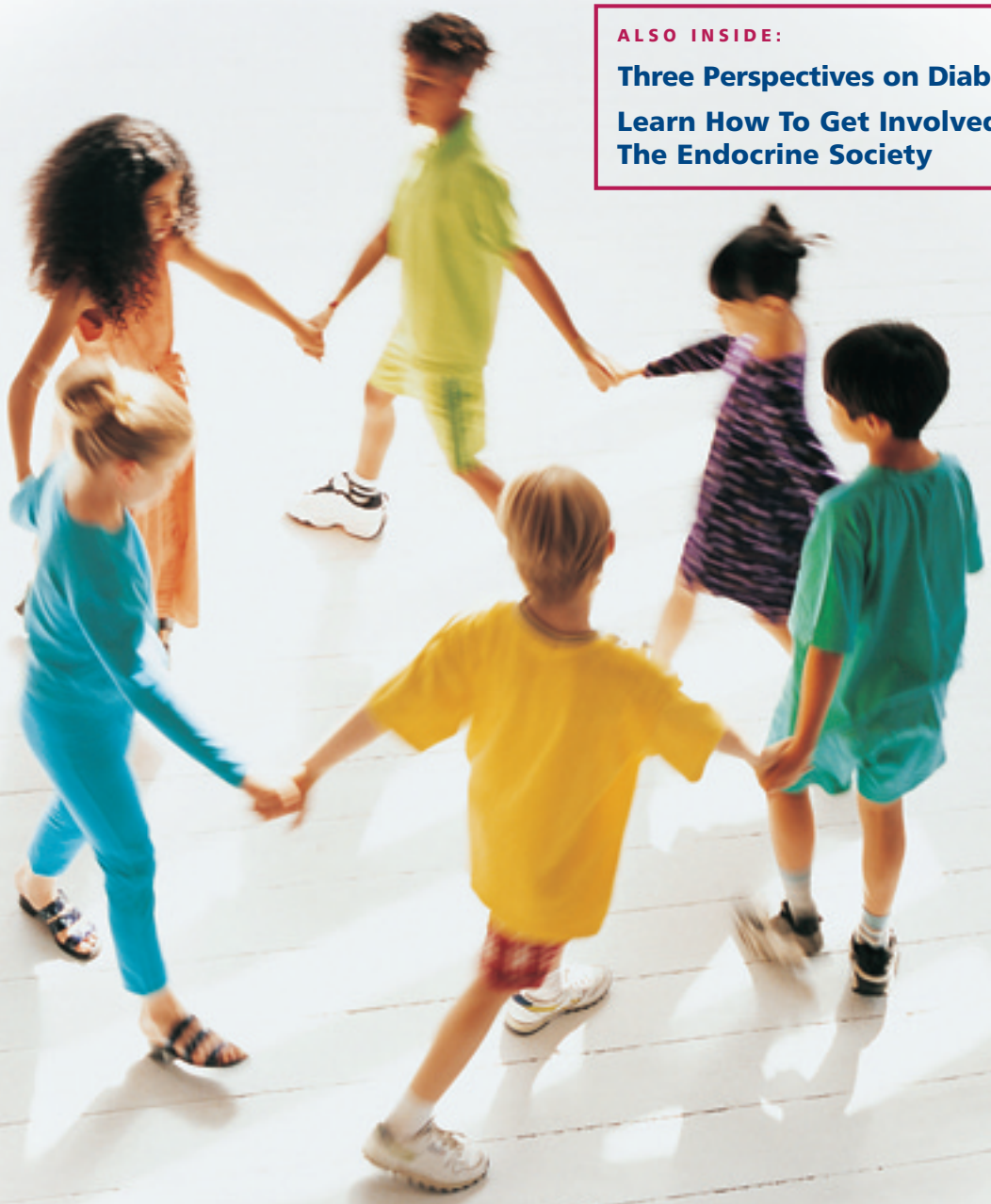
OCTOBER 2004 | VOLUME 29 | NUMBER 5

ENDOCRINE NEWS

NEWS AND INFORMATION FOR THE ENDOCRINE COMMUNITY



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A PUBLICATION OF THE ENDOCRINE SOCIETY

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Welcome Aboard!

Tony Means, Ph.D.

Dear Colleagues:

No one was more surprised than I when I heard that I was elected to the presidency of The Endocrine Society. It is an honor that I did not expect and one that, as I have watched Chip Ridgway and John Baxter serve in the chief elected officer's role, I have anticipated with increasing awe. As I prepare to write my first message to you, the members of our Society, I am comforted by the knowledge that the Society has a marvelous Strategic Plan that will serve as my roadmap and inspired by the outstanding initiatives of my predecessors.

Over this past year of apprenticeship I've learned that the Society is engaged in so much exciting activity in various stages of development and execution that the task of the president is more to shepherd, nurture and facilitate rather than to bring entirely new ideas to the fore. One need only reflect upon the recent June, 2004 Annual Meeting of the Society to comprehend the energy and scope of activities within our organization.

ENDO 2004 was a huge success, and I congratulate and thank its leadership—Beverly Biller, Stan McKnight, Paul Stewart, and Mike Jensen. Chip Ridgway's theme of obesity and the roll out of the Society's new public relations campaign on obesity and endocrinology combined to create a dynamite scientific program and an unparalleled public relations opportunity. I've learned that the press coverage of this year's ENDO is some of the highest quality that we have seen, and we are still early in the year. I have also heard many positive comments about the quality of the science presented in New Orleans.

Observing that the dynamic themes of the past few annual meetings still have great untapped potential, I approached the selection of the 2005 Annual Meeting theme in a different way than my recent predecessors. I have chosen to focus next year's meeting on the development and demonstration of a set of scientific concepts rather than on an endocrine disease state. My theme is titled: "Pathways to Discovery and Practice." My vision is that the 2005 annual meeting will highlight the magnificent scope and range of activities involved in bringing basic discoveries to clinical use in all the focused content areas relevant to endocrinology.

I made this choice in the context of numerous discussions occurring at all levels of the Society about the value of having themes for our Annual Meetings. Most recently, Council hosted a luncheon in New Orleans for the Past Presidents of the Society at which time the pros and cons of this question were debated. I was fascinated by the collective wisdom of this remarkable group of individuals who know the Society in a very unique way. Like most interesting questions, there is no single answer agreed upon by all. A theme focus facilitates attracting good public relations at the meeting and can serve to strategically position the Society as a significant contributor in a certain area. In addition, individuals attracted to the opportunity to learn more about a particular theme topic might be stimulated to attend a meeting that they otherwise would not attend.

On the other hand, theme-related programming is seen by some as stifling to other areas that also deserve their fair share of attention and as a disincentive to some individuals from attending due to feeling that the meeting content is not sufficiently broad to encompass their areas of interest. In addition, having a different theme (selected by successive presidents) for each ENDO does not allow any particular theme with broad-ranging facets (such as cardiovascular endocrinology or obesity) to be developed over more than a single year. Individuals attracted to the meeting by the theme in one year may not continue their attendance if they do not have a similar level of interest in the next president's choice of theme.

While this matter has been the subject of much debate internally, a definitive decision on the "theme vs. no theme" question has yet to be made by the Council of The Endocrine Society. I am very interested in what the members think about the issue. Please contact me with your thoughts. I can be reached by email at *president@endo-society.org*

In closing, I thank you for your confidence in electing me president of The Endocrine Society and for the opportunity to work with Society leaders (and long-time professional friends) as we join forces in fostering continual improvement of this esteemed organization. I accepted the position of president in order to give back to an organization that has meant so much to me over my career as an endocrinologist. I am always eager to hear from our members about what we do well and what we can do differently…and better. EN

Sincerely,

Anthony Means, Ph.D.

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- Caduet is indicated in patients for whom treatment with both amlodipine besylate and atorvastatin calcium is appropriate. Amlodipine besylate is indicated for the treatment of hypertension and chronic stable or vasospastic angina. Atorvastatin calcium is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
- Caduet is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases; in women who are pregnant or may become pregnant or who are nursing; in patients with hypersensitivity to any component of this medication
- Rare cases of rhabdomyolysis have been reported with the atorvastatin calcium component of Caduet and with other statins. With any statin, tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected, if creatine phosphokinase (CPK) levels rise markedly, or if the patient has risk factors for rhabdomyolysis
- Due to increased risk of myopathy seen with the atorvastatin calcium component of Caduet and other statins, physicians should carefully consider combined therapy with fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or niacin and carefully monitor patients for signs or symptoms of myopathy early during therapy and when titrating dose of either drug
- It is recommended that liver function tests be performed prior to and 12 weeks following both the initiation of Caduet therapy and any elevation in dose of the atorvastatin calcium component, and periodically thereafter. If ALT or AST values >3 x ULN persist, dose reduction or withdrawal of atorvastatin calcium is recommended
- In general, CCBs should be used with caution in patients with heart failure. In studies with amlodipine besylate, there has been no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF
- In a controlled clinical trial, the most common adverse events were edema, headache, and dizziness. These were similar to those reported previously with amlodipine besylate and/or atorvastatin calcium

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INDICATIONS AND USAGE: CADUET (amlodipine and atorvastatin) is indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate. **Amlodipine:** ***1. Hypertension:*** Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents; ***2. Chronic Stable Angina:*** Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal or antihypertensive agents; ***3. Vasospastic Angina (Prinzmetal's or Variant Angina):*** Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs. **Atorvastatin:** ***1. Heterozygous Familial and Nonfamilial:*** Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (*Fredrickson* Types IIa and IIb); ***2. Elevated Serum TG Levels:*** Atorvastatin is indicated as an adjunct to diet for the treatment of patients with elevated serum TG levels (*Fredrickson* Type IV); ***3. Primary Dysbetalipoproteinemia:*** Atorvastatin is indicated for the treatment of patients with primary dysbetalipoproteinemia (*Fredrickson* Type III) who do not respond adequately to diet; ***4. Homozygous Familial Hypercholesterolemia:*** Atorvastatin is indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable; ***5. Pediatric Patients:*** Atorvastatin is indicated as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL, or, b. LDL-C remains ≥ 160 mg/dL and: there is a positive family history of premature cardiovascular disease or two or more other CVD risk factors are present in the pediatric patients. Therapy with lipid-altering agents should be a component of multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used, in addition to a diet restricted in saturated fat and cholesterol, only when the response to diet and other nonpharmacological measures has been inadequate (see National Cholesterol Education *Program (NCEP) Guidelines,* summarized in Table 8).

Table 8. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[b]
2+ Risk Factors (10-year risk ≥20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor[c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease. [b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory. [c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category. Prior to initiating therapy with atorvastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile performed to measure total-C, LDL-C, HDL-C, and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation: LDL-C = total-C - (0.20 x [TG] + HDL-C). For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. The antidyslipidemic component of CADUET has not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons (*Fredrickson* Types I and V). The NCEP classification of cholesterol levels in pediatric patients with a familial history of hypercholesterolemia or premature cardiovascular disease is summarized as follows: Acceptable: total-C <170 mg/dL, LDL-C <110 mg/dL. Borderline: total-C 170-199 mg/dL, LDL-C 110-129 mg/dL. High: total-C ≥200 mg/dL, LDL-C ≥130 mg/dL.

CONTRAINDICATIONS: CADUET contains atorvastatin and is therefore contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. CADUET is contraindicated in patients with known hypersensitivity to any component of this medication. **Pregnancy and Lactation:** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. CADUET, WHICH INCLUDES ATORVASTATIN, SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated. **Liver Dysfunction:** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** In clinical trials in patients taking atorvastatin the following has been observed. One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients, with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of CADUET is recommended. CADUET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of CADUET (see **CONTRAINDICATIONS**). **Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of CADUET and with other drugs in the HMG-CoA reductase inhibitor class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see **ADVERSE REACTIONS**). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in the HMG-CoA reductase inhibitor class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with CADUET and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **In patients taking CADUET, therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**

PRECAUTIONS: General: Since the vasodilation induced by the amlodipine component of CADUET is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering CADUET as with any other peripheral vasodilator particularly in patients with severe aortic stenosis. Before instituting therapy with CADUET, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see **INDICATIONS AND USAGE**). **Use in Patients with Congestive Heart Failure:** In general, calcium channel blockers should be used with caution in patients with heart failure. The amlodipine component of CADUET (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF. **Beta-Blocker Withdrawal:** The amlodipine component of CADUET is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker. **Endocrine Function:** HMG-CoA reductase inhibitors, such as the atorvastatin component of CADUET interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity:** *Studies with atorvastatin:* Brain hemorrhage was seen in a female dog treated with atorvastatin calcium for 3 months at a dose equivalent to 120 mg atorvastatin/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses of atorvastatin calcium equivalent to up to 280 mg atorvastatin/kg/day. The 120 mg/kg dose of atorvastatin resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated with atorvastatin calcium at a dose equivalent to 10 mg atorvastatin/kg/day and one at a dose equivalent to 120 mg atorvastatin/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses of atorvastatin calcium equivalent to up to 400 mg atorvastatin/kg/day or in rats at doses equivalent to up to 100 mg atorvastatin/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg atorvastatin/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of the HMG-CoA reductase class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Information for Patients:** Due to the risk of myopathy with drugs of the HMG-CoA reductase class, to which the atorvastatin component of CADUET belongs, patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions:** Data from a drug-drug interaction study involving 10 mg of amlodipine and 80 mg of atorvastatin in healthy subjects indicate that the pharmacokinetics of amlodipine are not altered when the drugs are coadministered. The effect of amlodipine on the pharmacokinetics of atorvastatin showed no effect on the C_{max}: 91% (90% confidence interval: 80 to 103%), but the AUC of atorvastatin increased by 18% (90% confidence interval: 109 to 127%) in the presence of amlodipine. No drug interaction studies have been conducted with CADUET and other drugs, although studies have been conducted in the individual amlodipine and atorvastatin components, as described below: ***Studies with Amlodipine:*** *In vitro* data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine. Maalox® (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine. Sildenafil: A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect. Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol. Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. ***Studies with Atorvastatin:*** The risk of myopathy during treatment with drugs of the HMG-CoA reductase class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, or azole antifungals (see **WARNINGS, Skeletal Muscle**). Antacid: When atorvastatin and Maalox TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. Antipyrine: Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. Colestipol: Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. Digoxin: When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see **WARNINGS, Skeletal Muscle**). Oral Contraceptives: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking CADUET. Warfarin: Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment. **Drug/Laboratory Test Interactions:** None known. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** *Studies with amlodipine:* Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg amlodipine/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day*. For the rat, the highest dose level was, on a mg/m^2 basis, about twice the maximum recommended human dose*. Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis). *Studies with atorvastatin:* In a 2-year carcinogenicity study with atorvastatin calcium in rats at dose levels equivalent to 10, 30, and 100 mg atorvastatin/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given atorvastatin calcium at dose levels equivalent to 100, 200, and 400 mg atorvastatin/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. *In vitro,* atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. There were no effects on fertility when rats were given atorvastatin calcium at doses equivalent to up to 175 mg atorvastatin/kg/day (15 times the human exposure). There was aplasia and aspermia in the epididymides of 2 of 10 rats treated with atorvastatin calcium at a dose equivalent to 100 mg atorvastatin/kg/day for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg/day and epididymal weight was lower at 100 mg/kg/day. Male rats given the equivalent of 100 mg atorvastatin/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of atorvastatin calcium equivalent to 10, 40, or 120 mg atorvastatin/kg/day for two years. **Pregnancy: Pregnancy Category X (see CONTRAINDICATIONS):** Safety in pregnant women has not been established with CADUET. CADUET should be

administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking CADUET, it should be discontinued and the patient advised again as to the potential hazards to the fetus. *Studies with amlodipine:* No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg/day on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. *Studies with atorvastatin*: Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses of atorvastatin calcium equivalent to up to 300 mg atorvastatin/kg/day or in rabbits at doses of atorvastatin calcium equivalent to up to 100 mg atorvastatin/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given atorvastatin calcium at doses equivalent to 20, 100, or 225 mg atorvastatin/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity for pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 for pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses of atorvastatin correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. **Labor and Delivery:** No studies have been conducted in pregnant women on the effect of CADUET, amlodipine, or atorvastatin on the mother or the fetus during labor or delivery, or on the duration of labor or delivery. Amlodipine has been shown to prolong the duration of labor in rats. **Nursing Mothers:** It is not known whether the amlodipine component of CADUET is excreted in human milk. Nursing rat pups taking atorvastatin had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking CADUET should not breast-feed (see **CONTRAINDICATIONS**). **Pediatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in pediatric populations. *Studies with amlodipine:* The effect of amlodipine on blood pressure in patients less than 6 years of age is not known. *Studies with atorvastatin:* Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls. See **CLINICAL PHARMACOLOGY, Clinical Studies** section; **ADVERSE REACTIONS**, *Pediatric Patients*; and **DOSAGE AND ADMINISTRATION**, *Pediatric Patients (10-17 years of age) with Heterozygous Familial Hypercholesterolemia.* Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see **CONTRAINDICATIONS** and **PRECAUTIONS, Pregnancy**). **Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses of atorvastatin up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients. See **CLINICAL PHARMACOLOGY, Clinical Studies**, *Atorvastatin Effects in Homozygous Familial Hypercholesterolemia.* **Geriatric Use:** There have been no studies conducted to determine the safety or effectiveness of CADUET in geriatric populations. *In studies with amlodipine:* Clinical studies of amlodipine 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 of the amlodipine component of CADUET for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**). *In studies with atorvastatin:* The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1958 patients initiated therapy with atorvastatin calcium 10 mg. Of these, 835 were elderly (≥65 years) and 1123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin calcium 10 mg was –38.2% in the elderly patients versus –34.6% in the non-elderly group. The rates of discontinuation in patients on atorvastatin due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS: CADUET: (amlodipine besylate/atorvastatin calcium) has been evaluated for safety in 1092 patients in double-blind placebo-controlled studies treated for comorbid hypertension and dyslipidemia. In general, treatment with CADUET was well tolerated. For the most part, adverse experiences have been mild or moderate in severity. In clinical trials with CADUET, no adverse experiences peculiar to this combination have been observed. Adverse experiences are similar in terms of nature, severity, and frequency to those reported previously with amlodipine and atorvastatin. The following information is based on the clinical experience with amlodipine and atorvastatin. **The Amlodipine Component of CADUET:** Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose-related manner are as follows:

Adverse Event	amlodipine			
	2.5 mg (N=275)	5.0 mg (N=296)	10.0 mg (N=268)	Placebo (N=520)
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

	amlodipine (%) (N=1730)	Placebo (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

ADR	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitation	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in ≤1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia. **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea,** epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in <0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. ***Clinical Adverse Experiences (% of Patients)***: Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 10.

Table 10. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	**Placebo N=270**	**atorvastatin 10 mg N=863**	**20 mg N=36**	**40 mg N=79**	**80 mg N=94**
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients. **Body as a Whole:** *Chest pain,* face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** *Nausea,* gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** *Insomnia, dizziness,* paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. **Musculoskeletal System:** *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** *Urinary tract infection,* urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** *Peripheral edema,* hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. ***Postintroduction Reports with Atorvastatin***: Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. ***Pediatric Patients (ages 10-17 years)***: In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies** section and **PRECAUTIONS, Pediatric Use**).

OVERDOSAGE: There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mm Hg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin**: There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

*Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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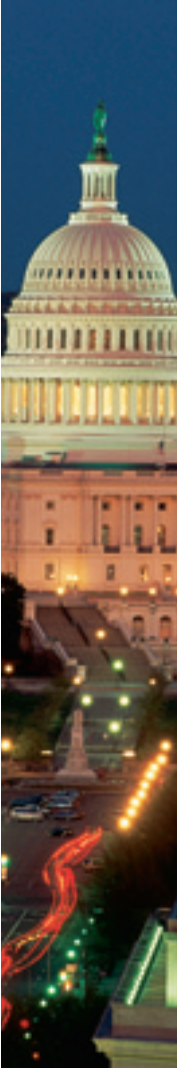

Stem Cell and Appropriations on Congressional Agenda Prior to Elections

Stem Cell Issue Heats Up

Debate surrounding the issue of stem cell research has seen resurgence since the passing of former President Ronald Reagan. Congress has introduced several new pieces of legislation since June and has contacted President Bush encouraging a new approach to stem cell research. Representative Diana DeGette (D-CO) and Representative Michael Castle (R-DE) have authored legislation that includes 150 Republican and Democratic co-sponsors. The Stem Cell Research Enhancement Act would reverse President Bush's policy by providing federal funding for research on embryonic stem cell lines derived since August 9, 2001.

Another piece of legislation is the Stem Cell Discovery Through Diversity Act introduced by Representative Peter Deutsch (D-FL). This bill is similar to the DeGette/Castle proposal but would require that the stem cell lines used for research are derived from members of all racial and ethnic minorities.

In April 2004, more than 200 members of the House sent a letter to President Bush urging him to change his policy. Fifty-eight Republican and Democratic Senators, led by Senator Arlen Specter (R-PA) and Senator Tom Harkin (D-IA) sent a similar letter to the President in July. In June, The Endocrine Society joined 140 patient organizations, scientific societies, universities and foundations in a letter that was sent to President Bush urging him to expand his current embryonic stem cell policy.

In response to the recent inquiries about the Bush Administration's stem cell policy, a statement was released on August 8th by Secretary of the Department of Health and Human Services (HHS), Tommy Thompson. The statement reads, "Under President Bush, federal funding for embryonic stem cell research has grown from zero under previous administrations to 24.8 million dollars in fiscal year 2003. The National Institute of Health (NIH) is taking new steps to create a National Embryonic Stem Cell Bank that will provide a ready source of human embryonic stem cells to scientists, ensure consistent quality of the lines and provide other technical support that will make it easier for scientists to use these lines. The NIH is also creating three new Centers of Excellence for Translational Stem Cell Research with the goal of exploiting new discoveries in basic embryonic and stem cell biology." The statement continues, "Unlike many countries, there are no limits in the United States on private stem cell research."

The full statement is available at *www.hhs.gov/news/press/2004pres/20040808.html*

Appropriations Update

The House Appropriations Committee approved the Fiscal Year 2005 (FY 2005) Labor, Health and Human Services (HHS), Education and Related Agencies Appropriations bill in July. The committee's reported bill included a 2.8 percent increase in funding for the NIH an increase of 782 million dollars. This increase is the same amount suggested by President Bush in his budget released in January.

The House Appropriations Committee also approved FY 2005 spending for the Veterans Health Administration and the National Science Foundation. As approved by the Committee, the FY05 VA-HUD Appropriations Bill will result in a 111 million dollar reduction in funding for the National Science Foundation. The overall budget for veteran's health increased, but the VA Medical and Prosthetic Research program is funded at the President's requested level of 385 million dollars. This is a 21 million dollar or five percent decrease from FY 2004.

Open Access Language Included in Appropriations Bill

Included in the FY 2005 Labor/HHS Appropriations Bill, which passed out of the House Appropriations Committee in July, is report language regarding open access for scientific publications. The language stipulates that as of FY 2005, any manuscript reporting work supported by NIH funding be provided to PubMed Central, the digital library maintained by the National Library of Medicine, either immediately (if any publications costs are paid out of grant/contract funds) or after six months (if no publications cost are borne by the grant).

The Endocrine Society supports open access and has made great strides in making its journal articles available to the scientific community and the public. However, as currently written, the report language would have major repercussions on the operations of The Endocrine Society and other organizations that publish research funded by NIH as well as potentially on the entire research enterprise. The language would mandate one open access policy on the entire publishing community without knowing the impact it will have on scientific societies. The Society is working with the NIH and Congress to encourage an open dialogue that will investigate what impact open access will have on the publishing community. EN

For more information about the Society's legislative activities, contact Chris Rorick, Manager, Government Relations, at crorick@endosociety.org

Keeping you informed about endocrinology in the news

Almost everyday, new developments in endocrinology are featured in the news. In each issue of Endocrine News, *Endocrine Edge will highlight some of the recent news stories.*

Turner Syndrome

According to research published in the July 2004 issue of *The Journal of Clinical Endocrinology & Metabolism,* using estradiol, a form of estrogen, on girls with immature sexual development, a trademark of Turner syndrome, gradually increases the development of secondary sexual characteristics and uterine growth. Researchers led by Dr. Sailia Piipo at Tampere University Hospital reported that the treatment can be individualized, with dose adjustments based on the signs of pubertal development and uterine growth measured by sonography and (hormone) concentrations. **EN**

For more information visit http://jcem.endojournals.org/content/vol89/issue7/

Obesity & Pediatrics

A study published in the August 2004 issue of *Pediatrics*, reports that only seven percent of pediatricians ordered laboratory tests to screen for weight-related problems. The researchers, led by Dr. Sarah O'Brien at Children's Hospital of Pittsburgh, reviewed more than 2,000 records and concluded that childhood obesity was being reported or treated by pediatric primary care providers in the study. Of note, only five percent of pediatricians in the study recommended a decrease in television watching to their obese patients, despite evidence linking television and pediatric obesity. **EN**

For more information visit http://pediatrics.aappublications.org/

Thyroid

Researchers of the Radiation Effects Research Foundation in Nagasaki, Japan have tied the common occurrence of subclinical hypothyroidism to an increased risk of heart disease. Dr. Misa Imaizumi and colleagues published the results of the three year study in the July 2004 issue of *The Journal of Clinical Endocrinology and Metabolism*. Researchers looked for a possible relationship between subclinical hypothyroidism and artery disease in 2,550 subjects who participated in thyroid disease screening. **EN**

For more information visit http://jcem.endojournals.org/content/vol89/issue7/

Visit www.obesityinamerica.org to learn how The Endocrine Society is promoting the role of endocrinology in the research and treatment of obesity and related conditions.

Grant Opportunities!

In August 2004, The National Institutes of Health (NIH) released the "Strategic Plan for NIH Obesity Research," creating an inroad for grant opportunities for interested Society members. Announced by Dr. Elias Zerhouni, Director of the NIH, this multi-dimensional research agenda promotes the development of new research in areas of greatest scientific opportunity and the coordination of obesity research across the NIH. The strategic plan emphasizes the importance of cross-cutting investigations and calls for interdisciplinary research teams to bridge the study of behavioral and environmental causes of obesity with the study of genetic and biologic causes. The plan also solidifies the 400.1 million dollar obesity research investment in FY 2004, and the projected FY 2005 budget of 440.3 million, a 10 percent increase over 2004.

The Endocrine Society supports the comprehensive plan to fight the obesity epidemic and encourages its members to apply and remain aware of the availability of grant funding to address the metabolic aspects of obesity.

Funding opportunities for NIH obesity research are available online at *http://obesityresearch.nih.go* **EN**

For more information about research and grant opportunities contact Janet Kreizman at jkreizman@endo-society.org

Tri-Point Perspectives in *Endocrine News*

The tri-point perspectives were initiated by The Endocrine Society's Research Affairs Committee in the fall of 2003 as an editorial feature that would appeal to all of the Society's members. The topics, authors and outside reviewers are selected by the committee to deal with subject areas from three different angles—that of the basic researcher, the clinical researcher and the physician-in-practice. The authors write their articles independently and later work together to coordinate them. The drafts are reviewed by the Research Affairs Committee chairs, by independent experts in the specific topic area and then by the Endocrine News *editors and staff for grammar and style.*

If you have any comments or questions about the tri-point perspectives feature, please email EndocrineNews@endo-society.org *If you would like to submit a Letter to the Editor responding to a tri-point perspective, please send your letter to* ENLetters@endo-society.org *(not longer than 200 words and the editorial staff reserves the right to edit each submission).*

DIABETES, HEART DISEASE AND INSULIN RESISTANCE

Diabetes, Heart Disease and Insulin Resistance

Management of Type II Diabetes Mellitus: Should We Target Insulin Resistance in Addition to Better Glycemic Control?

Barry Marc Forman, M.D., Ph.D.

Jean-Pierre Després Ph.D., FAHA

Francine Ratner Kaufman, M.D.

BASIC RESEARCHER VIEW

Thiazolidinediones and PPARγ Ligands: Insulin Sensitization and Beyond?

Barry Marc Forman, M.D., Ph.D.
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The Beckman Research Institute at City of Hope National Medical Center

It's been seven years since the first insulin-sensitizing thiazolidinedione (TZD) appeared on the market, and in that time, TZDs have produced a number of surprises. It is now clear that TZDs (e.g. rosiglitazone and pioglitazone) have effects on metabolic disease that extend well beyond glucose lowering.

PPARγ is thus a "force-multiplier" that allows TZDs to regulate not just a single gene, but large networks of physiologically-related genes.

TZDs are synthetic ligands for the nuclear receptor PPARγ [1,2]. Like most nuclear receptors, PPARγ binds to specific DNA sequences within its target genes. In the presence of ligand, the receptor undergoes a conformation change that allows the DNA-bound receptor to interact with transcriptional co-activator proteins. This ultimately leads to an increased rate of transcription. PPARγ is expressed in a number of tissues and modulates the expression of multiple genes within each tissue. PPARγ is thus a "force-multiplier" that allows TZDs to regulate not just a single gene, but large networks of physiologically-related genes. Herein lies the power of TZDs: whereas many drugs target a single enzyme, TZDs can regulate entire metabolic pathways.

Initial studies demonstrated that PPARγ is highly expressed in adipose tissue and that TZDs promote adipogenesis *in vitro* and increase white adipose mass *in vivo*. In fact, it is now clear that TZDs induce a battery of genes that coordinate nearly all steps of adipocyte triglyceride (TG) accumulation including: free fatty acid (FFA) release from circulating very low density lipoproteins, glycerol synthesis, uptake of FFA/glycerol into adipocytes, and induction of enzymes responsible for converting FFAs/glycerol into the immediate precursors for TG synthesis.

These findings raise a surprising question about TZD action: since obesity is a major risk factor for NIDDM, how can PPARγ ligands relieve insulin resistance while increasing adiposity? This paradox is partially explained by the observation that TZDs promote a shift of TGs from both visceral fat and peripheral tissues (e.g. skeletal muscle) toward subcutaneous fat[3]. In effect, TZDs preferentially increase adiposity in subcutaneous fat. This is consistent with recent findings that insulin resistance is associated with an over-accumulation of lipids in both visceral adipose depots and within the cells of insulin-resistant peripheral tissues[4]. Preferential responsiveness of subcutaneous fat may reflect a higher level of expression of PPARγ in this depot. It is also possible that different fat depots display depot-specific differences in their ability to induce certain lipogenic genes.

These findings raise a surprising question about TZD action: since obesity is a major risk factor for NIDDM, how can PPARγ ligands relieve insulin resistance while increasing adiposity?

In addition to adipose tissue, PPARγ is also expressed in vascular endothelial cells, macrophage/foam cells and vascular smooth muscle. This provides a means for TZDs to act directly on the vasculature. Indeed, PPARγ ligands raise HDL-cholesterol in NIDDM patients and reduce the number and size of atherosclerotic lesions in several rodent models. The effects on HDL-cholesterol and lesion size are mediated by induction of LXRα, another nuclear receptor that is co-expressed in the macrophage foam cell. LXRα promotes cholesterol efflux from atherosclerotic lesions by coordinately inducing a cholesterol efflux pump (ABCA1) and the HDL-associated cholesterol acceptor apolipoprotein-AI.

In contrast to the role of gene activation in the above processes, TZDs can also repress transcription. The precise mechanism un-

derlying transrepression is unclear. However, the net effect of TZDs is to inhibit the activity of transcription factors (NF-kb, AP-1) that regulate the expression of cytokines and other inflammatory mediators. Thus, TZDs can inhibit the initial inflammatory processes that promote atherosclerosis, including macrophage recruitment/attachment and vascular smooth muscle proliferation[5]. Some of the reported anti-inflammatory effects of TZDs occur via both PPARγ-dependent and independent pathways. Examples of this dual-mode of regulation include inducible nitric oxide synthase, matrix metalloprotease-9 and cycloxygenase-2: the promoters of these genes are suppressed via PPARγ-dependent and -independent mechanisms. Many other genes can be down-regulated by TZDs and it appears that PPARγ may also be a master regulator of inflammatory gene expression. However, there is an important cautionary note: many of the reported anti-inflammatory effects require supra-pharmacologic doses of TZDs. Therefore, it is not clear if all the reported effects occur at doses that are relevant to TZD-treated patients.

TZDs also reduce blood pressure and several potential mechanisms have been described[6]. For example, TZDs inhibit the expression of endothelin-1, a vasoconstrictive peptide expressed in endothelial cells. TZDs may also promote vasodilation by stimulating the release of nitric oxide from the endothelial cell. More recently, PPARγ was found to be expressed in renal glomeruli and collecting ducts. Although the targets genes in these cells have not been fully elucidated, it is possible that TZD action in the kidney contributes to blood pressure control. However, PPARγ activity in the kidney may be a double-edged sword. Approximately five percent of patients on TZDs develop peripheral or pulmonary edema and preliminary data suggest this could be secondary to TZD-induced sodium retention.

Although PPARγ and its ligands were once uniquely linked to fat homeostasis, it is now clear that they have multiple effects on insulin resistance, atherosclerosis and blood pressure regulation. These ligands have clearly provided many surprises in the past and we should look for this trend to continue. **EN**

Many other genes can be down-regulated by TZDs and it appears that PPARg may also be a master regulator of inflammatory gene expression.

Approximately five percent of patients on TZDs develop peripheral or pulmonary edema and preliminary data suggest this could be secondary to TZD-induced sodium retention.

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CLINICAL RESEARCHER VIEW

Managing CHD Risk in Type 2 Diabetes: Improving Insulin Resistance May be as Important as Glycemic Control

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The worldwide prevalence of type 2 diabetes has reached epidemic proportions and there is no evidence that this rapid growth will "plateau" in the coming years[1,2]. Changes in human behavior and lifestyle observed over the last century, which have promoted a positive energy balance, weight gain and obesity leading to the progressive development of a metabolic disease evolving to glucose intolerance and eventually to frank hyperglycemia, have resulted in a dramatic increase in the incidence of diabetes worldwide. Therefore, there has been a striking parallel increase in the prevalence of obesity and type 2 diabetes[3,4].

Because of its high prevalence in our population, the contribution of type 2 diabetes as a major risk factor for cardiovascular disease has received considerable attention from the medical community[5,6]. It has even been proposed that type 2 diabetes should be considered as an equivalent of coronary heart disease (CHD)[7,8]. As many complications of type 2 diabetes are related to hyperglycemia, achieving a better glycemic control is obviously a very important therapeutic objective. However, although it is clear that it is clinically important to reduce hemoglobin A1c (HbA1c) levels, there is also increasing evidence that hyperglycemia is not the main factor responsible for the increased CHD risk in type 2 diabetic patients [9]. It has rather been proposed that a cluster of metabolic complications referred to as the metabolic syndrome, which includes an atherogenic dyslipidemia, an insulin resistance state leading to a disturbed plasma glucose/insulin homeostasis, a thrombotic and inflammatory profile, as well as an endothelial dysfunction, could substantially increase the risk of CHD [10].

Furthermore, the impact of the metabolic syndrome on CHD risk could be largely independent from glycemic control or of the presence/absence of type 2 diabetes[11]. As the metabolic syndrome is largely a consequence of our "toxic" lifestyle, it has been shown that abdominal obesity, especially visceral obesity, could represent the main correlation of the metabolic syndrome in our population [8,12].

The recognition of the metabolic syndrome as a major and prevalent cause of CHD in the recently published National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III)[8] has generated considerable interest in the medical community. In addition, NCEP-ATP III has proposed simple clinical variables to identify individuals at risk of having the metabolic syndrome. Among the five parameters (waist circumference, triglycerides, high-density lipoprotein (HDL)-cholesterol, fasting glycemia, blood pressure) used to identify carriers of the metabolic syndrome, the introduction of waist circumference rather than the body mass index has been a giant conceptual leap, recognizing the significant role of abdominal obesity as the most prevalent cause of insulin resistance and of the metabolic syndrome in our affluent, sedentary population. Furthermore, these new guidelines recognize the importance of elevated triglycerides and of reduced HDL-cholesterol concentrations as useful lipid markers for the presence of an atherogenic "dysmetabolic" milieu that is now referred to as the metabolic syndrome.

There is also evidence that the increased CHD risk related to the presence of the metabolic syndrome associated with abdominal obesity and insulin resistance could be partly mediated by metabolic abnormalities that are not currently assessed in daily clinical practice (e.g. insulin, apolipoprotein B, low-density lipoprotein (LDL) size, C-reactive protein, adipokines such as interleukin-6, tumor necrosis factor-a and adiponectin concentrations)[13]. It is therefore suggested that in order to optimally manage CHD risk in type 2 diabetic patients, attention should be given not only to the level of glycemic control, but also to the improvement of insulin resistance and of features of the metabolic syndrome. For the time being, although we know that the metabolic syndrome substantially increases the risk of CHD[11,14], we do not know which of its features (insulin resistance/hyperinsulinemia, small LDL particles, reduced

adiponectin levels, increased C-reactive protein, etc.) are critical therapeutic targets for the optimal management of CHD risk in type 2 diabetic patients.

Results of clinical trials conducted on or including type 2 diabetic patients have shown the benefits of reducing blood pressure[15,16,] and of improving the dyslipidemic profile[17,18] of these patients. The introduction of insulin sensitizers (PPAR-g agonists) in clinical practice will provide an opportunity to test whether improving in vivo insulin action will slow the progression of atherosclerosis and reduce the risk of cardiovascular events in type 2 diabetes. Thiazolidinediones have been reported to have favourable effects on several features of the metabolic syndrome [19] including inflammation [20] and whether such metabolic improvements will translate into cardiovascular benefits beyond the impact of this class of drugs on glycemic control is currently under investigation.

Finally, as abdominal obesity represents the most prevalent form of the metabolic syndrome in our population, waist girth should be considered as one of the key screening tools to track patients with insulin resistance and the metabolic syndrome in clinical practice. Thus, in addition to improving insulin sensitivity and managing hypertension and the dyslipidemic state, clinicians should also consider lowering body weight and reducing the waist girth of their patients as important therapeutic targets[10,12].

Unfortunately, we have engineered for our population a toxic sedentary environment and easy access to inexpensive processed foods with high energy density and poor nutritional value. The battle against the epidemic of the metabolic syndrome and type 2 diabetes will not be successfully fought by our current medical system as it will clearly require a multi-disciplinary approach. **EN**

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CLINICAL PRACTITIONER VIEW

Insulin Resistance and Type 2 Diabetes in Youth

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As reported in 2002, 14 percent of youth in the United States are overweight (BMI ≥ 95th percentile for age and gender) and 31.5 percent are at risk for overweight (BMI ≥ 85th for age and gender)[1]. Insulin resistance occurs in overweight children and youth and is associated with the metabolic syndrome, dyslipidemia, vascular complications, and type 2 diabetes. Type 2 diabetes, which was rare in the early 1990s, now accounts for up to eight – 45 percent of new-onset cases of diabetes in youth[2].

There are several factors, in addition to overweight, that lead to insulin resistance in the pediatric population. These include: sedentary lifestyle; gender; age; onset of puberty; and genetics, which can be seen as a positive family history of type 2 diabetes and by the propensity for type 2 to occur in certain ethnic groups.

In overweight adolescents, approximately 50 percent of the variance seen in insulin sensitivity is accounted for by adiposity. As in adults, it is visceral fat, rather than total body fat, which correlates with basal and stimulated insulin levels and inversely correlates with insulin sensitivity[3]. African-American youth are more insulin resistant than Caucasian children. The Bogalusa Heart Study showed that African-American teens were more obese and had higher insulin levels to oral glucose and higher insulin to glucose ratios compared to their Caucasian counterparts[4]. Arslanian has shown lower resting energy expenditure, higher fasting and first phase insulin levels, and lower insulin sensitivity in African-American subjects[5]. Goran et al, has shown that Hispanic youth are also more insulin resistant compared to Caucasian children[6].

Puberty is a state of relative insulin resistance and there is an increase in basal and stimulated insulin secretion during the progression through normal puberty[7]. It has been shown that insulin-mediated glucose disposal is on average 30 percent lower in Tanner 2-4 puberty compared to that seen in Tanner 1 children during hyperinsulinemic euglycemic clamp studies. More female youth have type 2 diabetes than adolescent males. The female:male ratio is 1.7:1. It is hypothesized that this is due to elements of the polycystic ovary syndrome (PCOS)[8]. Physical activity increases insulin sensitivity and overweight youth undergoing regular exercise show a fall in fasting insulin levels that increase again with the return in sedentary lifestyle[9].

Puberty is a state of relative insulin resistance and there is an increase in basal and stimulated insulin secretion during the progression through normal puberty[7].

Metabolic syndrome occurs with a high rate in overweight youth. Recent cross-sectional data obtained from National Health and Nutrition Examination Survey III (NHANES III) evaluating 2430 youth between the ages of 12-19 years and using modified National Cholesterol Education Program (NCEP) criteria, found an overall prevalence of metabolic syndrome in youth to be 4.2 percent; however, this increased to 28 percent in overweight youth[10]. Cruz et al[11] reported a 30 percent prevalence of metabolic syndrome in overweight youth with a family history of type 2 diabetes, and Weiss et al reported a rate of 50 percent in subjects with severe obesity[12].

Pre-diabetes is common in children and youth, as well as in adults. Evaluation of overweight children and adolescents by Sinha et al[13] with oral glucose tolerance testing showed 25 percent of children four to 10 years of age and 21 percent of adolescents 11-18 years of age had impaired glucose tolerance (IGT). The best predictor of IGT was insulin resistance. Goran et al reported IGT in 28 percent of overweight Hispanic youth with a positive family history of type 2 diabetes[6].

In my experience, the presentation of type 2 diabetes in pediatric subjects is variable. Most of the patients I see are symptomatic from hyperglycemia at the time of diagnosis. In addition, I see many youth with type 2 diabetes who have significant co-morbidities. There are a number of studies that have shown a high prevalence of hypertension and dyslipidemia[14]. At present, few studies have been

done to determine the most effective treatment regimens, the role that physical activity and nutrition counseling play in improving glycemic outcome and the most effective ways to reduce cardiovascular risk. If patients are symptomatic from hyperglycemia at diagnosis, I start them on insulin. If they have a glucose level below 250 mg/dl and are relatively asymptomatic, I find that Metformin is effective as initial therapy. The occasional child found on screening can try lifestyle changes; however, I find this is rarely beneficial. The *Treatment Options for type 2 Diabetes in Adolescents and Youth* (TODAY) trial, an National Institutes of Health-funded multi-center (12 sites throughout the U.S.) study, was recently launched and will evaluate the glycemic outcome, indicators of insulin resistance and cardiovascular risk factors in youth randomized to one of three treatment modalities (Metformin alone, Metformin plus Rosiglitazone and Metformin) within two years of the diagnosis of type 2 diabetes.

In conclusion, obesity and sedentary lifestyle have a significant impact on the health of children. Low fitness levels, combined with ethnicity and family history of diabetes, are driving the epidemic of insulin resistance in increasingly younger children. With the onset of puberty comes even greater insulin resistance. Depending on the level of fitness, obesity, ethnicity and family history, patients will remain insulin resistant following puberty. The longer the pubertal insulin resistance remains, the greater the chance for the development of dyslipidemia, hypertension and, pre-diabetes and overt type 2 diabetes, which itself, is a risk factor for cardiovascular disease.

There is little doubt that insulin resistance has a major negative effect clinically. Improving insulin resistance should be a goal for those treating youth with obesity, metabolic syndrome, pre-diabetes and diabetes. How best to do this—lifestyle versus pharmacotherapy—has yet to be determined in youth, but should become a research priority. EN

There is little doubt that insulin resistance has a major negative effect clinically.

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Levothyroxine sodium should not be used in the treatment of male or female infertility unless this condition is associated with hypothyroidism.

In patients with nontoxic diffuse goiter or nodular thyroid disease, particularly the elderly or those with underlying cardiovascular disease, levothyroxine sodium therapy is contraindicated if the serum TSH level is already suppressed due to the risk of precipitating overt thyrotoxicosis (see **CONTRAINDICATIONS**). If the serum TSH level is not suppressed, LEVOXYL® should be used with caution in conjunction with careful monitoring of thyroid function for evidence of hyperthyroidism and clinical monitoring for potential associated adverse cardiovascular signs and symptoms of hyperthyroidism.

PRECAUTIONS

General

Levothyroxine has a narrow therapeutic index. Regardless of the indication for use, careful dosage titration is necessary to avoid the consequences of over- or under-treatment. These consequences include, among others, effects on growth and development, cardiovascular function, bone metabolism, reproductive function, cognitive function, emotional state, gastrointestinal function, and on glucose and lipid metabolism. Many drugs interact with levothyroxine sodium necessitating adjustments in dosing to maintain therapeutic response (see **Drug Interactions**).

Effects on bone mineral density – In women, long-term levothyroxine sodium therapy has been associated with decreased bone mineral density, especially in postmenopausal women on greater than replacement doses or in women who are receiving suppressive doses of levothyroxine sodium. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical response.

Patients with underlying cardiovascular disease – Exercise caution when administering levothyroxine to patients with cardiovascular disorders and to the elderly in whom there is an increased risk of occult cardiac disease. In these patients, levothyroxine therapy should be initiated at lower doses than those recommended in younger individuals or in patients without cardiac disease (see **WARNINGS; PRECAUTIONS, Geriatric Use;** and **DOSAGE AND ADMINISTRATION**). If cardiac symptoms develop or worsen, the levothyroxine dose should be reduced or withheld for one week and then cautiously restarted at a lower dose. Overtreatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac wall thickness, and cardiac contractility and may precipitate angina or arrhythmias. Patients with coronary artery disease who are receiving levothyroxine therapy should be monitored closely during surgical procedures, since the possibility of precipitating cardiac arrhythmias may be greater in those treated with levothyroxine. Concomitant administration of levothyroxine and sympathomimetic agents to patients with coronary artery disease may precipitate coronary insufficiency.

Patients with nontoxic diffuse goiter or nodular thyroid disease – Exercise caution when administering levothyroxine to patients with nontoxic diffuse goiter or nodular thyroid disease in order to prevent precipitation of thyrotoxicosis (see **WARNINGS**). If the serum TSH is already suppressed, levothyroxine sodium should not be administered (see **Contraindications**).

Associated endocrine disorders

Hypothalamic/pituitary hormone deficiencies – In patients with secondary or tertiary hypothyroidism, additional hypothalamic/pituitary hormone deficiencies should be considered, and, if diagnosed, treated (see **PRECAUTIONS, Autoimmune polyglandular syndrome**) for adrenal insufficiency.

Autoimmune polyglandular syndrome – Occasionally, chronic autoimmune thyroiditis may occur in association with other autoimmune disorders such as adrenal insufficiency, pernicious anemia, and insulin-dependent diabetes mellitus. Patients with concomitant adrenal insufficiency should be treated with replacement glucocorticoids prior to initiation of treatment with levothyroxine sodium. Failure to do so may precipitate an acute adrenal crisis when thyroid hormone therapy is initiated, due to increased metabolic clearance of glucocorticoids by thyroid hormone. Patients with diabetes mellitus may require upward adjustments of their antidiabetic therapeutic regimens when treated with levothyroxine (see **PRECAUTIONS, Drug Interactions**).

Other associated medical conditions

Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, with cardiovascular anomalies (pulmonary stenosis, atrial septal defect, and ventricular septal defect,) being the most common association.

Information for Patients

Patients should be informed of the following information to aid in the safe and effective use of LEVOXYL®:

1. Notify your physician if you are allergic to any foods or medicines, are pregnant or intend to become pregnant, are breast-feeding or are taking any other medications, including prescription and over-the-counter preparations.
2. Notify your physician of any other medical conditions you may have, particularly heart disease, diabetes, clotting disorders, and adrenal or pituitary gland problems. Your dose of medications used to control these other conditions may need to be adjusted while you are taking LEVOXYL®. If you have diabetes, monitor your blood and/or urinary glucose levels as directed by your physician and immediately report any changes to your physician. If you are taking anticoagulants (blood thinners), your clotting status should be checked frequently.
3. Use LEVOXYL® only as prescribed by your physician. Do not discontinue or change the amount you take or how often you take it, unless directed to do so by your physician.
4. The levothyroxine in LEVOXYL® is intended to replace a hormone that is normally produced by your thyroid gland. Generally, replacement therapy is to be taken for life, except in cases of transient hypothyroidism, which is usually associated with an inflammation of the thyroid gland (thyroiditis).
5. Take LEVOXYL® in the morning on an empty stomach, at least one-half hour before eating any food.
6. It may take several weeks before you notice an improvement in your symptoms.
7. Notify your physician if you experience any of the following symptoms: rapid or irregular heartbeat, chest pain, shortness of breath, leg cramps, headache, nervousness, irritability, sleeplessness, tremors, change in appetite, weight gain or loss, vomiting, diarrhea, excessive sweating, heat intolerance, fever, changes in menstrual periods, hives or skin rash, or any other unusual medical event.
8. Notify your physician if you become pregnant while taking LEVOXYL®. It is likely that your dose of LEVOXYL® will need to be increased while you are pregnant.
9. Notify your physician or dentist that you are taking LEVOXYL® prior to any surgery.
10. Partial hair loss may occur rarely during the first few months of LEVOXYL® therapy, but this is usually temporary.
11. LEVOXYL® should not be used as a primary or adjunctive therapy in a weight control program.
12. Keep LEVOXYL® out of the reach of children. Store LEVOXYL® away from heat, moisture, and light.

Laboratory Tests

General

The diagnosis of hypothyroidism is confirmed by measuring TSH levels using a sensitive assay (second generation assay sensitivity 0.1 mIU/L or third generation assay sensitivity 0.01 mIU/L) and measurement of free-T_4.

The adequacy of therapy is determined by periodic assessment of appropriate laboratory tests and clinical evaluation. The choice of laboratory tests depends on various factors including the etiology of the underlying thyroid disease, the presence of concomitant medical conditions, including pregnancy, and the use of concomitant medications (see **PRECAUTIONS, Drug Interactions and Drug-Laboratory Test Interactions**). Persistent clinical and laboratory evidence of hypothyroidism despite an apparent adequate replacement dose of LEVOXYL® may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T_4 potency of the drug product.

Adults

In adult patients with primary (thyroidal) hypothyroidism, serum TSH levels (using a sensitive assay) alone may be used to monitor therapy. The frequency of TSH monitoring during levothyroxine dose titration depends on the clinical situation but it is generally recommended at 6–8 weeks intervals until normalization. For patients who have recently initiated levothyroxine therapy and whose serum TSH has normalized or in patients who have had their dosage or brand of levothyroxine changed, the serum TSH concentration should be measured after 8–12 weeks. When the optimum replacement dose has been attained, clinical (physical examination) and biochemical monitoring may be performed every 6–12 months, depending on the clinical situation, and whenever there is a change in the patient's status. It is recommended that a physical examination and a serum TSH measurement be performed at least annually in patients receiving LEVOXYL® (see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

Pediatrics

In patients with congenital hypothyroidism, the adequacy of replacement therapy should be assessed by measuring both serum TSH (using a sensitive assay) and total- or free- T_4. During the first three years of life, the serum total- or free- T_4 should be maintained at all times in the upper half of the normal range. While the aim of therapy is to also normalize the serum TSH level, this is not always possible in a small percentage of patients, particularly in the first few months of therapy. TSH may not normalize due to a resetting of the pituitary-thyroid feedback threshold as a result of *in utero* hypothyroidism. Failure of the serum T_4 to increase into the upper half of the normal range within 2 weeks of initiation of LEVOXYL® therapy and/or of the serum TSH to decrease below 20 mIU/L within 4 weeks should alert the physician to the possibility that the child is not receiving adequate therapy. Careful inquiry should then be made regarding compliance, dose of medication administered, and method of administration prior to raising the dose of LEVOXYL®.

The recommended frequency of monitoring of TSH and total or free T_4 in children is as follows: at 2 and 4 weeks after the initiation of treatment; every 1–2 months during the first year of life; every 2–3 months between 1 and 3 years of age; and every 3 to 12 months thereafter until growth is completed. More frequent intervals of monitoring may be necessary if poor compliance is suspected or abnormal values are obtained. It is recommended that TSH and T_4 levels, and a physical examination, if indicated, be performed 2 weeks after any change in LEVOXYL® dosage. Routine clinical examination, including assessment of mental and physical growth and development, and bone maturation, should be performed at regular intervals (see **PRECAUTIONS, Pediatric Use** and **DOSAGE AND ADMINISTRATION**).

Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism

Adequacy of therapy should be assessed by measuring serum free-T_4 levels ,which should be maintained in the upper half of the normal range in these patients.

Drug Interactions

Many drugs affect thyroid hormone pharmacokinetics and metabolism (e.g., absorption, synthesis, secretion, catabolism, protein binding, and target tissue response) and may alter the therapeutic response to LEVOXYL®. In addition, thyroid hormones and thyroid status have varied effects on the pharmacokinetics and action of other drugs. A listing of drug-thyroidal axis interactions is contained in Table 2.

The list of drug-thyroidal axis interactions in Table 2 may not be comprehensive due to the introduction of new drugs that interact with the thyroidal axis or the discovery of previously unknown interactions. The prescriber should be aware of this fact and should consult appropriate reference sources. (e.g., package inserts of newly approved drugs, medical literature) for additional information if a drug-drug interaction with levothyroxine is suspected.

Table 2: Drug – Thyroidal Axis Interactions

Drug or Drug Class	Effect
Drugs that may reduce TSH secretion -the reduction is not sustained; therefore, hypothyroidism does not occur	
Dopamine / Dopamine Agonists Glucocorticoids Octreotide	Use of these agents may result in a transient reduction in TSH secretion when administered at the following doses: Dopamine (≥ 1 mcg/kg/min); Glucocorticoids (hydrocortisone ≥ 100 mg/day or equivalent); Octreotide (> 100 mcg/day).
Drugs that alter thyroid hormone secretion	
Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism	
Aminoglutethimide Amiodarone Iodide (including iodine-Containing Radiographic contrast agents) Lithium Methimazole Propylthiouracil (PTU) Sulfonamides Tolbutamide	Long-term lithium therapy can result in goiter in up to 50% of patients, and either subclinical or overt hypothyroidism, each in up to 20% of patients. The fetus, neonate, elderly and euthyroid patients with underlying thyroid disease (e.g., Hashimoto's thyroiditis or with Grave's disease previously treated with radioiodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Oral cholecystographic agents and amiodarone are slowly excreted, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Long-term aminoglutethimide therapy may minimally decrease T_4 and T_3 levels and increase TSH, although all values remain within normal limits in most patients.
Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism	
Amiodarone Iodide (including iodine-containing Radiographic contrast agents)	Iodide and drugs that contain pharmacologic amounts of iodide may cause hyperthyroidism in euthyroid patients with Grave's disease previously treated with antithyroid drugs or in euthyroid patients with thyroid autonomy (e.g., multinodular goiter or hyperfunctioning thyroid adenoma). Hyperthyroidism may develop over several weeks and may persist for several months after therapy discontinuation. Amiodarone may induce hyperthyroidism by causing thyroiditis.
Drugs that may decrease T_4 absorption, which may result in hypothyroidism	
Antacids - Aluminum & Magnesium Hydroxides - Simethicone Bile Acid Sequestrants - Cholestyramine - Colestipol Calcium Carbonate Cation Exchange Resins - Kayexalate Ferrous Sulfate Sucralfate	Concurrent use may reduce the efficacy of levothyroxine by binding and delaying or preventing absorption, potentially resulting in hypothyroidism. Calcium carbonate may form an insoluble chelate with levothyroxine, and ferrous sulfate likely forms a ferric-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.
Drugs that may alter T_4 and T_3 serum transport – but FT_4 concentration remains normal; and, therefore, the patient remains euthyroid	
Drugs that may increase serum TBG concentration	**Drugs that may decrease serum TBG concentration**
Clofibrate Estrogen-containing oral contraceptives Estrogens (oral) Heroin / Methadone 5-Fluorouracil Mitotane Tamoxifen	Androgens / Anabolic Steroids Asparaginase Glucocorticoids Slow-Release Nicotinic Acid
Drugs that may cause protein-binding site displacement	
Furosemide (> 80 mg IV) Heparin Hydantoins Non Steroidal Anti-Inflammatory Drugs - Fenamates - Phenylbutazone Salicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT_4. Continued administration results in a decrease in serum T_4 and normal FT_4 and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T_4 and T_3 to TBG and transthyretin. An initial increase in serum FT_4 is followed by return of FT_4 to normal levels with sustained therapeutic serum salicylate concentrations, although total-T_4 levels may decrease by as much as 30%.
Drugs that may alter T_4 and T_3 metabolism	
Drugs that may increase hepatic metabolism, which may result in hypothyroidism	
Carbamazepine Hydantoins Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in increased levothyroxine requirements. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T_4 may be reduced by 20% to 40%, but most patients have normal serum TSH levels and are clinically euthyroid.
Drugs that may decrease T_4 5'-deiodinase activity	
Amiodarone Beta-adrenergic antagonists - (e.g., Propranolol > 160 mg/day) Glucocorticoids - (e.g., Dexamethasone > 4 mg/day) Propylthiouracil (PTU)	Administration of these enzyme inhibitors decreases the peripheral conversion of T_4 to T_3, leading to decreased T_3 levels. However, serum T_4 levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T_3 and T_4 levels change slightly, TSH levels remain normal, and patients are clinically euthyroid. It should be noted that actions of particular beta-adrenergic antagonists may be impaired when the hypothyroid patient is converted to the euthyroid state. Short-term administration of large doses of glucocorticoids may decrease serum T_3 concentrations by 30% with minimal change in serum T_4 levels. However, long-term glucocorticoid therapy may result in slightly decreased T_3 and T_4 levels due to decreased TBG production (see above).
Miscellaneous	
Anticoagulants (oral) - Coumarin Derivatives - Indandione Derivatives	Thyroid hormones appear to increase the catabolism of vitamin K-dependent clotting factors, thereby increasing the anticoagulant activity of oral anticoagulants. Concomitant use of these agents impairs the compensatory increases in clotting factor synthesis. Prothrombin time should be carefully monitored in patients taking levothyroxine and oral anticoagulants and the dose of anticoagulant therapy adjusted accordingly.
Antidepressants - Tricyclics (e.g., Amitriptyline) - Tetracyclics (e.g., Maprotiline) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)	Concurrent use of tri/tetracyclic antidepressants and levothyroxine may increase the therapeutic and toxic effects of both drugs, possibly due to increased receptor sensitivity to catecholamines. Toxic effects may include increased risk of cardiac arrhythmias and CNS stimulation; onset of action of tricyclics may be accelerated. Administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidediones - Insulin	Addition of levothyroxine to antidiabetic or insulin therapy may result in increased antidiabetic agent or insulin requirements. Careful monitoring of diabetic control is recommended, especially when thyroid therapy is started, changed, or discontinued.
Cardiac Glycosides	Serum digitalis glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digitalis glycosides may be reduced.
Cytokines - Interferon-α - Interleukin-2	Thereapy wih interferon-α has been associated with the development of antithyroid microsomal antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antithyroid antibodies before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painless thyroiditis in 20% of patients. Interferon-β and -γ have not been reported to cause thyroid dysfunction.
Growth Hormones - Somatrem - Somatropin	Excessive use of thyroid hormones with growth hormones may accelerate epiphyseal closure. However, untreated hypothyroidism may interfere with growth response to growth hormone.
Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methylxanthine Bronchodilators - (e.g., Theophylline)	Decreased theophylline clearance may occur in hypothyroid patients; clearance returns to normal when the euthyroid state is achieved.
Radiographic Agents	Thyroid hormones may reduce the uptake of ^{123}I, ^{131}I, and ^{99m}Tc.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetics or thyroid hormone. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethionamide Lovastatin Metoclopramide 6-Mercaptopurine Nitroprusside Para-aminosalicylate sodium Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and / or TSH level alterations by various mechanisms.

Oral anticoagulants – Levothyroxine increases the response to oral anticoagulant therapy. Therefore, a decrease in the dose of anticoagulant may be warranted with correction of the hypothyroid state or when the LEVOXYL® dose is increased. Prothrombin time should be closely monitored to permit appropriate and timely dosage adjustments (see **Table 2**).

Digitalis glycosides – The therapeutic effects of digitalis glycosides may be reduced by levothyroxine. Serum digitalis glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 2**).

Drug-Food Interactions – Consumption of certain foods may affect levothyroxine absorption thereby necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium from the GI tract.

Drug-Laboratory Test Interactions – Changes in TBG concentration must be considered when interpreting T_4 and T_3 values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T_4 index (FT-I). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypoproteinemia, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also **Table 2**). Familial hyper- or hypo-thyroxine binding globulinemias have been described, with the incidence of TBG deficiency approximating 1 in 9000.

Carcinogenesis, Mutagenesis, and Impairment of Fertility – Animal studies have not been performed to evaluate the carcinogenic potential, mutagenic potential or effects on fertility of levothyroxine. The synthetic T_4 in LEVOXYL® is identical to that produced naturally by the human thyroid gland. Although there has been a reported association between prolonged thyroid hormone therapy and breast cancer, this has not been confirmed. Patients receiving LEVOXYL® for appropriate clinical indications should be titrated to the lowest effective replacement dose.

Pregnancy – Category A – Studies in women taking levothyroxine sodium during pregnancy have not shown an increased risk of congenital abnormalities. Therefore, the possibility of fetal harm appears remote. LEVOXYL® should not be discontinued during pregnancy and hypothyroidism diagnosed during pregnancy should be promptly treated.

Hypothyroidism during pregnancy is associated with a higher rate of complications, including spontaneous abortion, pre-eclampsia, stillbirth and premature delivery. Maternal hypothyroidism may have an adverse effect on fetal and childhood growth and development. During pregnancy, serum T_4 levels may decrease and serum TSH levels increase to values outside the normal range. Since elevations in serum TSH may occur as early as 4 weeks gestation, pregnant women taking LEVOXYL® should have their TSH measured during each trimester. An elevated serum TSH level should be corrected by an increase in the dose of LEVOXYL®. Since postpartum TSH levels are similar to preconception values, the LEVOXYL® dosage should return to the pre-pregnancy dose immediately after delivery. A serum TSH level should be obtained 6–8 weeks postpartum.

Thyroid hormones do not readily cross the placental barrier; however, some transfer does occur as evidenced by levels in cord blood of athyreotic fetuses being approximately one-third maternal levels. Transfer of thyroid hormone from the mother to the fetus, however, may not be adequate to prevent in utero hypothyroidism.

Nursing Mothers – Although thyroid hormones are excreted only minimally in human milk, caution should be exercised when LEVOXYL® is administered to a nursing woman. However, adequate replacement doses of levothyroxine are generally needed to maintain normal lactation.

Pediatric Use

General

The goal of treatment in pediatric patients with hypothyroidism is to achieve and maintain normal intellectual and physical growth and development.

The initial dose of levothyroxine varies with age and body weight (see **DOSAGE AND ADMINISTRATION, Table 3**). Dosing adjustments are based on an assessment of the individual patient's clinical and laboratory parameters (see **PRECAUTIONS, Laboratory Tests**).

In children in whom a diagnosis of permanent hypothyroidism has not been established, it is recommended that levothyroxine administration be discontinued for a 30-day trial period, but only after the child is at least 3 years of age. Serum T_4 and TSH levels should then be obtained. If the T_4 is low and the TSH high, the diagnosis of permanent hypothyroidism is established, and levothyroxine therapy should be reinstituted. If the T_4 and TSH levels are normal, euthyroidism may be assumed and, therefore, the hypothyroidism can be considered to have been transient. In this instance, however, the physician should carefully monitor the child and repeat the thyroid function tests if any signs or symptoms of hypothyroidism develop. In this setting, the clinician should have a high index of suspicion of relapse. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, an alternate approach is to reduce the replacement dose of levothyroxine by half during the 30-day trial period. If, after 30 days, the serum TSH is elevated above 20 mU/L, the diagnosis of permanent hypothyroidism is confirmed, and full replacement therapy should be resumed. However, if the serum TSH has not risen to greater than 20mU/L, levothyroxine treatment should be discontinued for another 30-day trial period followed by repeat serum T_4 and TSH.

The presence of concomitant medical conditions should be considered in certain clinical circumstances and, if present, appropriately treated (see **PRECAUTIONS**).

Congenital Hypothyroidism (see **PRECAUTIONS, Laboratory Tests and DOSAGE** and **ADMINISTRATION**)

Rapid restoration of normal serum T_4 concentrations is essential for preventing the adverse effects of congenital hypothyroidism on intellectual development as well as on overall physical growth and maturation. Therefore, LEVOXYL® therapy should be initiated immediately upon diagnosis and is generally continued for life.

During the first 2 weeks of LEVOXYL® therapy, infants should be closely monitored for cardiac overload, arrhythmias, and aspiration from avid suckling.

The patient should be monitored closely to avoid undertreatment or overtreatment. Undertreatment may have deleterious effects on intellectual development and linear growth. Overtreatment has been associated with craniosynostosis in infants, and may adversely affect the tempo of brain maturation and accelerate the bone age with resultant premature closure of the epiphyses and compromised adult stature.

Acquired Hypothyroidism in Pediatric Patients

The patient should be monitored closely to avoid undertreatment and overtreatment. Undertreatment may result in poor school performance due to impaired concentration and slowed mentation and in reduced adult height. Overtreatment may accelerate the bone age and result in premature epiphyseal closure and compromised adult stature.

Treated children may manifest a period of catch-up growth, which may be adequate in some cases to normalize adult height. In children with severe or prolonged hypothyroidism, catch-up growth may not be adequate to normalize adult height.

Geriatric Use

Because of the increased prevalence of cardiovascular disease among the elderly, levothyroxine therapy should not be initiated at the full replacement dose (see **WARNINGS, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to therapeutic overdosage. They include the following:

General: fatigue, increased appetite, weight loss, heat intolerance, fever, excessive sweating;

Central nervous system: headache, hyperactivity, nervousness, anxiety, irritability, emotional lability, insomnia;

Musculoskeletal: tremors, muscle weakness;

Cardiac: palpitations, tachycardia, arrhythmias, increased pulse and blood pressure, heart failure, angina, myocardial infarction, cardiac arrest;

Pulmonary: dyspnea;

GI: diarrhea, vomiting, abdominal cramps;

Dermatologic: hair loss, flushing;

Reproductive: menstrual irregularities, impaired fertility.

Pseudotumor cerebri and slipped capital femoral epiphysis have been reported in children receiving levothyroxine therapy. Overtreatment may result in craniosynostosis in infants and premature closure of the epiphyses in children with resultant compromised adult height.

Seizures have been reported rarely with the institution of levothyroxine therapy.

Inadequate levothyroxine dosage will produce or fail to ameliorate the signs and symptoms of hypothyroidism.

Hypersensitivity reactions to inactive ingredients have occurred in patients treated with thyroid hormone products. These include urticaria, pruritus, skin rash, flushing, angioedema, various GI symptoms (abdominal pain, nausea, vomiting and diarrhea), fever, arthralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

MANUFACTURER

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St. Louis, MO 63146

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†The thyroid shape is a registered trademark.

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SPOTLIGHT ON...

Elliot Rayfield Raises Thousands for Educational Programs

During ENDO 2004, Endocrine Society member Elliot Rayfield, M.D. was acknowledged by Chip Ridgway, M.D. the 2003-2004 President of The Endocrine Society, for raising more than $30,000 from grateful patients to support educational programs at ENDO focusing on endocrine research.

"The Society's meetings and journals have always provided me with many opportunities to network and educate myself on new research to treat my patients," he explains. "They allow me to remain current on findings and share ideas and experiences with colleagues."

Dr. Rayfield who is in private practice in New York City says that, despite the large amount of money raised, the majority of his patients are not wealthy and often donate as little as five to ten dollars. "It all adds up in the end," he explains. "You have to get them excited. I believe in the Society's mission and purpose and my belief adds strength to my words and inspires others to donate."

As a member of the Society's Development Committee, Dr. Rayfield, realized that he could be used as a vehicle to raise funds for the Society. His daily interactions with patients allowed him to customize his approach to suit each individual patient. "I try to help my patients understand the concept of what the Society does for its members. The ultimate cure for their ailment, be it diabetes, thyroid disease, osteoporosis or Cushing's syndrome will come from basic and clinical research by endocrinologists—and we need the patients' support."

Dr. Rayfield notes that other physicians can use his approach to raise additional funds, "Any practicing physician can do what I did—the worst a patient can do is say 'no' and that's not often the case. Usually, patients are looking for tangible ways to express their appreciation for the treatment we provide," he adds. Dr. Rayfield also extends his gratitude for the support he received from Mark Hartman, M.D., Chair of the Development Committee, Chip Ridgway, M.D., 2003-2004 Society President, Nancy Chill, Director, Development & Client Services as well as Paris L.A. Moore, Manager, Development & Client Services. He is determined to continue building upon his incredulous success.

"This is just the beginning," he says with excitement and he is right. The Development Committee is currently working to create a program with resources for physicians-in-practice to use to expand on Dr. Rayfield's success. "We have to start somewhere," Dr. Rayfield adds, "and I'd say this is a pretty good stepping stone!" EN

For more information about contributions contact Nancy Chill, Director, Development & Client Services at 1-301-941-0203 or nchill@endo-society.org

Power through Participation

How You Can Become Involved with The Endocrine Society

Are you interested in becoming involved with The Endocrine Society or The Hormone Foundation? Whether you are serving on a committee or reviewing fact sheets, there are multiple ways that members of the endocrine community can participate in The Endocrine Society or its patient education affiliate, The Hormone Foundation. The following two pages highlight the many ways that you can get involved with these two exciting and growing organizations!

The Hormone Foundation

The Hormone Foundation, the public education affiliate of The Endocrine Society, relies on the expertise of Society members for the development of programs and materials. The Foundation invites Endocrine Society members to serve as an advisory council to develop programs; edit the Foundation's publications and Web site content; and speakers/panelist for public education forums and media roundtables. Through the involvement of members, The Hormone Foundation is able to serve as a resource of hormone-related information for the public. EN

To volunteer for The Hormone Foundation contact Paula Correa, Program Manager of The Hormone Foundation at *pcorrea@endo-society.org*

Above: Dr. Anthony Means, current President of The Endocrine Society, visits with students and fellows to promote the field of endocrinology.

Journal Editorial Board Member

Candidates for editorial board member of the Society's four journals are selected by the Editor-in-Chief of each journal and approved by the Publications Committee. Board members review manuscripts submitted for publication using E-review, an online peer review and manuscript tracking system. The appointment is for four years and includes one face-to-face meeting a year at the Society's Annual Meeting. Editorial Board members receive a complimentary subscription to the journal on which they serve. EN

For more information contact Maggie Haworth, Managing Editor, *Endocrine Reviews and Molecular Endocrinology* at *mhaworth@endo-society.org* or Scott Herman, Managing Editor *Endocrinology and The Journal of Clinical Endocrinology & Metabolism* (2005) *sherman@endo-society.org*

Take Action! Join the Grassroots Network

Support The Endocrine Society's government relations efforts on Capitol Hill and in your state. Participants attend meetings with elected officials and participate in letter writing campaigns, which are vital to expressing the Society's concerns on issues that involve the entire endocrine community. Your presence in the local districts of federal representatives and in state government offices will help the Society's representation nationwide. EN

For more information contact Chris Rorick, Government Relations Manager, at 1-301-941-0251 or by email *crorick@endo-socety.org*

Join in the Search for Young Endocrinologists!

The Society for the Advancement of Chicanos and Native Americans in Science (SACNAS) and the Annual Biomedical Research Conference for Minority Students (ABRCMS) are attended annually by members of The Endocrine Society. During these conferences, members are asked to identify and judge poster presentations on topics related to endocrinology to receive cash awards. Work with members of the Minority Affairs Committee to discover the next wave of endocrinologists by volunteering to judge student posters. **EN**

For more information, please email us at *mac@endo-society.org*

Dr. Chip Ridgway, Past-President of The Endocrine Society, meets and greets mentors and mentees during a dinner meeting at ENDO 2004.

ENDO Abstract Reviewers

Interested in reviewing the latest research in endocrinology? Abstracts for ENDO 2005, the 87th Annual Meeting of The Endocrine Society, are selected by volunteer members of the Society! Volunteer and work with the Annual Meeting Steering Committee to review abstracts submitted for ENDO 2005 based on your expertise in a given category. **EN**

For more information contact Carol Balsamo, Program Coordinator, Meetings and Education, at 1-301-951-2605 or by email *cbalsamo@endo-society.org*

Shortcourses in Endocrinology

Interested in presenting Shortcourse lectures at minority undergraduate institutions? The Minority Affairs Committee is seeking volunteer lecturers to provide endocrine Shortcourses aimed at exposing minority students to the science of endocrinology. **EN**

For more information on how to become a volunteer lecturer, please contact Veronica Parcan, NIGMS Grant Manager, at 1-301-951-2601 or email *vparcan@endo-society.org*

Coding and Valuation Workgroup

Make a difference for endocrine clinicians! The Society's Clinical Affairs Committee needs your help with the review and development of coding reimbursement tools. Join the Coding and Valuation Workgroup to help serve the Common Procedural Terminology (CPT) Panel and the Resource-Based Relative Value Update Committee (RUC). The Society's active participation in these processes is crucial to having endocrinology services appropriately valued and reimbursed. **EN**

For more information contact Janet Kreizman, Director, Program and Policy Affairs at *jkreizman@endo-society.org*

Volunteer for Committee Service

This is your opportunity to express your interest and willingness to serve in a Society committee. Appointments for the June 2005 committee vacancies will begin in October 2004. As an Endocrine Society Committee member, you can use your expertise and experience to make a difference in diverse communities. Become a thought leader and take advantage of the different opportunities available for committee service. Please visit the Society's Web site at *http://www.endo-society.org/membersonly/committees/nominating/call_for_committee.cfm* and complete the Online Submission form. **EN**

For more information contact Elizabeth Kan at *ekan@endo-society.org*

Volunteer opportunities at the Annual Meeting

Great opportunity to get involved at the Annual Meeting! The Minority Affairs Committee is seeking volunteers to mentor minority undergraduate students attending the Annual Meeting. Mentors will be asked to allow students to shadow them throughout the meeting acting as advisors and assisting students in selecting the most relevant topics and programs to attend. Impact today's young scientists by participating in the ENDO 2005 Minority Mentoring Reception! Volunteer mentors share their career experiences with minority students, postdocs, fellows and faculty at this networking event hosted annually by the Minority Affairs Committee. **EN**

For more information on these events or how to serve as mentors, please email us at *mac@endo-society.org*

The Endocrinology of PEDIATRIC OBESITY

BY: PATRICIA STEPHENS, PH.D.

The Endocrine Society's 86th Annual Meeting, ENDO 2004, focused on the obesity epidemic that is threatening public health worldwide. Among the many educational opportunities related to this serious issue was a Continuing Medical Education Services (CMES) ancillary symposium on the increasingly prevalent problem of childhood obesity. Sponsored by The Endocrine Society Strategic Plan Initiative, "The Endocrinology of Pediatric Obesity," included presentations by Robert Lustig, M.D., University of California, San Francisco, CA; Daniel Marks, M.D., Ph.D., Oregon Health Sciences University, Portland, OR; and Jack Yanovski, M.D., Ph.D., National Institutes of Health, Bethesda, MD.

The program had three overall educational goals:

- Review the neuroendocrine coordination of appetite and energy balance in the context of childhood obesity.
- Describe the short- and long-term endocrine and metabolic consequences of childhood obesity.
- Discuss the risks and benefits of currently available pharmacological and surgical intervention methods for treatment of childhood obesity.

Neuroendocrinology of Childhood Obesity

Dr. Daniel Marks observed that the weight set point hypothesis is key to understanding the neuroendocrine coordination of appetite and energy balance. In brief, humans all have a genetically inherited set point governing our "ideal" body mass. However, environmental factors influence this set point and determine actual body mass. That the brain remembers its weight set point has been shown in studies of gurus who go through a fattening session in which they gain about 30 kilograms (kg) of pure body fat. Once the session ends, the participants resume their regular diet and their body returns to its previous weight.

Within the brain, numerous hormones act directly to produce a variety of metabolic outputs. Four of these hormones—leptin, insulin, ghrelin, and $PYY_{3\text{-}36}$—illustrate how body weight seems to be regulated. Leptin and insulin are long-term regulators, whereas ghrelin

and PYY_{3-36} are short-term, meal-to-meal regulators. Body weight regulation has two pathways in the brain: feeding inhibition and increased metabolism, and feeding stimulation and decreased metabolism. The melanocortin system is one of the most important feeding inhibitory pathways in the brain.

Melanocortin system. One melanocortin pathway consists of proopiomelanocortin (POMC), which releases α-melanocyte-stimulating hormone (α-MSH), which then binds to the type 4 melanocortin receptor (MC4-R) in the brain to inhibit feeding and to increase metabolic rate. One of the primary feeding stimulation pathways in the brain is the neuropeptide Y (NPY) system. Because it would not make sense for both of these pathways to be turned on at the same time, the NPY system also produces agouti-related peptide (AGRP) that acts to turn off the melanocortin system when the NPY system is activated.

Obesity in humans has been linked to mutations in the POMC and MC4-R genes. It's likely that we will be learning a great deal about POMC mutations as a cause for obesity, especially in children. At present much more is understood about MC4-R mutations. About five percent of all pediatric obesity is associated with MC4-R mutations, making it the most common monogenic obesity syndrome known. Its clinical features are well identified:

- Both autosomal dominant and autosomal recessive inheritance
- Severe early-onset obesity
- Increased linear growth
- Late puberty relative to bone age
- Increased bone mineral density
- Food seeking, decreasing somewhat with age
- Hyperinsulinemia (corrected for obesity); not diabetic
- Normal reproductive axis as an adult
- Normal thyroid and adrenal function

Long-term regulation of weight. Leptin is an important energy-regulating hormone, and disorders of leptin signaling are associated with obesity in humans. Secreted by adipocytes, leptin plays a key role in long-term regulation of body weight. With receptors present within the hypothalamus on both POMC and AGRP neurons, leptin acts directly on the brain to stimulate the POMC pathway and to inhibit the AGRP/NPY pathway. It serves as a gatekeeper to tell the brain when nutrition levels are sufficient. Its deficiency produces an endocrine profile similar to starvation. Leptin levels are very high in obese persons. Just as type 2 diabetes is an insulin-resistance syndrome, much obesity is a leptin-resistance syndrome.

Short-term regulation of satiety. Along with leptin and insulin, the hormones ghrelin and PYY_{3-36} exert their effects, at least in part, via the melanocortin pathway. Human ghrelin is a gastric peptide that functions as a short-term satiety signal. Released from the stomach, ghrelin's profile in the serum is exactly the opposite of insulin's. Levels of this appetite-stimulating hormone rise when the stomach is empty, inducing hunger. Levels fall quickly when the stomach is full, but the feeling of satiety takes at least 30 minutes. Ghrelin thus participates in meal-to-meal control of eating.

PYY_{3-36}, a member of the NPY protein family, is secreted by the colon in response to a meal. It inhibits pancreatic exocrine secretion, decreases gut motility. It also appears to be increased after ileojejunal bypass. Like insulin, leptin, and ghrelin, PYY_{3-36} activity seems to involve the arcuate nucleus in the hypothalamus. Studies have shown that an infusion of PYY_{3-36} can reduce food intake by about 35 percent, a finding that may have important implications for future therapy. Like ghrelin, PYY_{3-36} levels rise after a meal, but it takes 30 minutes for satiety.

Consequences of Childhood Obesity

Dr. Jack Yanovski focused on the epidemiology and endocrine and metabolic consequences of childhood obesity. Among children and adolescents, overweight (obesity) is defined by an age- and sex-relative metric. A child's body mass index (BMI) is calculated by dividing his or her weight in kilograms by height in meters squared (kg/m^2). Those whose BMI is greater than the 85th percentile are considered at risk for overweight. Those whose BMI exceeds the 95th percentile are termed overweight.

Since the 1960s, age-specific trends in overweight for boys and for girls have risen sharply for both sexes and in all age groups. Among boys, over 10 percent of two- to five-year-olds and over 15 percent of six- to 19-year-olds are now clinically overweight. The same pattern is seen in girls. Pediatric obesity has numerous endocrine and metabolic consequences, of which Dr. Yanovski discussed four groups: hyperinsulinemia, cardiovascular risks, disorders of puberty, and effects on the growth hormone (GH)—insulin-like growth factors (IGF)-1 axis.

Hyperinsulinemia. Studies in children, as in adults, have shown a tight correlation between fasting hyperinsulinemia and adiposity. Among children in the BMI ≥95th percentile group, 35 percent had abnormal (≥15 μIU/mL) fasting insulin levels. Only five percent of those in the BMI <95th percentile group had levels this high. One of the immediate endocrine consequences of pediatric obesity is insulin resistance. Insulin-stimulated glucose uptake has been shown to decrease by 20 percent-40 per-

cent. One study found that over two percent of adolescents with a BMI >75th percentile developed type 2 diabetes by age 30, whereas none of the leaner adolescents did. The 10-fold rise in the prevalence of type 2 diabetes between 1982 and 1994 is likely a result of increasing rates of obesity. It's not only insulin's effects on glucose uptake that are altered by obesity. Just as in adults, free fatty acid suppression is affected in children.

Cardiovascular risks. About 60 percent of overweight children will have at least one cardiovascular risk factor. The association between pediatric obesity and hypertension is more marked for systolic than diastolic blood pressure, but both show a relationship with BMI. Elevated blood pressure has been seen in up to 30 percent of severely obese children. In addition, overweight children have nine times the risk of developing hypertension as an adult. The same holds true for the relationship between pediatric obesity and triglycerides: as the BMI increases, so do triglyceride levels. It is much the same story with low-density lipoprotein (LDL) cholesterol, and not surprisingly high-density lipoprotein (HDL) cholesterol is inversely proportional to BMI. This dyslipidemia persists into adulthood. Overall, hemostatic measures are also positively correlated with adiposity in children, as in adults. The prevalence of the metabolic syndrome is about 39 percent in moderately obese children and adolescents and about 50 percent in the severely obese. Each half-unit increase in the BMI-SD score is associated with a 1.5-fold increase in risk for the syndrome.

Disorders of puberty. Advancement of maturation is unique to pediatric obesity. Overweight leads to early growth, early puberty, and early cessation of growth. Height charts for two-year-old boys and girls, but not for 18-year-olds, show a high correlation with BMI. Skeletal maturation (bone age minus chronological age) is also advanced in obese children. One possible explanation of why obesity leads to early maturation is that adipose tissue contains the enzyme aromatase. As obesity increases, production of both estradiol and estrone increases. Also, as BMI increases, sex hormone binding globulin levels drop. Consequently, whatever total levels of estrogen are present will be more effective because more of the hormone will be unbound. Polycystic ovarian disease is frequently seen in overweight adolescent girls.

Effects on the GH–IGF-1 axis. Spontaneous GH secretion values are lower in both obese boys and girls, a phenomenon that holds true in adults as well. Interestingly, these lower values do not cause problems with growth plate development. Although the total IGF1 is lower in the obese than in the non-obese, the free IGF1 levels are twice as high in the obese group. The IGF binding proteins (IGBP1, IGBP2, IGBP3) are suppressed in the obese. Thus, the net effect is greater IGF-1 activity even though the GH levels are somewhat lower.

Pharmacological & Surgical Therapy

Dr. Robert Lustig described the current pharmacotherapeutic and surgical interventions available for treating obesity.

Leptin. Although leptin does promote weight loss in leptin-deficient patients, only 11 such patients have been reported. Typically, obese persons are leptin resistant, and this resistance prevents leptin-induced weight loss. In fact, a study of leptin as a primary therapy for obesity in adults showed that only the highest dose had any effect on weight loss, and 16 of the 18 patients in the cohort had severe side effects. At this time, leptin is not on the market.

Anorectic agents. These drugs limit food intake or absorption. Primary data on the effects of the drugs themselves are lacking, and so they should complement a diet and exercise program. Modest effects on total weight have been seen. The highly variable responses are a possible reflection of the heterogeneity in the etiology of the obesity. Most of the benefit is achieved within the first 4 months, and regain of weight is the norm if the medication is stopped.

Sibutramine is the best-studied anorectic agent. It's a nonselective inhibitor of neuronal reuptake of serotonin and norepinephrine. It mimics what the sympathetic nervous system would be telling the hypothalamus in terms of energy intake. The response rate to this drug is enormously variable, and side effects are a concern. Even though the Food and Drug Administration (FDA) has approved it for patients older than 16 years, it is not for routine use.

Orlistat inhibits the gastrointestinal lipase that breaks triglycerides down into monoglycerides for absorption through the gut. By inhibiting the lipase, the triglycerides end up in the stool. A company-sponsored double-blind placebo-controlled trial in 12- to 16-year-olds found variable responses and had high dropout rates. There were no data in the absence of behavioral intervention. Side effects included deficiencies of fat-soluble vitamins, flatulence, diarrhea, and "leakage." Orlistat requires highly motivated patients. That the drug is FDA approved for children over age 12 speaks to the severity of the pediatric obesity problem.

Insulin disorders. There are two insulin disorders in pediatric obesity. Insulin resistance is characterized by fasting hyperinsulinemia probably due to liver and/or muscle dysfunction. The phenomeno seems

to be responsive to metformin. Insulin hypersecretion is characterized by postprandial hyperinsulinemia due to vagal and/or pancreatic dysfunction. It appears to be responsive to octreotide.

Metformin reduces hepatic gluconeogenesis and hepatic glucose production. It increases hepatic insulin sensitivity and lowers fasting insulin levels. Although it decreases food intake, it isn't an anorectic agent. Metformin may be appropriate for obese children or adolescents with severe insulin resistance, or for obese teenage girls with polycystic ovary syndrome (PCOS). One study has shown that an especially effective use of metformin was in adolescents who became obese as a result of psychotropic drugs. The side effects in obese adolescents include transient abdominal discomfort or diarrhea, lactic acidosis (very rare), and urinary loss of B vitamins. Metformin is approved for type 2 diabetes in children but not for obesity.

Octreotide reduces glucose-dependent insulin secretion by binding to somatostatin-5 receptor and thereby inhibiting β-cell calcium channel opening. It is useful in children with hypothalamic obesity due to central nervous sysyem (CNS) insult, with vagally driven insulin hypersecretion. Its limitations include high cost (1000 dollars per month) and parenteral administration. The side effects are transient gastrointestinal distress, gallstones, and suppression of GH and thyroid-stimulating hormone (TSH) secretion. Octreotide is not yet approved for hypothalamic obesity, but Phase III studies are ongoing.

Surgery. The rationale for surgical treatment includes the following:

- Persistence of pediatric obesity into adulthood
- Adolescents presenting with adult diseases
- Increases in obesity-related health care costs
- Limited efficacy of behavioral approaches for the severely obese
- Surgical weight loss ameliorates or resolves most obesity-related co-morbidities in adults

Two surgical approaches are now in use: laproscopic adjustable gastric banding (LAGB) and Roux-en-Y gastric bypass (RYGB). A comparison of the two surgical options shows that LAGB is a shorter procedure (~ one hour vs. 1.5-3.5 hours), requires a shorter length of stay (one day vs. 1-3 days), and has a lower mortality (0.05 percent vs. 0.5 percent) and morbidity (seven percent vs. 17 percent) rate. RYGB has more weight loss initially, but after three years the final weight loss is about the same for the two procedures. LAGB is favored worldwide, whereas RYGB is favored in the United States. **EN**

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Minority Affairs Committee Reaches Out

Members of The Endocrine Society's Minority Affairs Committee (MAC) attended the Annual Convention and Scientific Assembly of the National Medical Association (NMA) on July 31 – August 5, 2004 in San Diego, California. The event hosted approximately 3,000 African-American physicians and health care professionals from across the country. The MAC members were on hand to show their support to the NMA and to promote the visibility and participation of minority physicians in the programs offered by the Society. MAC members encouraged attendees to explore the benefits of membership, involvement in MAC activities and provided information on upcoming Society meetings and patient education resources. In addition, members identified several minority speakers and issues in minority health to be incorporated into future Society meetings. EN

Dr. Thomas Chien and Dr. James Story visit the Society's booth and discuss volunteer programs.

Women in Endocrinology 2005 Mentor Award

The primary mission of Women in Endocrinology (WE) is to promote the scientific advancement and recognition of female endocrinologists. With this goal, WE presents an annual Mentor Award at the WE dinner during The Endocrine Society's annual meeting to recognize outstanding individuals who have encouraged and promoted female endocrinologists and who have been instrumental in changing institutional policy toward professional women. The WE Mentor Award is sponsored by a generous grant from Pfizer. The awardee receives an honorarium of $1000 and travel expenses to the Annual WE Meeting. Past recipients of the WE Mentor Award include Neena B. Schwartz, Peng Loh, Anita Payne, William F. Crowley, Jack Gorski, Anne Klibanski, Phyllis Wise, William Chin, and Jo Anne Brasel.

WE encourages the nomination of mentors (female or male) who have impacted a person's careers and have had a positive impact on the careers of female endocrinologists.

For more information about the nomination process please see: *http://www.women-in-endo.org/Pages/mentor_award_nom.html*

Nominations for the 2005 WE Mentor Award should be sent to the Chair of the WE Awards Committee, Ursula B. Kaiser, M.D. by fax 1-617-732-5764 or email *ukaiser@partners.org*

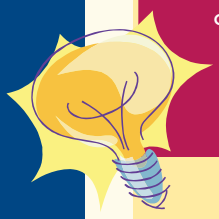
Applications must be received by **January 14, 2005**. EN

DONATE YOUR JOURNALS NOW!

In this issue, we are highlighting three journals that are needed to pursue the Societys online Legacy Data Project. The Endocrine Society is seeking donations for the following journals:

- *The Journal of Clinical Endocrinology & Metabolism,* Volume 29, 1969
- *The Journal of Clinical Endocrinology & Metabolism,* Volume 28, 1968
- *The Journal of Clinical Endocrinology & Metabolism,* Volume 27, 1967

If you have and are willing to donate the requested issues or volumes, please contact Adrienne Weber, Journal Publications Coordinator, at 1-301-941-0238 or **aweber@endo-society.org** for shipping information. You can view the complete list of other outstanding issues and volumes for the journals at **www.endo-society.org/journals/legacy.pdf**



The Endocrine Society would like to thank the following contributors to this project thus far.

Ron Brown, M.D.
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William Rosner, M.D.
Janet Rubin, M.D.
Marjorie Safran, M.D.
Jessica Schwartz, Ph.D.
Allen Shore, M.D.
Guy Van Vliet, M.D.

Congratulations!

Dr. Kathryn B. Horowitz

Dr. Kathryn B. Horowitz, the 1998 President of The Endocrine Society, has been awarded the prestigious title of Distinguished Professor Colorado University-Health Sciences Center. The title is the highest honor granted by the Colorado University Board of Regents, honored to members of the faculty who have distinguished themselves as exemplary teachers, scholars and public servants, and who are individuals having extraordinary international importance and recognition. EN

Thanks for Stopping By!

Four distinguished members visited The Endocrine Society offices during the month of August. Newly appointed President, Dr. Anthony Means, spent a day meeting staff members and discussing his 2004-2005 Presidential agenda. Following Dr. Means' visit, President-Elect, Dr. Andrea Dunaif toured the Society offices and worked with several departments to outline her 2005-2006 agenda. Dr. Paul W. Ladenson, who was recently appointed Editor-In-Chief, of *The Journal of Clinical Endocrinology & Metabolism*, also stopped in to visit with his future Journals & Publications staff. And finally, Dr. Martin Surks, current member of the Society's Council and Chair of the Self-Assessment Committee, toured the offices and met with staff.

If you are in the Washington, D.C. area and would like to visit The Endocrine Society offices please contact Elizabeth Kan, Manager, Executive Office *ekan@endo-society.org* EN

New Format and Look for ESN Live!

The Endocrine Society's email newsletter, **ESN Live!** has a new look and format. In addition to being easier to read, the newsletter is now customized to feature information that is most relevant to each constituency first!

By creating these different versions, the Society is able to disseminate the news and information of most interest to each constituency.

For more information contact Janet Ballonoff, Portal Manager, *jballonoff@endo-society.org* EN

History Project Opportunities

Interested in a particular endocrine-related topic? Ever wanted to discuss historical endocrine discoveries? The History Project is offering members the opportunity to interview senior members for The Endocrine Society archives. If you are willing to volunteer and interview senior members in your geographic area, contact Dr. Adolph Friedman at 1-301-951-2607 or *afriedman@endo-society.org* EN

Got Questions?

Meet the team with answers to all your Endocrine Society needs!

By offering a variety of services to the entire endocrine community, the Society Services Center is dedicated to assisting with all of your Society needs, including:

Updates to Membership Record
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- Demographic information
- Member Directory and Physician Referral Directory listings

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- Dates and locations
- CME certificates

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- Annual Membership Dues
- Book orders
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- Payment receipts and invoices

If you have a question or concern please call 1-301-941-0210 or email SocietyServices@endo-society.org EN

The Society Services Team! From left to right: Danielle Jordan, Crystal Macon, Kelly Fischer and Aneesah Chandler.

IN MEMORIAM

Clark T. Sawin, M.D.

Medical Inspector, Veterans Administration's, Washington, D.C.
Chief of the Endocrine-Diabetes Section, Boston VA Medical Center
May 23, 1934 – August 11, 2004

It is with great sadness that we announce the passing of Clark T. Sawin, M.D.

Dr. Sawin was a member of The Endocrine Society for over 34 years and served as the Chair of the History Committee for the past five years. Dr. Sawin's research interests were in clinical thyroid disease, especially focusing on issues around treatment of hypothyroidism and changes in thyroid function with aging. Over the past two decades, Dr. Sawin focused on the history of endocrinology. He published widely in this area and was a regular speaker at national and international endocrinology meetings on this topic.

Dr. Sawin is survived by his wife, Leslie, of 22 years and three children, Jennifer, Philip and Kenneth.

Other Society members who have passed

Dr. Eleanor F. Dempsey
Quincy, Massachusetts
June 6, 1916 – August 3, 2004

Dr. Carlos Marti-Henneberg
Barcelona, Spain
April 8, 1942 – July 6, 2004

Dr. Jan L. Touber
Ede GLD, Netherlands
January 21, 1932 – July 21, 2004

Thank You to Shortcourse Program Institutions and Mentors

The Minority Affairs Committee thanks all participating institutions and volunteer mentors that participated in the 2003/2004 grant year of the Shortcourse Program. The program is funded by a grant from the National Institute of Health's National Institute of General Medical Sciences (NIGMS) to promote the science of endocrinology with minority undergraduate students.

Volunteer lecturers during the current academic year offered courses in basic and advanced endocrinology, provided seminars on the lecturer's area of research and participated in community outreach programs to discuss endocrine health issues and how they affect minorities. Lectures also scheduled face to face sessions on career counseling discussing opportunities in academics and industry. **A total of 43 Shortcourses were held throughout the United States serving approximately 3000 students.**

The Committee thanks all participants in making this academic year a success! Special thanks are extended to Dr. James Mrotek, Ph.D., current principal investigator of the NIGMS grant, Thomas Landefeld, Ph.D. and Theresa Duello, Ph.D., for their work in getting the Shortcourse Program off the ground. EN

For more information about serving as a host institution, guest lecturer, or attending a shortcourse, visit the Society Web site at www.endo-society.org/diversity/courses.cfm *or contact Veronica Parcan, Grant Manager at 1-301-951-2601 or* vparcan@endo-society.org

SCHOOL	LECTURER
FALL 2003	
Albany State University, GA	James Mrotek
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Florida A&M University, FL	Thomas Landefeld
Santa Monica, CA	David Cooke
Tennessee State University, TN	Thomas Landefeld
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Medgar Evers College, NY	Simon Rhodes
MMC/TSU (MT Program), TN	James Mrotek
Meharry Medical College (PB Program), TN	James Mrotek
Prairie View A&M University, TX	Thomas Landefeld
Savannah State University, GA	Thomas Chen
South Mountain Comm. College, AZ	Richard Falvo
Southern University, Baton Rouge, LA	Thomas Landefeld
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Texas A&M Corpus Christi, TX	Kenneth Campbell
Tougaloo, MS	Thomas Landefeld
Tuskegee, AL	Clayton Yates
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University of Puerto Rico, Mayaguez	Kenneth Campbell
University of Virgin Islands, St Thomas	Thomas Landefeld
University of Virgin Islands, St Croix	Thomas Landefeld
Virginia State University, VA	Thomas Landefeld
Voorhees College, SC	Evangeline Motley
Xavier University, LA	Vernon Gay
SUMMER 2004	
Jackson State University, MS	James Mrotek
Meharry Medical College, TN	James Mrotek
Montana State University, MT	Vernon Gay

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Patient Information Page

Low Testosterone and Men's Health

PLEASE CUT HERE

What is the role of testosterone in men's health?

Testosterone is the most important sex hormone that men have. It is responsible for the typical male characteristics and helps maintain sex drive, sperm production, pubic and body hair, muscle, and bone. The brain controls the production of testosterone by the testes.

Low testosterone (also called hypogonadism) can cause:

- A drop in sex drive
- Poor erections
- Low sperm count
- Enlarged breasts

Over time, low testosterone may cause a man to lose body hair, bulk and strength, have weaker bones (osteoporosis), mood changes, and have less energy and smaller testes.

What causes low testosterone?

Low testosterone can be caused by injury (e.g., trauma, castration, radiation or chemotherapy), hormonal disorders (e.g., pituitary tumors or diseases, high levels of prolactin), or other systemic diseases (e.g., HIV/AIDS, chronic liver and kidney disease, too much body fat, and type 2 diabetes and associated obesity). Some medications and several genetic conditions (e.g., Klinefelter syndrome, hemochromatosis, Kallmann syndrome, Prader-Willi syndrome, and mytonic dystrophy) also can cause low testosterone. In many cases, however, the cause is not known.

How is low testosterone diagnosed?

During a physical exam, your doctor will examine body hair, breast size, size and consistency of the testes, scrotum, penis size, and ability to see in all directions. Your doctor will also use blood tests to see if the total testosterone level is within the normal range. This is generally 300 to 1,000 ng/dL but this may differ depending on the laboratory. To diagnose low testosterone you may need more than one early-morning (7 – 10 AM) blood test and, sometimes, other tests of the pituitary gland.

How is low testosterone treated?

Testosterone replacement therapy can improve sexual interest, erectile function, mood and energy, body hair growth, bone density, and muscle mass. There are several methods of testosterone replacement:

- Injections
- Patches
- Gel
- Tablets (stick to the gums)

The best method will depend on the cause of the problem, the patient's preference and tolerance, and cost.

There are risks with long-term use of any testosterone delivery method for men over 50.

Possible Risks of Testosterone Treatment

- A high red blood cell count
- Occasional stopping of breathing during sleep (sleep apnea)
- An increase in prostate enlargement or prostate cancer growth
- Fluid build-up (rarely)

African American men and men over 40 years of age who have close relatives with prostate cancer, and all men over 50 years of age should be carefully monitored for prostate cancer during testosterone treatment. Men with breast cancer or known or suspected prostate cancer should not receive testosterone therapy.

What should you do with this information?

If you have symptoms, talk with a specialist. An endocrinologist, an expert in hormones, can help determine the cause. Be open with your doctor about your medical history, all prescription and nonprescription drugs you are now taking, sexual problems, and any major changes in your life.

Resources

"Find an Endocrinologist" (referrals): *www.hormone.org* or call 1-800-467-6663

Patient's Guide to Low Testosterone: *www.hormone.org/pdf/patients_guide_low_testosterone.pdf*

American Foundation for Urologic Disease: *www.reproductive-health.org*

MedlinePlus: *www.nlm.nih.gov/medlineplus*

TESTOSTERONE

EDITORS:
Glenn R. Cunningham, MD
Alvin M. Matsumoto, MD
Ronald Swerdloff, MD
May 2004

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/bilingual* or call 1-800-HORMONE. 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. The development of this fact sheet was supported by an unrestricted educational grant from Unimed Pharmaceuticals, Inc., a Solvay Pharmaceuticals, Inc. Company, and may be reproduced non-commercially by healthcare professionals and health educators to share with patients and students. Translation by MEDI-FLAG Corp. © The Hormone Foundation 2004

La testosterona baja y la salud masculina

¿Qué papel desempeña la testosterona en la salud masculina?

La testosterona es la hormona sexual más importante que tienen los hombres. De ésta dependen las características típicamente masculinas y ayuda a mantener el impulso sexual, la producción de esperma, el vello púbico y corporal, los músculos y los huesos. El cerebro controla la producción de testosterona por medio de los testículos.

La deficiencia de testosterona (condición a la que también se llama hipogonadismo) puede causar una reducción del impulso sexual, disfunción eréctil, insuficiente esperma, o agrandamiento de las glándulas mamarias (pechos). Con el tiempo, la testosterona baja puede producir la pérdida del vello del cuerpo, disminución de masa muscular y fuerza, debilitación de los huesos (osteoporosis), alteraciones del carácter, pérdida de la energía y reducción en el tamaño de los testículos.

¿Qué causa la deficiencia de testosterona?

La testosterona baja puede ser producida por una lesión (por ejemplo, trauma, castración, radiación o quimioterapia), desórdenes hormonales (por ejemplo, tumores o enfermedades en la glándula pituitaria, niveles elevados de prolactina), u otras enfermedades (por ejemplo, VIH/SIDA, enfermedad crónica del higado y los riñones, exceso de grasa en el cuerpo, la diabetes tipo 2 y la obesidad que acompaña a esta condición). Algunos medicamentos y varias condiciones genéticas (por ejemplo, el syndrome de Klinefelter, hemocromatosis, el síndrome de Kallmann, el syndrome de Prader-Willi, y distrofia miotónica) también pueden resultar en una deficiencia de testosterona. Sin embargo, en muchos casos no puede descubrirse la causa.

¿Cómo se diagnostica la deficiencia de testosterona?

Durante un examen físico, su médico le examinará la cantidad y distribución del vello del cuerpo, el tamaño de las glándulas mamarias y el pene, el tamaño y consistencia de los testículos y el escroto, y le hará un análisis del campo visual. Su médico también le hará exámenes de sangre para comprobar si su nivel de testosterona está dentro de los valores normales, los cuales son de 300 a 1,000 ng/dL (nanogramos por decilitro), aunque esta medida puede variar según el laboratorio. Para diagnosticar la deficiencia de testosterona, es posible que sea necesario hacerle más de un análisis de sangre a primera hora de la mañana (entre las 7 y 10 de la mañana) y, a veces, otros análisis de la pituitaria.

¿Cómo se trata la deficiencia de testosterona?

La terapia para restituir la testosterona puede estimular el interés sexual, la función eréctil y el nivel de energía, puede mejorar el carácter, estimular el crecimiento del vello corporal, y aumentar la densidad de los huesos y masa muscular. Hay diversos métodos para restituir la testosterona: inyecciones, parches, gelatinas y una tableta que se adhiere a la encía. El mejor método depende de la causa del problema, la preferencia y tolerancia del paciente, y el costo.

Hay riesgos con el uso prolongado de la testosterona para hombres mayores de 50 años.

Riesgos asociados con el uso de la testosterona

- Elevación de los glóbulos rojos
- Interrupción de la respiración durante el sueño
- Crecimiento de la próstata o de cánceres en la próstata
- Acumulación de fluido (ocurre raramente)

Durante el tratamiento con testosterona, los hombres afroamericanos y los mayores de 40 años que tienen parientes que han sufrido cáncer de la próstata, y todos los hombres de más de 50 años de edad, deben mantenerse bajo estrecha observación. Los hombres que sufren cáncer de las glándulas mamarias o que tienen, o se sospecha que tienen, cáncer de la próstata, no deben recibir terapia para restitución de la testosterona.

¿Qué debe hacer usted con esta información?

Si usted tiene síntomas, hable con un especialista. Un endocrinólogo—que es un experto en hormonas—puede ayudarle a determinar la causa. Hable francamente con su médico respecto a su historial; dígale todos los medicamentos que está tomando, ya sean recetados o no, los problemas sexuales y cualquier otro cambio importante en su vida.

Recursos

Encuentre un endocrinólogo: *http://www.hormone.org* o 1-800-467-6663

Guía para pacientes sobre la testosterona baja (Inglés): *http://www.hormone.org/pdf/patients_guide_low_testosterone.pdf*

Fundación Americana para Enfermedades Urológicas: *http://www.reproductive-health.org*

MedlinePlus: *http://medlineplus.gov/spanish*

EDITORES:
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Alvin M. Matsumoto, MD
Ronald Swerdloff, MD
May 2004

Para más información sobre cómo encontrar un endocrinólogo, obtener publicaciones de la Internet, traducir esta hoja de datos a otros idiomas, o hacer una contribución monetaria a la Fundación de Hormonas, visite a *www.hormone.org/bilingual* o llame al 1-800-HORMONE (1-800-467-6663). La Fundación de Hormonas, la filial de enseñanza pública de la Sociedad de Endocrinología (*www.endo-society.org*), sirve de recurso al público para promover la prevención, tratamiento y cura de condiciones hormonales. La creación de esta página de datos fue apoyada por una donación educacional de Unimed Pharmaceuticals, Inc., una compañia de Solvay Pharmaceuticals, Inc. La página puede ser reproducida para fines no comerciales por los profesionales médicos y educativos que deseen compartirla con sus pacientes y estudiantes. Traducción hecha por MEDI-FLAG Corp.
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ENDO 2005 Abstract Submission Site
Opens November 15, 2004

The ENDO 2005 Abstract Submission site ***www.endo-society.org/scimeetings/index.cfm*** will open Monday, November 15, 2004. Follow the step-by-step instructions to upload and submit your abstract. The entire process, including proofing and approving your abstract for the Program & Abstracts Book, can be completed electronically. Please note that you will be required to create a user name and password in order to begin the submission process. Students and nonmembers will need to secure an active or Emeritus member sponsor for their abstract submissions and will be required to provide the identification number of the sponsoring member.

The deadline for abstract submissions is Monday, January 10, 2005, 11:59 pm Central Time.

For coding information please review the *Coding News Special Feature* included with this month's domestic mailing. This special feature is provided to you by Dr. Richard A. Dickey, Chair of The Endocrine Society's Clinical Affairs Committee. Full text will be available on The Endocrine Society's Web site *www.endo-society.org* during the first week in October.

If you would like to learn more about the Society's reimbursement efforts contact Janet Kreizman, Director of Program and Policy Affairs, at *jkreizman@endo-society.org*

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November 3 – 6, 2004: ISPAD 2004: 30th Annual Meeting of the International Society of Pediatric and Adolescent Diabetes, Raffles City Convention Centre, Singapore. For more information visit *http://www.ispad.org/events.html* or email *ispad2004@mpgroupasia.com*

November 4 – 7, 2004: SSSS 46th Annual Meeting: Sexual Science and Politics: Mutual Interactions, Orlando, Florida. For more information visit *http://www.sexscience.org/*

November 4 – 6, 2004: 3rd EFES Czech-Hungarian-Polish-Romanian-Slovak Regional Postgraduate Course in Endocrinology, Prague, Czech Republic. For more information visit *http://www.euro-endo.org/courses.htm* call 1-42-022-491-9780 or email *mkrse@lf1.cuni.cz*

November 6 – 10, 2004: 26th Endocrinology and Metabology Brazilian Congress, Florianópolis, SC, Brazil. For more information visit *http://www.congressoendocrinologia.com.br* or contact Oceano Eventos by phone 1-55-48-322-1021, fax 1-55-48-222-3985 or email *informacoes@congressoendocrinologia.com.br*

November 7 – 11, 2004: AAPS Annual Meeting, Baltimore, MD. For more information visit *http://www.aaps.org/*

November 7 – 9, 2004: Enhancing the Safety of Parenteral and Enteral Nutrition, Cambridge, MA. For more information call 1-617 667-2651 or visit *http://www.nutritioncare.org/events/harvardschedual04.pdf*

November 10 – 13, 2004: 12th National Conference on Issues in Women's Health Care, St Thomas, Virgin Islands. For more information visit *http://www.symposiamedicus.org/calendar.asp*

November 10 – 13, 2004: Annual Biomedical Research Symposium for Minority Students (ABRCMS), Dallas, TX. For more information visit *http://www.abrcms.org*

November 11 – 14, 2004: American Indian Science and Engineering Society (AISES) 2004 National Conference, Anchorage, AK. For more information visit *http://www.aises.org*

November 11 – 13, 2004: 12th EFES Postgraduate Course in Clinical Endocrinology, Sitges, Spain. For more information visit *http://www.euro-endo.org/courses.htm* call 1-34-93-291-9042, fax 1-34-93-291-9270 or email *swebb@santpau.es*

November 11 – 12, 2004: Association of British Clinical Diabetologists Autumn Meeting 2004, London, United Kingdom. For more information visit *http://www.diabetologists.org.uk*

November 14 – 18, 2004: NAASO 2004 Annual Scientific Meeting, Las Vegas, NV. For more information visit *http://web.diabetes.org/naaso-04/index.asp* or contact Ms. Shirley Ash by email *sash@diabetes.org*

November 14 – 17, 2004: 14th World Congress of the International Society for the Study of Hypertension in Pregnancy, Vienna, Austria. For more information visit *http://www.isshp2004-vienna.at*

November 18 – 20, 2004: 2nd Annual World Congress on the Insulin Resistance Syndrome, Universal City, CA. For more information contact Nava Mekel by phone 1-818-342-1889, fax 1-818-342-1538 or email *insulinresistance@pacbell.net*

November 28 – December 1, 2004: National Osteoporosis Society 10th Conference on Osteoporosis, Harrogate, United Kingdom. For more information visit *http://www.nos.org.uk* or contact Jackie Brown by phone 1-44-017-614-73116 or email *j.brown@nos.org.uk*

DECEMBER

December 1 – 4, 2004: 10th Annual Conference on Care of Women Over 40, Maui, HI. For more information visit *http://www.symposiamedicus.org/calendar.asp*

December 3 – 5, 2004: Endocrinology in Practice, Palm Beach, FL. For more information visit *http://www.endoinpractice.com* or contact Mr. Paul Albright by phone 1-512-301-5032, fax 1-512-301-5039 or email *paul@cmmglobal.com*

December 6, 2004: Deciphering Growth, Paris, France. For more information contact Ms. Jacqueline Mervaillie by phone 1-33-144-96-1010, fax 1-33-144-96-1199 or email *jacqueline.mervaillie@ipsen.fr*

December 9, 2004: The Role of Insulin in the Critically Ill Patient: Basic and Clinical Evidence, Natcher Conference Center, Bethesda, MD. For more information visit *http://www.niddk.nih.gov/fund/other/insulin/index.htm* or contact Mr. Iain Mackenzie by phone 1-301-897-2789 ext. 124, fax 1-301-897-9587 or email *imackenzie@thehillgroup.com* EN

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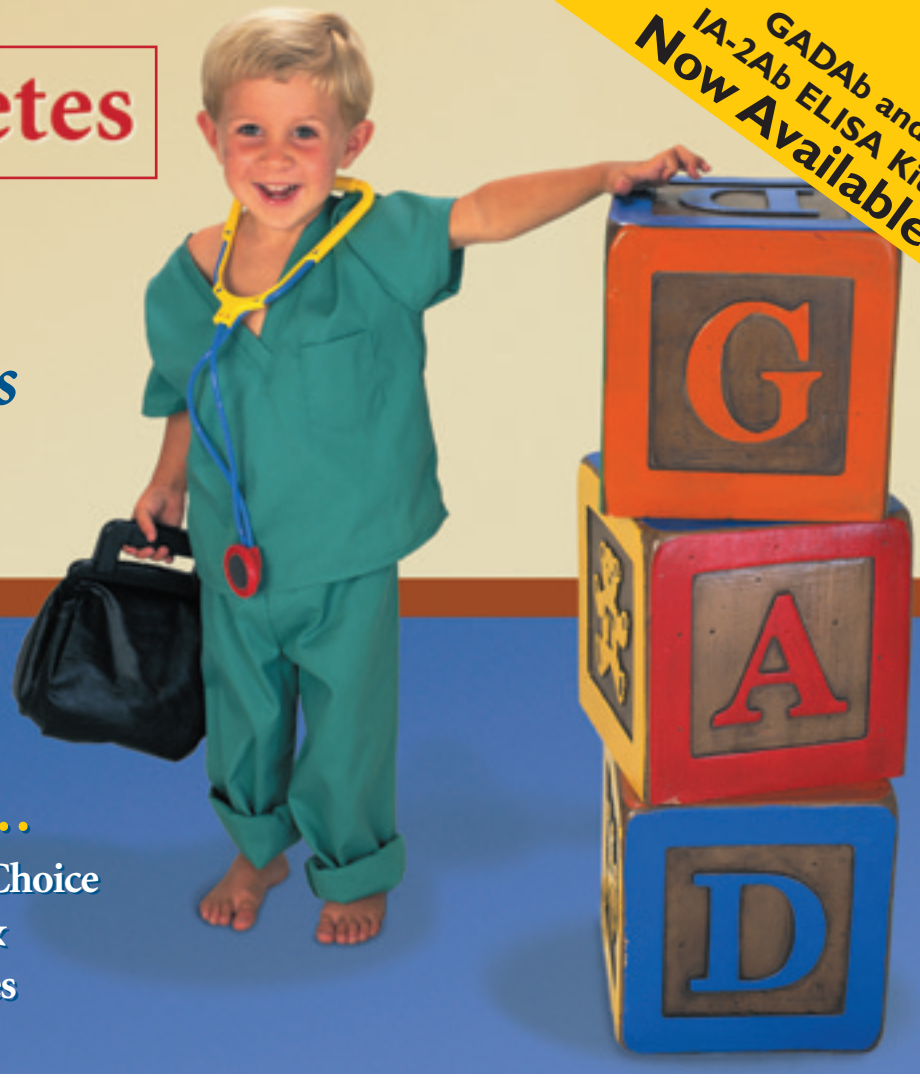

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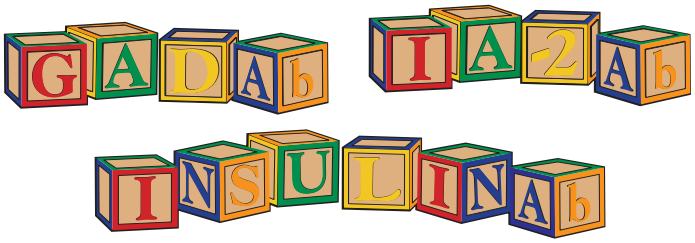

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