileus, facial edema, generalized edema, hematuria, orthostatic hypotension, diabetes mellitus, intestinal obstruction, peptic/gastric ulcer, appendicitis, creatinine increased, CK increased, arthritis, joint effusion, pitting edema, breast carcinoma, suicide attempt, paranoia, migraine, urticaria, facial edema, generalized edema, hematuria, orthostatic hypotension, Raynaud’s syndrome, glaucoma, pulmonary nodule, pneumothorax, cellulitis, Bell’s palsy, diabetes insipidus, gynecomastia, galactorrhea, gallbladder polyph, fatty liver, abdomen enlarged, libido decrease and petechiae.

7. Drug Interactions

7.1 Cyclosporine

Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

7.2 Insulin and Oral Hypoglycemic Drugs

Cyclosporine inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when Sandostatin LAR treatment is initiated or when the dose is altered and anti-diabetic treatment should be adjusted accordingly.

7.3 Bromocriptine

Concomitant administration of octreotide and Bromocriptine increases the availability of bromocriptine.

7.4 Other Concomitant Drug Therapy

Concomitant administration of bradycardia inducing drugs (e.g., beta blockers) may have an additive effect on the reduction of heart rate associated with octreotide. Dose adjustments of concomitant medication may be necessary.

Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs.

7.5 Drug Metabolism Interactions

Limited published data indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

8. Use in Specific Populations

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been performed in rats and rabbits at doses up to 16 times the highest recommended human dose and have revealed no evidence of harm to the fetus due to octreotide. However, because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [see Nonclinical Toxicology (13.2) in the full prescribing information].

8.3 Nursing Mothers

It is not known whether octreotide is excreted into human milk. Because many drugs are excreted in human milk, caution should be exercised when Sandostatin LAR Depot is administered to a nursing woman.

8.4 Pediatric Use

In pediatric patients with hypothalamic obesity, the mean octreotide concentration after 6 doses of 40-mg Sandostatin LAR Depot administered by IM injection every four weeks was approximately 3 ng/mL. Steady-state concentration was achieved after 3 injections of a 40-mg dose. The efficacy and safety of Sandostatin LAR Depot were examined in a randomized, double-blind, placebo-controlled six month study in 60 pediatric patients ages 6-17 years with hypothyroidism obesity resulting from cranial insult. Mean BMI increased 0.1 kg/m² in Sandostatin LAR Depot treated subjects compared to 0.0 kg/m² in saline control-treated subjects. Diarrhea occurred in 11 of 30 (37%) patients treated with Sandostatin LAR Depot. No unexpected adverse events were observed. However, with Sandostatin LAR Depot 40 mg once a month, the incidence of new cholelithiasis in this pediatric population (33%) was higher than that seen in other adult indications such as acromegaly (22%) or malignant carcinoid syndrome (24%), where Sandostatin LAR Depot was 10 to 30 mg once a month.

8.5 Geriatric Use

Clinical studies of Sandostatin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

In patients with renal failure requiring dialysis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. In patients with mild, moderate or severe renal impairment there is no need to adjust the starting dose of Sandostatin. The maintenance dose should be adjusted thereafter based on clinical response and tolerability as in non-renal patients [see Clinical Pharmacology (12) in the full prescribing information].

8.7 Hepatic Impairment - Cirrhotic Patients

In patients with established liver cirrhosis, the starting dose should be 10 mg. This dose should be up titrated based on clinical response and speed of response as deemed necessary by the physician. Once at a higher dose, patient should be maintained or dose adjusted based on response and tolerability as in any non-cirrhotic patients [see Clinical Pharmacology (12) in the full prescribing information].

16 HOW SUPPLIED/STORAGE AND HANDLING

Sandostatin LAR Depot is available in single-use kits containing a 5-mL vial of 10 mg, 20 mg or 30 mg strength, a syringe containing 2.5 mL of diluent, two sterile 1½” 19 gauge needles, and two alcohol wipes. An instruction booklet for the preparation of drug suspension for injection is also included with each kit.

Drug Product Kits

10 mg kit..........................NDC 0078-0340-61
20 mg kit..........................NDC 0078-0341-61
30 mg kit..........................NDC 0078-0342-61
Demonstration kit................NDC 0078-9342-61

For prolonged storage, Sandostatin LAR Depot should be stored at refrigerated temperatures between 2°C and 8°C (36°F–46°F) and protected from light until the time of use. Sandostatin LAR Depot drug product kit should remain at room temperature for 30-60 minutes prior to preparation of the drug suspension. However, after preparation the drug suspension must be administered immediately.
The cloud of thyroid disorders may have a silver lining, with the presence of thyroid autoantibodies apparently reflecting lower frailty rates in elderly women, according to a surprising new study.

“We imagined that the frailest elderly would have higher levels of thyroid autoantibodies, but the results went in the opposite direction,” said George C. Wang, M.D., who with Patrizio Caturchi, M.D., led the study* at Johns Hopkins University School of Medicine, Baltimore, Md. He expects that the findings, to be published in The Journal of Clinical Endocrinology & Metabolism in March, will spur further research, not least into how and why this might be happening. Autoantibodies are generally detrimental to health, causing scores of diseases, from type 1 diabetes to lupus to Goodpasture’s syndrome.

“We are not saying the thyroid autoantibodies are beneficial, but we are not ruling it out, either,” he said in an interview with Endocrine News. “It will be very interesting to know whether we are looking at a snapshot [taken] at the end of a pathophysiological mechanism in which the thyroid is burned out from chronic autoimmune responses, or whether thyroid autoantibodies somehow protect against frailty,” he said.

The study began straightforwardly enough, with Dr. Wang’s team hypothesizing that autoimmunity, triggering or triggered by inflammation, might fuel the development of frailty in some older adults. This geriatric syndrome, demarcated in this research as shrinkage, exhaustion, low energy expenditure, slowness, and weakness reflected in hand grip, is a large burden in the aged. It strikes 7%–17% of men and women over 65 years of age and 25%–30% of those over 85 years.

Little is understood about how much autoimmunity contributes to frailty, but inflammation and autoimmunity are linked, as are frailty and higher concentrations of the inflammation markers interleukin (IL)-6 and C-reactive protein. Based on the thyroid’s key role in regulating metabolism and energy homeostasis, the team focused their research on thyroid autoimmunity—one of the commonest categories of autoimmunity, with thyroglobulin antibodies (TgAB) and thyroid peroxidase antibodies (TPOAb) found in more than 11% of those aged 30–39 years and as many as 22% of 70- to 79-year-olds.

The cross-sectional study examined 641 community-dwelling older women, aged 70–79 years, who participated in the prospective, observational Women’s Health and Aging Studies I and II. The team measured serum levels of thyroid antibodies and also, for control purposes, of antinuclear antibodies (ANA)—systemic autoantibodies that contrast well with the organ-specific thyroid antibodies.

Among the women, 175 were TgAB or TPOAb positive and 318 were ANA positive, including 89 who were also thyroid autoantibody–positive.

The researchers discovered that women with TgAB or TPOAb had an incrementally lower likelihood of being “pre-frail” (having 1 or 2 of the 5 elements) or frail. In contrast, women positive for ANA did not have lower odds for frailty than their ANA-negative counterparts. The analysis used a multinomial regression model, with data adjusted for age, race, education, body mass index, thyroid medication use, smoking, diabetes, cardiovascular disease, IL-6 concentration, and thyroid-stimulating hormone (TSH).

Commenting on the paper, Kenneth D. Burman, M.D., at Washington Hospital Center in D.C., said, “The authors have extensively analyzed possible confounding factors, and the relationship persists even following adjustments for serum TSH concentrations. This unexpected finding requires confirmation and extension, as it may provide insights into the pathophysiology of the aging process.”

Further studies should clarify whether these findings originate from differences in the immune system or thyroid organ changes, the researchers say. For now, the most clinicians can do is keep an eye on the euphemistic cloud. “It’s a long way between finding a mechanism and actually affecting thyroid practice,” Dr. Wang said.

Reference:
The battle over the bulge may have seen its first victory. Two recent JAMA studies from the Centers for Disease Control and Prevention (CDC) suggest that the obesity level in the United States might be stabilizing. Obesity rates have remained constant for 5 years in men and closer to 10 years in women and children.

Don’t blow the bugles just yet—the percentages have stalled at high levels. Nearly 34% of U.S. adults are now obese, double what was reported 30 years ago. And the percentage of obese children has tripped during this time to 17%. In fact, one group, the very heaviest boys aged 6–19 years (≥ 97th percentile) has steadily increased to 15% from 9% in 1999–2000.

“It’s a mixed message,” said Daniel Bessesen, M.D., chief of endocrinology at the Denver Health Medical Center and associate director of the Colorado Center for Human Nutrition. “While reassuring, obesity is still a big, big problem that causes health problems such as heart disease, hypertension, and diabetes.” These problems, he indicated, are driving the costs of health care. An accompanying editorial to these studies mentions that obesity-related conditions accounted for an estimated 10% of annual medical spending expenses in 2008, or $147 billion.

Some specialists say this tapering off may be biological—a sort of natural limit on how obese people can get. True success, most say, will occur when the rates start to drop. Others optimistically point out that these numbers represent a tipping point in how society views weight gain with more people, eschewing the supersized meal portions and embracing physical activity.

The agency has targeted six behaviors to help keep obesity at bay: more physical activity, breastfeeding, fruit and vegetable intake, reduced TV time, high-calorie foods, and sweetened beverage intake. However, more troops are needed in this fat fight, specifically support from restaurants, schools, food manufacturers, and even physicians.

“We’re still not at the point of celebrating anything,” said Joy Bunt, M.D., Ph.D., medical director of the Obesity & Diabetes Clinical Research Section, National Institute of Diabetes and Digestive and Kidney Diseases, in Phoenix, Ariz. “A lot of physicians out there still need to be educated about obesity, to think about it as a disease and not a character defect,” she stated, noting that some of her obese patients have been made to feel like it’s all their fault and failed to get proper collaboration with their primary providers who were too strapped for time to deal with the issue adequately.

Other countries have also seen a leveling effect. An 11-year study of Greek boys and girls aged 8–9 years in January’s Obesity1 showed that after forging upward, the prevalence of obesity evened off in the past 4 years. Similarly, a large cohort study of German children and adolescents revealed that although overweight and obesity prevalence continued to surge in boys aged 12–16 years between 2004 and 2008, it respectively dropped and smoothed out in boys 4–12 years and in girls 4–16 years.4

U.S. obesity rates are the world’s highest, but rates in many other countries are not far behind. For global data, see www.nationmaster.com/graph/hea_obe-health-obesity.

References:
Public uproar recently followed a scientific panel’s announcement to the U.S. Department of Health and Human Services that mammograms should not be routinely recommended to women under 50 years old. This generalized advice flies in the face of studies showing that African American women are more likely than white women to develop breast cancer before age 50 and—at all ages—to die of the disease. This gap in the mortality rate has been widening since the mid-1980s. Genetic studies suggest that primarily environmental rather than hereditary factors cause this discrepancy.

Specifically, breast cancer risk and mortality requires considering an individual’s social environment, not just chemical exposure, according to Sarah J. Gehlert, Ph.D., speaking at a December 2009 lecture sponsored by the National Institutes of Health Office of Behavioral and Social Sciences Research. The link between upstream, social causes and downstream, genetic changes is best studied using a transdisciplinary approach, “a way of doing science in which investigators work entirely outside their disciplines,” she said.

Safety (and Health) in Numbers

Working at Washington University in St. Louis, Mo., Dr. Gehlert is part of a team of social scientists, molecular biologists, geneticists, surgeons, breast oncologists, and psychologists investigating the role of race—a surrogate for socioeconomic status in the United States—in breast cancer mortality. In their approach, animal study findings inform the direction of community-based participatory research (CBPR) on the social environment of African American women with breast cancer living in impoverished neighborhoods, and vice versa. For instance, the researchers found that socially isolated female rats were much more likely to develop mammary tumors than those in social groups. In response to environmental changes, the isolated rats became “hypervigilant”—fearful and reluctant to explore—and their stress hormone levels peaked higher and returned to normal more slowly compared with controls. In isolated mice, as mammary tumors became more invasive, they expressed more stress hormone and fewer estrogen and progesterone receptors. 1

“In the same way we manipulated the social environment to cause this acquired vigilance in the animals and alter their behavior, distressed neighborhoods can do the same thing to women: They alter their social functioning, they change their psychological functioning, and as we’re finding, that changes biology,” Dr. Gehlert said.

The CBPR study (unpublished results) enrolled 230 African American women from Chicago’s South Side upon diagnosis. The women represented a broad socioeconomic spectrum, including those with and without insurance and on Medicare. They were interviewed in-depth in their homes every 6 months for 1½ years about various aspects of their lives including their social networks, health behaviors, perceived discrimination, and major life events, for 18 hours total face-
to-face time. Participants kept a diary and collected data for daily salivary cortisol measurements. The researchers also evaluated their neighborhoods for dilapidated housing, crime, collective efficacy, and socioeconomic status.

For the study women, living in a neighborhood with poor infrastructure, high crime rates, and unsafe housing—and the variation in these factors almost block by block is significant—gave rise to psychosocial effects through increased likelihood of sexual assault and decreased collective efficacy, i.e., the faith that positive outcomes are achievable for the community as a whole. The participants had high rates of clinical depression (32%), loneliness (relative to African American women in more affluent Cook County), and sexual assault (compared with Centers for Disease Control and Prevention reports). They also moved frequently (68% within the last 10 years).

**Stress Hormones**

Endocrine changes apparently linked psychosocial causes with biological effects. Women who were depressed, lonely, or had been sexually assaulted were more likely to have their diurnal salivary cortisol rhythms disrupted. The diurnal cortisol cycles of 67% of the women in the study were relatively flat. These women were more likely to be living under the most desperate circumstances, homeless, or near-homeless. “When we asked these women what was going on in their lives, what were the worst things, they made breast cancer third or fourth,” Dr. Gehlert said. Furthermore, the researchers’ preliminary results link stress response to cancer virulence in study participants: glucocorticoid receptors were up-regulated in 70% of invasive cancers but in only 28% of ductal carcinomas.

Their research has received a lot of fanfare. “It’s fascinating work, well-conceived, and worth a lot of attention,” said Robert A. Hiatt, M.D., Ph.D., chair of the Department of Epidemiology and Biostatistics and deputy director of the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco. Dr. Hiatt is leading a prospective investigation of environmental influences, including exposure to endocrine disruptors and other chemicals, lifestyle exposures, and the social environment, on pubertal development in a cohort of racially and ethnically diverse girls—part of a transdisciplinary study of early menarche and breast cancer etiology.

Researchers with “non-traditional” backgrounds like geography (contributors to Dr. Hiatt’s study) or social work (Dr. Gehlert’s) enrich transdisciplinary research with new perspectives. Regarding himself as a “quantitative person,” Dr. Hiatt emphasized that “an in-depth understanding of qualitative relationships—that’s what anthropologists, sociologists, or ethnographers can tell us from looking at things like social isolation—are good data and provide valuable scientific insights. If combined appropriately with quantitative data, they can give you a better understanding of a phenomenon than quantitative data alone.”

JoAnn Manson, M.D., Dr.P.H., professor at Harvard Medical School in Boston, Mass., agreed on the value of Dr. Gehlert’s work and pointed out another health effect that could be exacerbated by living in a neighborhood without safe or welcoming outdoor spaces. “It would be of great interest to assess whether vitamin D deficiency, a condition that is more prevalent in African Americans, contributes to racial/ethnic disparities in breast cancer incidence and mortality,” she said. Studies have suggested that sufficient vitamin D might protect against breast cancer.

**Neighbor Helping Neighbor**

Dr. Gehlert suggested that closing the breast cancer mortality disparity between African American and white women could best be achieved with interventions targeted at neighborhood factors. In her ongoing work, she is evaluating how “support coordinators” who live in the neighborhood can help women with breast cancer improve their adherence to chemotherapy and decrease their stress. She is also beginning a study of impoverished African American and white women in the Missouri Bootheel, to help tease apart the roles of race and socioeconomic status.

---

Reference:

* Jennifer Grant Lee is a freelance science writer living in Silver Spring, Md.
Furtheing the interests of its members and endocrinology in general, The Endocrine Society had another successful year in 2009. Efforts on several issues important to basic scientists, clinical researchers, and physicians-in-practice, yielded important advances for endocrinologists and their patients. Major advocacy efforts included briefing Capitol Hill staff on obesity research and treatment and steps to combat dual X-ray absorptiometry (DXA) payment cuts; collaborating with congressional offices on endocrine-disrupting chemicals (EDC) legislation; and advancing recommendations on increasing minority participation in clinical research. The Society will build on these achievements in 2010.

Biomedical Research Funding Increase

Congress and President Obama recognized the important work done by the National Institutes of Health (NIH) to ensure the health of American citizens by allocating it more than $10 billion in the American Recovery and Reinvestment Act of 2009 and through a 2.25% budget increase for fiscal year 2010. These increases are directly related to the scientific community’s work to demonstrate the value of biomedical research, including steps by many coalitions in which the Society participates. Grassroots efforts by researchers also play a significant role in shaping how congressional members regard biomedical research funding. Society action alerts prompted more than 1,000 letters and calls to members of Congress.

In 2009, the Society joined United for Medical Research, a new coalition of academia, industry, patient advocacy, and non-profit organizations. The coalition is developing a report that highlights the health and economic outcomes associated with the stimulus money given to NIH; hosting salon dinners with thought leaders from academia, Capitol Hill, and the administration; and meeting with administration officials. The Society also continues to work with the Federation of American Societies for Experimental Biology, the Ad Hoc Group for Medical Research, Friends of NICHD, Friends of VA Medical Care and Health Resources, the Alliance for Aging Research, and the National Association of Biomedical Research/Foundation for Biomedical Research.

Briefing Capitol Hill Staff on Obesity

In February, Endocrine Society members, in collaboration with Research!America, briefed congressional health policy staff about the prevention and treatment of obesity and engaged in discussions about possible legislative solutions to this public health problem. The briefing, attended by more than 50 representatives from congressional offices, the administration, and non-profits, included presentations by Leonard Wartofsky, M.D., chairman of the Department of Medicine at Washington Hospital Center; Daniel Bessesen, M.D., chief of endocrinology at the Denver Health Medical Center and associate director of the Colorado Center for Human Nutrition; and Myron Genel, M.D., professor emeritus of pediatrics and senior research scientist at Yale University School of Medicine. Congresswoman Carolyn McCarthy (D-NY) sponsored the briefing and opened it by stressing the importance of tackling the obesity epidemic.

This briefing illustrates the value of the Society’s investment in advocacy for solutions to make the public aware of this urgent problem. For the last several years, the Society has been working to educate Congress, the media, and the public about the role of endocrinology in fighting and treating obesity and the importance of research in this area. These efforts have focused on advancing public policy solutions that meet the needs of Society members and their patients. Through this briefing, the Society has identified many new partners to engage in its advocacy efforts.
**DXA Provision Passed in Health Reform**

The Senate passed the Patient Protection and Affordable Care Act (HR 3590) on December 24, 2009, and included a 2-year fix of the payment cuts to DXA services performed in the physician’s office. If the provision remains in the bill signed by the President, payment rates will be set at 70% of the 2006 level (approximately $98) for 2010 and 2011.

Since early 2007, a group of specialty societies have worked actively with members of Congress, including Sens. Blanche Lincoln (D-AR) and Olympia Snowe (R-ME) and Reps. Shelley Berkley (D-NV) and Michael Burgess (R-TX), to identify a solution to the cuts that have lowered payment rates by more than 65% since 2007. The Society has worked aggressively to identify a solution to these cuts to support members who provide this vital test to patients in their offices. Earlier in the year, the Society and the National Osteoporosis Foundation identified a sponsor in the Senate. Since that time, the coalition has been building support for the legislation on Capitol Hill, which ultimately led to Sen. Lincoln’s inclusion of the language in the health reform legislation developed by the Senate Finance Committee.

**EDC Legislation**

To support the goals outlined in its Scientific Statement and position statement on EDCs, the Society endorsed the “Endocrine Disruption Prevention Act of 2009” (HR 4190/S 2828), introduced in December by Rep. Jim Moran (D-VA) and Sen. John Kerry (D-MA). Entirely in line with the Society’s positions, the bill will advance endocrine science in the field of EDCs and improve the regulatory process by ensuring that the best science informs it. Specifically, the bill addresses the need for more research on EDCs and for coordinated output of research results, proposing to develop a research program under the auspices of the National Institute of Environmental Health Sciences.

To help strengthen EDC regulation, the Society has discussed its scientific and position statements with the staff of committees that have jurisdiction over this issue, including the House Energy and Commerce Committee and the Senate Environment and Public Works Committee, and with the staff of Reps. Moran, Slaughter (D-NY), Rush (D-IL), and Markey (D-MA). The Society also provided comments on draft language to overhaul the Toxic Substance Control Act and will continue to offer support to this process in the coming months. The American Medical Association also supported a Society-sponsored resolution calling for improved EDC regulation.

**Disparity Recommendation Included in Health Reform**

In late 2007, The Endocrine Society Task Force to Increase Minority Participation in Clinical Research, supported by a grant from the Robert Wood Johnson Foundation, completed its work by publishing a white paper. This discusses the barriers that patients and researchers face in minority recruitment and the tools needed to ensure significant participation in clinical research, and makes recommendations to policy makers in Congress, the NIH, the Food and Drug Administration (FDA), and the pharmaceutical industry. As a result of the Society’s ongoing work with the Congressional Black Caucus, a recommendation from this white paper to establish an Office of Minority Health at the FDA was included in the “Health Equity and Accountability Act” (HR 3090), and subsequently the House health reform legislation.

**Focus on Diabetes through Coalitions, Legislation, and Provider Statements**

The Society continued its advocacy efforts to increase funding for diabetes research and treatment. It joined two new coalitions focused on different aspects of diabetes care and management, including the National Changing Diabetes Program and the Intensive Diabetes Management Coalition. These new coalitions complement work the Society is already involved in with the National Diabetes Education Program and with other organizations such as the American Diabetes Association and the Juvenile Diabetes Research Foundation.

In addition to its coalition work, the Society actively lobbied in support of the “National Diabetes Coordinator Act,” legislation that would coordinate the diabetes-related activities of all federal agencies. The Society endorsed the legislation in the 110th Congress and supported Jay Inslee’s (D-WA) efforts to reintroduce the bill in the 111th Congress. At this time, the congressman is unsure of his intentions to reintroduce the bill. The Society also endorsed the “Eliminating Disparities in Diabetes Prevention, Access and Care Act of 2009” (HR 1995/S 844), introduced by Rep. Diana DeGette (D-CO) and Sen. Frank Lautenberg (D-NJ).

Finally, to keep members informed of new diabetes-related studies, the Society released statements about a report on the link between insulin glargine and cancer, and about the NICE-SUGAR study.  

* Stephanie Kutler is Associate Director, Government Affairs, The Endocrine Society.
Below are summaries of selected studies to be published in Endocrine Society journals. Once edited, the papers will be posted online pre-publication. See www.endojournals.org, choose the journal, and click "Rapid Electronic Publications." To subscribe, if not a member, please email societieservices@endo-society.org.

Studies Coming in
Molecular Endocrinology

➤ TBT sensitizes MSCs to differentiate into adipocytes, providing possible insight into the link between obesity and bone loss that result from PPAR treatment activators.
Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes.

➤ Regulation of osteoblast maturation depends on cross-talk between the Wnt and TGF-β pathways, which converge on Runx2.
McCarthy TL, Centrella M. Novel links among Wnt and TGF-β1 signaling, and Runx2.

➤ Some of these metabolites were not associated with insulin resistance.

Studies Coming in
Endocrinology

➤ Endothelial function, but not carotid IMT, is affected early in menopause, with hot flush severity the main predictor.
Bechlioulias A, Kalantaridou SN, Naka KK, et al. Endothelial function, but not carotid intima-media thickness, is affected early in menopause and is associated with severity of hot flushes.

➤ Patients with presumed EAS warrant initial imaging with thoracic CT/MRI plus LOCT scans.

➤ IgG4 and non-IgG4 thyroiditis present significantly different clinical and histopathological characteristics, so serum IgG4 levels should be measured for classification purposes.
Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A, Kennichi K. Distinct clinical, serological, and sonographic characteristics of Hashimoto’s thyroiditis based with and without IgG4-positive plasma cells.

➤ Metabolic syndrome especially influences LUTS and overactive bladder in women with T2D, most likely by compounding peripheral neuropathy’s effect.

Studies Coming in
Endocrine Reviews

➤ CDK2 nuclear–cytoplasmic trafficking and cyclin E are involved in 1,25-(OH)2D–mediated growth inhibition in prostate cancer cells.

➤ Dmrt1 repression of aromatase transcription, a possible mechanism favoring the male pathway in tilapia.

➤ In obese mice, leptin drives fatty acid metabolism in cardiac tissue by reducing CPT-1 activity via an Akt-related signaling pathway.

➤ NCoR declines in neonatal rat amygdalas increases anxiety-like behavior in males and females and boosts juvenile social play behavior in males.
Jessen HM, Kolodkin MH, Bychowski ME, Auger CJ, Auger AP. The nuclear receptor corepressor, NCoR, has organizational effects within the developing amygdala on juvenile social play and anxiety-like behavior.

Studies Coming in
The Journal of Clinical Endocrinology & Metabolism

➤ Froy O. Metabolism and circadian rhythms—implications for obesity.

➤ Page-Langenickel I, Bao J, Pang L, Sack MN. The role of mitochondria in the pathophysiology of skeletal muscle insulin resistance.

➤ Kowluru A. Small G proteins in islet β-cell function.

➤ Vuong C, Van Uum SHM, O’Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems.

➤ Hel Z, Stringer E, Mestecky J. Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection.
High Blood Calcium (Hypercalcemia)

What is high blood calcium?

People with high blood calcium, also called hypercalcemia, have above-normal levels of calcium in their blood.

Calcium is a mineral found mostly in your bones, where it builds and maintains bone strength. A small amount of calcium is also found in muscle and blood cells, where it plays several important roles:

- Helps muscles contract
- Helps nerves and the brain work properly
- Helps regulate your heart rhythm and blood pressure

High blood calcium often does not cause any health problems. But over time, some causes of high blood calcium can lead to osteoporosis (thinning of the bones) and kidney stones. Very high blood calcium can cause more serious problems, including kidney failure, heart rhythm abnormalities, mental confusion, and even coma.

How does your body control blood calcium levels?

Normally, your body controls blood calcium by adjusting the levels of several hormones.

When blood calcium levels are low, your parathyroid glands (four pea-sized glands in your neck) secrete a hormone called parathyroid hormone (PTH). PTH helps your bones release calcium into the blood.

Vitamin D is also important in keeping calcium levels in the normal range. Vitamin D, which is actually a hormone, helps your body absorb calcium and move it from your intestines into your bloodstream.

Together, PTH and vitamin D, along with other hormones and minerals, help move calcium in or out of body tissues to keep your blood calcium at a normal level.

What causes high blood calcium?

The most common cause of high blood calcium is a condition called primary hyperparathyroidism. In this condition, one or more of the parathyroid glands produces too much PTH, which causes the bones to release too much calcium into the blood. Women over the age of 50 are more likely than others to have hyperparathyroidism.

Certain types of cancer, such as breast cancer, lung cancer, or multiple myeloma (a type of blood cancer), can also cause high blood calcium. This usually occurs late in the course of cancer.

Less common causes of hypercalcemia include:

- A genetic condition called familial hypocalciuric hypercalcemia
- Some types of infectious diseases, such as tuberculosis
- Some types of autoimmune disease, such as sarcoidosis
- Hormone disorders, such as hyperthyroidism
- Some medicines, such as lithium (used for psychiatric conditions) or rarely, thiazide diuretics
- Intake of very large amounts of calcium or large amounts of milk plus antacids
- Immobility—being confined to bed for at least several weeks—in combination with some bone conditions
- Kidney failure
- Tube feeding or being fed through a vein (TPN)
- Severe dehydration

How is high blood calcium diagnosed?

High blood calcium is diagnosed through a blood test that measures calcium levels. To help pinpoint the cause, your health care provider may check PTH and vitamin D levels, as well as kidney function and levels of calcium in your urine. Your provider may do other tests to further assess your condition, such as checking your phosphate levels, bone mineral density, or performing ultrasound or other types of scans.

Symptoms of high blood calcium

High blood calcium may cause no symptoms, or may cause symptoms such as:

- Muscle weakness
- Fatigue
- Constipation
- Nausea
- Confusion

How is high blood calcium treated?

Your treatment will depend on the cause of your high blood calcium. In general, the best treatment is to take care of the condition that is causing the high blood calcium. For example, people with primary hyperparathyroidism who have symptoms usually have surgery to remove the problem-causing parathyroid gland.

Until the underlying problem is resolved, treatment may include medicines to improve blood calcium levels. When high blood calcium is very severe, people may need to be treated in a hospital to return their blood calcium to a safe level.

You might not need any treatment if your blood calcium is only slightly high or you haven’t developed any health problems. Instead, your health care provider will continue to check your condition over time.

Talk with your health care provider about the best treatment for your particular condition.

Resources

Find-an-Endocrinologist: www.hormone.org or call 1-800-HORMONE (1-800-467-6663)
MedlinePlus: www.medlineplus.gov

For more information on how to find an endocrinologist, download free publications, translate this fact sheet into other languages, or make a contribution to The Hormone Foundation, visit www.hormone.org or call 1-800-HORMONE (1-800-467-6663). The Hormone Foundation, the public education affiliate of The Endocrine Society (www.endo-society.org), serves as a resource for the public by promoting the prevention, treatment, and cure of hormone-related conditions. This page may be reproduced non-commercially by health care professionals and health educators to share with patients and students.

© The Hormone Foundation 2009
EXCESO DE CALCO EN LA SANGRE (HIPCERCALCEMIA)

¿Qué es el exceso de calcio en la sangre?

Las personas con exceso de calcio en la sangre, también denominada hipercalemia, tienen un nivel de calcio en la sangre que está por encima de lo normal.

El calcio es un mineral que se encuentra mayormente en los huesos, donde se acumula y los mantiene fuertes. También hay una pequeña cantidad de calcio en los músculos y las células de la sangre, donde desempeña varias funciones importantes:

- contribuye a la contracción de los músculos
- ayuda a que los nervios y el cerebro funcionen debidamente
- ayuda a regular el ritmo cardíaco y la presión arterial

El exceso de calcio en la sangre puede llevar a problemas de salud. Pero con el tiempo, algunas de las causas del exceso de calcio en la sangre pueden resultar en osteoporosis (debilitamiento de los huesos) y cálculos del riñón. Un nivel muy alto de calcio en la sangre puede causar problemas más serios, como faltas renales, ritmo cardíaco anormal, confusión mental e incluso llevar a un coma.

¿Cómo controla el cuerpo el nivel de calcio en la sangre?

Normalmente, el cuerpo controla el calcio en la sangre ajustando los niveles de varias hormonas.

Cuando el nivel de calcio está bajo, las glándulas paratiroideas producen una hormona llamada hormona paratiroidea. Ésta ayuda a los huesos a liberar calcio en la sangre.

La vitamina D también es importante para mantener el nivel de calcio normal. La vitamina D, que en realidad es una hormona, ayuda al cuerpo a absorber calcio y sacarlo de los intestinos para llevarlo a la sangre.

La hormona paratiroidea y la vitamina D, junto con otras hormonas y minerales, ayudan a trasladar el calcio dentro y fuera de los tejidos para mantener un nivel normal de calcio en la sangre.

¿Qué causa el exceso de calcio en la sangre?

La causa más común de exceso de calcio en la sangre es un trastorno llamado hiperparatiroidismo primario. Este trastorno hace que una o más de las glándulas paratiroideas produzcan demasiada hormona paratiroidea, lo que causa que los huesos liberen demasiado calcio en el torrente sanguíneo. Las mujeres mayores de 50 años tienen más probabilidades de sufrir de hiperparatiroidismo.

Algunos tipos de cáncer, como el cáncer de mama y pulmón, o el mieloma múltiple (un tipo de cáncer en la sangre), pueden causar exceso de calcio en la sangre. Esto usualmente ocurre en las etapas finales del cáncer.

Otras razones menos comunes para la hipercalemia:

- una enfermedad genética llamada hipercalemia hipocalciúrica familiar
- algunas enfermedades infecciosas como la tuberculosis
- algunas enfermedades autoinmunes como la sarcoidosis
- trastornos hormonales, como el hipertiroidismo
- algunos medicamentos, como el litio (usado para enfermedades psiquiátricas)
- en casos poco comunes, los diuréticos con tiazídicos
- consumo de gran cantidad de calcio o de leche, combinado con antiácidos
- inmovilidad; haber estado en cama varias semanas, en combinación con algunos trastornos óseos
- insuficiencia renal
- alimentación por sonda nasogástrica o intravenosa (TPN)
- deshidratación severa.

¿Cómo se diagnostica el exceso de calcio en la sangre?

El exceso de calcio en la sangre se diagnosticaba con pruebas de sangre que miden el nivel de calcio. Para ayudar a encontrar la causa, su médico puede examinar el nivel de hormona paratiroidea y vitamina D, el funcionamiento de los riñones y el nivel de calcio en la orina. Su médico puede hacerle otros exámenes para evaluar mejor su condición, como medir el nivel de fósforo o la densidad mineral ósea, o realizar una ecografía u otro tipo de prueba.

¿Cuál es el tratamiento en caso de exceso de calcio en la sangre?

El tratamiento para usted dependerá de la causa del exceso de calcio en la sangre. En general, el mejor tratamiento es tratar el trastorno que está causando el exceso de calcio en la sangre. Por ejemplo, a los pacientes con hiperparatiroidismo primario que presentan síntomas, generalmente se les opera para extirpar la glándula paratiroidea que está causando los problemas.

Hasta que no se resuelva el problema de fondo, el tratamiento puede incluir medicamentos para mejorar el nivel de calcio. Cuando el exceso de calcio en la sangre es severo, el paciente puede requerir hospitalización para que vuelva a un nivel que no comprometa su salud.

Quizá no necesite ningún tratamiento si su nivel de calcio en la sangre no es muy alto o si no presenta problemas de salud. En ese caso, su médico continuará vigilando su condición por un tiempo.

Consulte con su médico o proveedor de salud acerca del mejor tratamiento para su situación en particular.

Recursos

Encuentre un endocrinólogo: www.hormone.org o llame al 1-800-467-6663
MedlinePlus: www.medlineplus.gov
Exceso de calcio en la sangre (Hipercalcemia)

¿Cómo controla el cuerpo el nivel exceso de calcio en la sangre puede resultar en exceso de calcio en la sangre. Para mantener el nivel de calcio dentro de los límites normales, algunas de las causas del exceso de calcio en la sangre.

- Aumento de la liberación de calcio de los huesos.
- Producción excesiva de calcio por el hígado.
- Ingesta de calcio en exceso.
- Enfermedades genéticas que causan liberación de calcio.
- Trastornos hormonales, como hiperparatiroidismo.
- Infecciones o procesos inflamatorios que causan liberación de calcio.
- Drogas que aumentan la liberación de calcio.

Las consecuencias de un exceso de calcio en la sangre pueden incluir:

- Cambios en el funcionamiento muscular y nervioso.
- Problemas en la absorción de vitaminas D.
- Problemas en la función renal.
- Problemas en la función ósea.
- Problemas en la función intestinal.

El tratamiento del exceso de calcio en la sangre dependerá de la causa subyacente. En algunos casos, puede ser necesario tomar medicamentos para reducir la liberación de calcio. En otros casos, el tratamiento puede incluir cambios en la dieta y estilo de vida.

Para más información, consulte el sitio web de la Fundación de Hormonas (www.endo-society.org).


Lose Pounds, Gain Currency

La pérdida de peso puede ser un objetivo complicado, pero con el apoyo adecuado y el enfoque correcto, puede ser posible. Algunas organizaciones ofrecen incentivos económicos para animar a las personas a adoptar un estilo de vida saludable. Estos incentivos pueden ser en forma de fondos o regalos.

Por ejemplo, el sitio web HealthyWage.com ofrece incentivos para quienes pueden perder peso. Los participantes pueden apostar una cantidad determinada y si logran perder peso, reciben el monto apostado más el 10% de la suma apostada. Sin embargo, si no logran perder peso, deben pagar el monto apostado. Este tipo de incentivos puede ser una forma de motivar a las personas a adoptar hábitos saludables y perder peso.


Fat Fighters

By Jacqueline Ruttimann, Ph.D., Staff Writer

Una estrategia no convencional de tratar el tipo 2 de diabetes y obesidad ha recibido su bendición de los reguladores. Un dispositivo gastrointestinal llamado EndoBarrier™ ahora está aprobado para su uso en la Unión Europea.

Desarrollado por GI Dynamics, una empresa de dispositivos médicos en Lexington, Mass., el dispositivo se utiliza creando una barrera entre la comida y el sistema digestivo. Al controlar la liberación de calcio de los huesos, el nuevo tratamiento evita el exceso de calcio en la sangre que puede ser perjudicial para la salud.

Los beneficios de un tratamiento con EndoBarrier™ incluyen el control del peso, la mejora de la tolerancia a la glucosa y la disminución de la enfermedad cardiovascular. También puede ayudar a prevenir la necesidad de cirugía bariátrica.

El tratamiento con EndoBarrier™ es un enfoque no quirúrgico y por tanto, puede ser una opción para aquellos que desean evitar la cirugía. Sin embargo, también es importante considerar los posibles efectos secundarios asociados con este tratamiento.

Para más información, consulte el sitio web de la Fundación de Hormonas (www.endo-society.org).
Hurry! Vote in Society Elections

➤ The window for The Endocrine Society’s annual elections is open, and eligible members are encouraged to cast their ballots before it closes on March 8, at midnight U.S. Eastern Time.

Members who have active or emeritus status, and students with a doctoral degree, can vote via the online ballot.

Positions open for voting are:
- President-Elect—Clinical Scientist
- Vice President—Physician-in-Practice
- Council—Basic Scientist seat
- Council—At Large seats (two)

Eligible members were sent an email ballot in early January. To report any missing ballots or to seek more information, visit www.endo-society.org/membership/election.cfm. Election results will be announced online mid March.

Nominate for Society’s Journalism Award Now!

➤ The Society is seeking worthy nominations for the third annual Award for Excellence in Science and Medical Journalism. The award will honor one journalist for outstanding reporting that enhances public understanding of medical and science issues pertaining to the field of endocrinology. Submissions must be received by March 2, 2010.

The award is open to all credentialed journalists in print (both “hard” and electronic) or broadcast. Candidates can self-nominate or be nominated by someone else. Only one nomination is permitted for each nominee. Submissions can include any work first published between March 1, 2009 and February 28, 2010.

Weight will be given to entries that contribute to the public understanding of endocrinology and demonstrate thorough research, accurate reporting, and originality.

The honor consists of an award to be presented at the Society’s annual meeting in June 2010 in San Diego, Calif. The recipient will also receive complimentary travel and hotel accommodations to attend this meeting.

Nomination forms and eligibility and submission requirements can be found at www.endo-society.org/media/Journalism-Award.cfm. To apply, please submit the completed nomination form and three copies of the article/work, whether published or taped, to Aaron Lohr, The Endocrine Society, 8401 Connecticut Ave., Ste. 900, Chevy Chase, MD 20815.

Fact Sheet on Endocrine Disruptors

➤ The Hormone Foundation has produced a new consumer fact sheet, Environmental Endocrine-Disrupting Chemicals (EDCs), based on The Endocrine Society’s 2009 scientific statement on the same topic. The fact sheet is designed to educate readers about the classes of chemicals known to have endocrine-disrupting effects—such as industrial solvents, plasticizers, and pesticides—and the routes through which individuals can be exposed.

It touches on known and suspected health consequences of EDC exposure and explains the greater vulnerability of a developing fetus or infant. A list of additional resources encourages readers to learn more about how they can protect themselves and their children.

The fact sheet is available at www.hormone.org/upload/EDC-FINAL.pdf.

MAC Exhibits Target Minority Students

➤ In the fall of 2009, the Minority Affairs Committee (MAC), in its continuing mission to increase cultural diversity in The Endocrine Society and in the field of endocrinology, participated in the annual conference of the Society for Advancement of Chicanos and Native Americans in Science, October 15–18, in Dallas, Tex. MAC representatives also participated in the Annual Biomedical Research Conference for Minority Students held in Phoenix, Ariz., November 4–8. These conferences target minority students from around the country who are interested in pursuing graduate education or advanced degrees in scientific contributions and achievements in the field of endocrinology. All nominations must be submitted by an Active or Emeritus Member of the Society, through the Laureate Awards’ home page, www.endo-society.org/awards/LaureateAwards/index.cfm.

Nominations and supportive documentation must be received by April 1, 2010. Please direct questions to Jeanie Dow at laureate@endo-society.org.
research or teaching careers.

MAC representatives disseminated information on MAC and Society programs, recruited new members, and networked. Exhibitors included academic institutions, non-profit organizations, and private foundations.

Four students who participated in the Society’s Minority Access Program during the 2009 summer recess received travel grants to present their endocrine research projects at these conferences. Congratulations to:

- Andres Betancourt-Torres—University of Puerto Rico (UPR), Cayey
- Frenzy Mendoza—Chaminade University of Honolulu
- Rosan Nieves-Borges—UPR, Cayey
- Nelitza Rivera—UPR, Cayey

Fellowship Awards

➤ Trainees, remember to apply for these awards. Applications are due on February 12, 2010:
  - Summer Research Fellowships
  - Lilly Endocrine Scholars Award
  - Solvay Clinical Research Award
Find out how at www.endo-society.org/awards/research_fellowship.

New Year, New Look for Society Journals

➤ A new and exciting look has been given to the covers of three of The Endocrine Society’s journals—Endocrinology, Endocrine Reviews, and The Journal of Clinical Endocrinology & Metabolism (JCEM). Designed to have a more contemporary look and to promote a unified appearance in the family of journals published by the Society, the new covers feature a centralized image against a bold color background and prominent title treatment. The newly designed journals meet the approval of each Editor-in-Chief (EIC).

> “I love the new cover design with its bold, brick-red cover,” raves Jeffry D. Blaustein, Endocrinology EIC. “Now the cover of our journal, as well as its content, will stand out among all the other journals on our colleagues’ shelves.”

Leonard Wartofsky, JCEM EIC, adds, “Although the bold, new design on the outside may reflect exciting innovative features soon to appear in the journal, JCEM will continue to provide on the inside the same outstanding science and timely attention to what is new and relevant in clinical endocrinology!”

Comments R. Paul Robertson, Endocrine Reviews EIC: “The new, deep, and cool color is consistent with the major goals of Endocrine Reviews: restful reflection, deep thinking, and broad vision.”

Hormones & Cancer Now Accepting Manuscripts

➤ Calling all authors! Here’s your chance to get in on the ground floor of the newly minted Hormones & Cancer, published jointly by the Society and Springer Publishing. Linking the sometimes disparate but often related fields of endocrinology and oncology, the journal publishes translational science, including basic research on the structure and function of the endocrine system and cancer, as well as clinical and epidemiology studies involving endocrine-related cancers. Hormones & Cancer is published 6 times a year and is available in print and online at SpringerLink.com.
To submit articles online, go to www.editorialmanager.com/hoca.

Become a Member: Save on ENDO Registration

➤ If you become a new member or renew your membership in The Endocrine Society, you can save up to $500 on registration for ENDO 2010 in San Diego, June 19–22.

By joining or renewing, you can expand your networking with colleagues from around the world and learn about the latest advancements in research and new treatment trends. You can use all of the benefits that membership has to offer. To join or renew and secure your discounted registration rate, go to www.endo-society.org/membership.
Diabetes Center Director

The Division of Endocrinology, Metabolism and Diabetes at the University of Utah, School of Medicine, is recruiting a Medical Director (CMD) for adult clinics housed at the Utah Diabetes Center (UDC). The CMD will also oversee the strategic expansion of clinical endocrinology and diabetes services in community clinics within the University of Utah Health Care Network (UUHN). The CMD will report to the Chief of the Division of Endocrinology, Metabolism and Diabetes, and will work closely with UUHN administrative and support staff at the UDC and community clinics. The incumbent will provide management oversight of clinical and support staff at all Endocrinology and Diabetes practice sites. The scope of responsibility includes management oversight of the UDC and community endocrinology and diabetes operations, including but not limited to quality oversight, program development, care coordination, referring physician coordination, and patient satisfaction. The CMD will also work closely with the School of Medicine, Department of Internal Medicine, and Division of Endocrinology, Metabolism and Diabetes. This position requires a medical degree with board certification in Endocrinology and Metabolism and with strong clinical interest and experience. Candidates should be eligible for appointment at the rank of associate professor and administrator. Leadership experience is desirable. Additional qualities include: results-oriented management style; clear communication skills; strong interest and experience in business administration and operational efficiency; and, the ability to work in a collaborative, team-based environment. The University of Utah is situated in Salt Lake City and is the major tertiary referral center for a five-state region. To apply or request additional information about this opportunity, please send curriculum vitae, summary of accomplishments and career goals with contact information to: E. Dale Abel, M.D., Ph.D., c/o Jessica Kuo, Internal Medicine Administration, 30 North 1900 East, Room 4C104, Salt Lake City, UT 84132-2406 or to jessica.kuo@hsc.utah.edu. The University of Utah is an Affirmative Action/Equal Opportunity employer and does not discriminate based on race, national origin, color, religion, sex, age, sexual orientation, gender identity/expression, disability, or status as a Protected Veteran. Upon request, reasonable accommodations in the application process will be provided to individuals with disabilities. To inquire about the University’s nondiscrimination policy or to request disability accommodation, please contact: Director, Office of Equal Opportunity and Affirmative Action, 201 S. Presidents Circle, Rm 135, 801-581-8365. The University of Utah values candidates who have experience working in settings with students from diverse backgrounds, and possess a demonstrated commitment to improving access to higher education for historically underrepresented students.

Endocrinologist, Bloomington, Illinois

OSF Saint Joseph Medical Center seeks BDC/BDE Endocrinologist. Limited call. Enjoy a strong referral base from OSF Medical Group primary care physicians in the area. Practice in the area’s most complete multi-specialty healthcare practice with more than 60 providers representing 20+ specialties. Very competitive salary; full benefit package. Call or send CV to: Rachel Reliford, OSF Recruitment Ph: 309-683-8352 or 800-232-3129 (8) Email: rachel.reliford@osfhealthcare.org Web: www.osfhealthcare.org.

Endocrinologist, Rockford, Illinois

OSF Saint Anthony Medical Center, a 254-bed, Level 1 Regional Medical Center and tertiary care facility, seeks BDC/BDE Endocrinologist. Join our community with a population of 400,000+ and enjoy a strong referral base from OSF Medical Group primary care physicians in the area. Very competitive salary; full benefit package. Call or send CV to: Rachel Reliford, OSF Recruitment Ph: 309-683-8352 or 800-232-3129 (8) Email: rachel.reliford@osfhealthcare.org Web: www.osfhealthcare.org.

Endocrinologist: Fee for Service

Bayside, Queens, or Brooklyn. A member of the YAI Network, Premier HealthCare has out-patient medical facilities recognized by the US Surgeon General as a national model for providing healthcare to people with disabilities. Award winning, professional, positive, and collaborative team environment. Apply online at yai.org/careers. EOE.
**ENDOCRINOLOGISTS**

**Geisinger Health System is seeking 2 BC/BE Endocrinologists**

Join a growing practice at Geisinger Medical Center in Danville, PA, or Geisinger Gray’s Woods in State College, PA. Help develop quality programs in endocrinology, while providing inpatient and outpatient care. Be part of a dynamic practice while enjoying a superb quality of life.

Visit Join-Geisinger.org/46/Endo to learn more about this position or contact John Kennedy, c/o Kathy Kardisco, Physician Recruiter, at 1-800-845-7112 or kkardisco@geisinger.edu.

---

**Los Angeles, California**

**September 30 – October 3, 2010**

Join colleagues for the premier professional educational conference on the current standard of care in endocrinology, diabetes and metabolism.

This is your opportunity to learn from nationally recognized faculty, explore common and evolving topics, connect with colleagues, and earn CME.

**MARK YOUR CALENDAR TODAY!**

Plan now to attend CEU 2010 at the Hyatt Regency Century Plaza. To learn more, visit: www.endo-society.org/meetings/CEU
San Diego Welcomes You to ENDO 2010

By Courtney Singer*

San Diego is home to palm tree–lined beaches, a temperate climate, award-winning restaurants, and a world-renowned zoo. San Diego will also be home to The Endocrine Society’s ENDO 2010: 92nd Annual Meeting & Expo, June 19–22. Meeting attendees can participate in forums and lectures led by highly respected luminaries, all while drinking in the sun-soaked charms of this beautiful city.

City Information

San Diego is California’s second largest city, and the eighth largest in the United States. Nestled in greater San Diego County and located between Los Angeles and the Mexican border, the city is home to 1.3 million residents. The greater county comprises 4,200 square miles and houses another 3 million.

With an average temperature of 70.5 °F (21.4 °C) and sunshine percentages consistently above 50%, it is hard to imagine a more predictably gorgeous place than San Diego city.

There are more than 6,000 eating establishments serving the trendiest and best in modern cuisine. And Balboa Park, the largest cultural park in the United States, is home to 15 museums, countless art galleries, gardens, the Tony Award–winning Globe Theaters, and the famous San Diego Zoo.

County Highlights

The county includes 18 incorporated cities along with many other neighborhoods and communities. A few well-known areas worth looking into are the Gaslamp Quarter, Little Italy, La Jolla, Del Mar, Escondido, and Carlsbad.

If you enjoy variation, coastal, mountain, and desert terrains are all located within a day’s drive from the city. The 59-mile Scenic Drive is a 3-hour route devised to take visitors through all the must-see San Diego county spots. To learn more, visit www.sandiego.org/article_set/Visitors/11/338.

For those who crave sun and surf, the county offers many water-based attractions. Seventy miles of coastline stretches from the northern part of the county down to the Mexican border, encompassing 33 separate beaches, each offering its own brand of fun in the sand. Many area surfing schools offer lessons to folks of all ages. Jet skis, wave runners, sailboats, kayaks, and other ocean equipment can be rented from a variety of boating companies.

For a more in-depth look at the local marine life, visit the San Diego La Jolla Underwater Park—an Ecological Reserve and a Marine Life Refuge. Snorkeling and scuba diving are encouraged.

Traveling to Mexico

To travel into Mexico, visitors will need valid passports and multiple-entry visas or visa waivers to re-enter the United States. Drivers should ensure their insurance extends to Mexico. Minors traveling with one parent must have a notarized permission note signed by the other, and must also present a birth certificate issued by a federal, state, provincial, county, or municipal authority. For further information, please go to www.sandiego.org/article/Visitors/959.

Convention Center

The San Diego Convention Center is conveniently located downtown, beside the harbor, less than 4 miles from the Lindbergh International Airport. Due to the variety and availability of transportation within the city, including trolleys, buses, and taxis, the Society will not arrange shuttle buses during ENDO. For any questions while traveling within the city, ask personnel wearing khaki and blue ball caps with prominent identification cards. These city representatives have been trained to help visitors as a part of the new “Clean and Safe” initiative.

For more information about ENDO 2010 registration and events, visit www.endo-society.org/endo2010/index.cfm. We look forward to seeing you this summer in sunny San Diego!

* Courtney Singer is publications specialist, Publications Department, The Endocrine Society.
DIABETES
Glutamic Acid Decarboxylase (GAD) Antibody
IA-2 Autoantibody
Insulin Antibody
GAD/IA-2 Antibody Screen†

THYROID
Thyroglobulin Antibody
Thyroid Peroxidase (TPO) Antibody
TSH Receptor Antibody (TRAb)
Serum Thyroglobulin

ADRENAL
21-Hydroxylase (21-OH) Antibody†

NEUROMUSCULAR
Acetylcholine Receptor Antibody (AChRAb):
• Binding Antibody
— RIA Test Kits
— ELISA Test Kits†
• Blocking Antibody

Titin Antibody†
Voltage-Gated Calcium Channel Antibody†

NEUROIMMUNOLOGIC
Aquaporin-4 (AQP4) Autoantibody†

When it comes to selecting a company to meet your specialized diagnostic test kit needs, the decision is quite simple…

For more than twenty years, KRONUS has provided specialized ELISA and RIA immunoassay test kits to medical professionals at the world's most respected commercial, university, research, and testing hospital laboratory facilities.

To obtain additional information on KRONUS' unique and progressive product line, please call us toll-free at 800 4 KRONUS* or visit us at our web site at www.kronus.com.

*For calls originating outside of USA and Canada, please contact KRONUS at +208 377 4800.

†For Research Use Only. Not for use in diagnostic procedures.

Our Source for Sensitive Autoimmune Diagnostics

NEW!
Aquaporin-4 Autoantibody ELISA†
NOW AVAILABLE

Look No Further.
I have type 2 diabetes. This is... my 24/7 glucose control.

Indications and usage
Levemir® is indicated for once- or twice-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

Important safety information
Levemir® is contraindicated in patients hypersensitive to insulin detemir or one of its excipients.

Hyperglycemia is the most common adverse effect of all insulin therapies, including Levemir®. As with other insulins, the timing of hypoglycemic events may differ among various insulin preparations. Glucose monitoring is recommended for all patients with diabetes. Levemir® is not to be used in insulin infusion pumps. Any change of insulin dose should be made cautiously and only under medical supervision. Concomitant oral antidiabetes treatment may require adjustment.

Inadequate dosing or discontinuation of treatment may lead to hyperglycemia and, in patients with type 1 diabetes, diabetic ketoacidosis. Levemir® should not be diluted or mixed with any other insulin preparations. Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy. Dose and timing of administration may need to be adjusted to reduce the risk of hypoglycemia in patients being switched to Levemir® from other intermediate- or long-acting insulin preparations. The dose of Levemir® may need to be adjusted in patients with renal or hepatic impairment.

Other adverse events commonly associated with insulin therapy may include injection site reactions (on average, 3% to 6% of patients in clinical trials) such as lipodystrophy, redness, pain, itching, hives, swelling, and inflammation.

Whether these observed differences represent true differences in the effects of Levemir®, NPH insulin, and insulin glargine is not known, since these trials were not blinded and the protocols (eg, diet and exercise instructions and monitoring) were not specifically directed at exploring hypotheses related to weight effects of the treatments compared. The clinical significance of the observed differences in weight has not been established.

For your patients with type 2 diabetes, start once-daily Levemir®

Levemir® helps patients with diabetes achieve their A1C goal.1,2
- 24-hour action at a once-daily dose3,4
- Provides consistent insulin absorption and action, day after day5,6
- Less weight gain7