

AUGUST 2004 | VOLUME 29 | NUMBER 4

# ENDOCRINE NEWS

NEWS AND INFORMATION FOR THE ENDOCRINE COMMUNITY



## *Viewpoints on* **Polycystic Ovary Syndrome**



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## Reflections On A Rewarding Year

### Dear Colleagues,

It was after the 2003 ENDO in Philadelphia that I sat down to write my first President's Message to the members of The Endocrine Society. I was energized and inspired by the excellent science and the rewarding interactions. I was also a little stunned by the responsibilities of the Presidential year that loomed ahead.



*Chip Ridgway, M.D.*

It's a year later as I now sit down to share my reflections. I couldn't be happier about the fine efforts of the Annual Meeting Steering Committee (AMSC) and its four leaders—Beverly Biller, Stan McKnight, Paul Stewart and Theme Chair Mike Jensen. The theme content of the meeting was extremely well received by the attendees, many of whom were new to The Endocrine Society. To say that ENDO 2004 exceeded my most optimistic expectations is true, and it reflects the quality of our members and the professionalism of The Endocrine Society staff! Additionally, the strong non-theme scientific content of the meeting brought accolades from all quarters. It was very important to me and to the AMSC that the Annual Meeting continue the tradition of featuring theme content that is woven into the context of a rich, diverse medley of scientific programming. I heard many comments from those who appreciated the obesity focus, and even more from attendees who applauded the broad range of exceptional scientific and practice topics that were covered.

Perhaps one of the most rewarding aspects of my role this year was the opportunity to provide leadership to a larger and more diverse Council and governing structure. By virtue of the timing of my election, I was the first President charged with mentoring the new Vice Presidents as they found their way within the fabric of Council and the committee structure. It is widely recognized that these individuals—John Nilson, Carolyn Becker, and Janet Hall—have made an excellent start in integrating themselves and providing insightful representation of the three major Endocrine Society constituencies. Presiding over this “new” Council has brought great reward and some challenges.

One great surprise was learning, first hand, just how much time commitment is required in the role of President to do justice to the Society. I was fortunate that the demands of my “day job” were flexible within the schedule of The Endocrine Society. However, the realization that

the role of President has ballooned to consume approximately 80 to 100 days of commitment per year on the part of the last few Presidents led Council to seriously consider financial compensation for the leadership. This concern is valid for all of the constituencies, but possibly most pressing for our practicing clinicians who have schedules packed with patients.

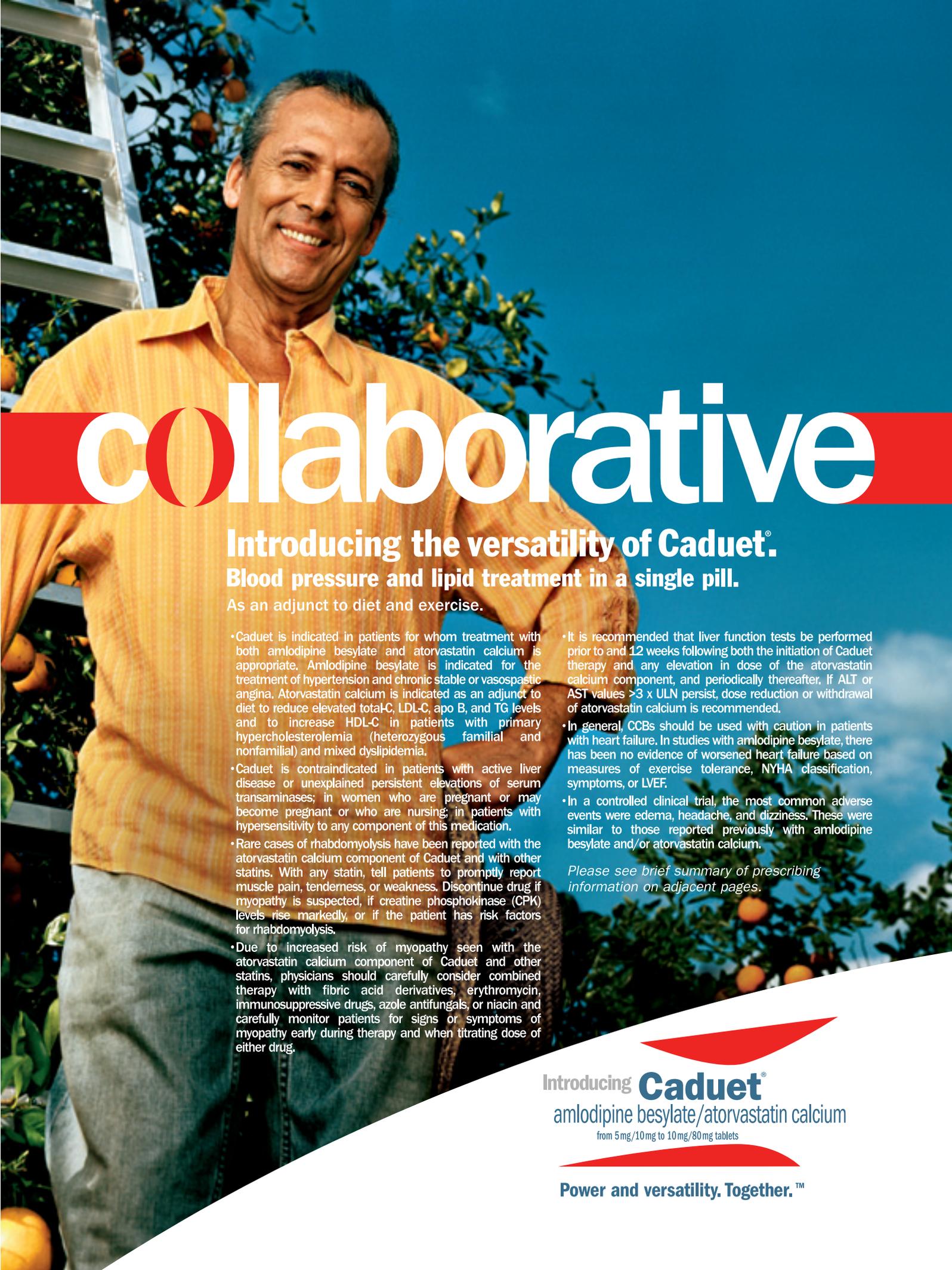
Council grappled with this issue over several months, collected data on practices from similar

**“For myself, as I look back over the past year, I am particularly pleased with the Society's new commitment to advocacy for our members and our mission, particularly at a national level within the context of the NIH Roadmap.”**

societies and ultimately approved annual compensation for the President and the President-elect (irrespective of the constituency of the individual in the office) in the amounts of \$50,000 and \$30,000 respectively. It is understood that individuals elected to office will be free to utilize the compensation for a broad variety of reasons—including administrative assistance in their home locations or to replace lost wages due to Society meeting requirements. The demands to realize the vision we have crafted on behalf of our field will ask much of future Presidents, and we will need them able and willing to meet these demands. My successor Tony Means will be the first President to be provided these funds, and he has elected to redirect the funds back to the Society to speed up the implementation of a new strategic initiative near and dear to his heart.

For myself, as I look back over the past year, I am particularly pleased with the Society's new commitment to advocacy for our members and our mission, particularly at a national level within the context of the NIH Roadmap. We need to have the “grit” to sustain that effort. I loved our efforts to institutionalize outreach to our international colleagues by creating the International Relations Committee. The re-engineering of the Research Affairs Committee (with subcommit-

*Continued on page 28.*



# collaborative

## Introducing the versatility of Caduet®. Blood pressure and lipid treatment in a single pill.

As an adjunct to diet and exercise.

- 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  $>3 \times$  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.

*Please see brief summary of prescribing information on adjacent pages.*

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**Brief Summary:** for full prescribing information, see package insert.

**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 postmenarcheal 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  $\geq 190$  mg/dL, or b. LDL-C remains  $\geq 160$  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 Outpoints 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 <sup>a</sup> or CHD risk equivalents (10-year risk >20%)	<100	$\geq 100$	$\geq 130$ (100-129: drug optional) <sup>b</sup>
2+ Risk Factors (10-year risk $\geq 20\%$ )	<130	$\geq 130$	10-year risk 10%-20%: $\geq 130$ 10-year risk $\geq 10\%$ : $\geq 160$
0-1 Risk Factor <sup>c</sup>	<160	$\geq 160$	$\geq 190$ (160-189: LDL-lowering drug optional)

<sup>a</sup> CHD, coronary heart disease. <sup>b</sup> 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. <sup>c</sup> 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 antidiabetic 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  $\geq 200$  mg/dL, LDL-C  $\geq 130$  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 I/II 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 100 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 (Wallenian degeneration of retinoganglionate 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<sub>max</sub>, 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. **Antipyrene:** Because atorvastatin does not affect the pharmacokinetics of antipyrene, 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%, respectively. 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 alasia 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, sperm 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<sup>2</sup> 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<sup>2</sup>). 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 postmenarcheal 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 ( $\geq 65$  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 ( $\geq 65$  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	1.6
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 (%)		Placebo (%)	
	(N=1730)	(N=1250)	(N=1730)	(N=1250)
Headache	7.3	7.8	7.8	7.8
Fatigue	4.5	2.8	2.8	2.8
Nausea	2.9	1.9	1.9	1.9
Abdominal Pain	1.6	0.3	0.3	0.3
Somnolence	1.4	0.6	0.6	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  $\leq 1\%$  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, hypertension, peripheral ischemia, syncope, tachycardia, tachypnea, dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoaesthesia, neuropathy, peripheral paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia, \*\* dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia, \*\* back pain, hot flashes, 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, hypertension, 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  $\geq 2\%$  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	atorvastatin				
	Placebo N=270	10 mg N=863	20 mg N=36	40 mg N=79	80 mg N=94
<b>BODY AS A WHOLE</b>					
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
<b>DIGESTIVE SYSTEM</b>					
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
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
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  $\geq 2\%$  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, hypoaesthesia, hypoaesthesia.* **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, plebicitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Echinymosis, 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 postmenarcheal 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 overdose 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<sup>2</sup> basis) caused a marked peripheral vasodilation and hypotension. Overdose might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdose of amlodipine is limited. Reports of intentional overdose 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 overdose. 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.

Rx only

Rev.O January 2004

## Introducing Hershel Raff, Ph.D.

### 2004-2007 Secretary-Treasurer

During ENDO 2004, the annual meeting of The Endocrine Society, Margaret Shupnik, Ph.D., completed her term as Secretary-Treasurer for the Society. Her successor, Hershel Raff, Ph.D., assumed the Secretary-Treasurer position at the Annual Business Meeting on Saturday, June 19, 2004. With the guidance of the Strategic Plan, and the abundance of new initiatives aimed at plan implementation, Dr. Raff will oversee several exciting activities as the Society continues to meet the needs of its constituencies.

of Arts from Union before moving to Baltimore, MD where he received his Ph.D. in Environmental Physiology from Johns

recently at the Milwaukee Heart Ball.

Prior to attending graduate school, Dr. Raff spent one year in

**With no increase in subscriptions, dues, and registration rates for Society members in 2005, it seems that Dr. Raff has had a positive start.**

Hopkins University School of Public Health. Dr. Raff pursued his post-doctoral fellowship training in endocrinology, in the lab of Dr. Mary F. Dallman at the University

the business office at St. John's Episcopal Hospital in Brooklyn, NY. Here he learned, "the life of an accountant without Microsoft Excel—can you imagine?" he asks with a laugh. Besides tracking Medicare and Medicaid billing, Dr. Raff gained a strong understanding of proformas (financial budget projections) and government reimbursement for medical costs.

Currently, Dr. Raff is a Professor of Medicine and Physiology at the Medical College of Wisconsin at Milwaukee and the Director of Endocrine Research at St. Luke's Medical Center, also in Milwaukee. His work embodies the Society's multi-constituency nature by working as a basic researcher and doing clinical research with private practice physicians.

Dr. Raff's basic research focuses on the endocrine and metabolic adaptation to low oxygen (hypoxia) at the organismal, cellular and molecular levels. His clinical research focuses on the creation of new methods to diagnose pituitary and adrenal disease with special attention to Cushing's syndrome. Realizing the lack of availability of certain diagnostic tests, Dr. Raff extended his lab to help private practice physicians. His research team made salivary cortisol—used as a screening test for Cushing's syndrome—readily available for use by physicians. In addition, Dr. Raff

*Continued on page 9.*



*Hershel Raff, Ph.D.*

"One of my main priorities as Secretary-Treasurer will be to make sure that all of the Society's voices are heard," Dr. Raff explained. "I am extremely aware of providing programs to meet the needs for collaboration between all three constituencies."

Dr. Raff was first introduced to the field of endocrinology by studying the pineal gland with Dr. Willard Roth as an undergraduate at Union College in Schenectady, New York. He earned a Bachelor

of California at San Francisco.

Throughout his career, Dr. Raff found a way to develop and hone a passion—music. Beginning at age five with the piano and going on to train at Manhattan School of Music and Union College, Dr. Raff has developed into an accomplished musician—not with just one instrument but with several, including the guitar, bass, trumpet, French horn, saxophone and drums. He has played in several venues in the New York area and

# Stem Cell Legislation Introduced in House While Appropriations Committee Reviews 2005 Budget

## Budget Update

The House Appropriations Committee has begun action on the Fiscal Year 2005 budget. On July 8th, the House Labor, Health and Human Services, and Education Appropriations Subcommittee (which has authority over National Institutes of Health (NIH) funding) approved its FY 2005 appropriations bill. The approved measure funded NIH at the same level suggested by the President which was \$28.5 billion (a 2.6 percent increase) or a \$727 million increase over FY 2004.

According to the NIH, an increase of 2.6 percent would require NIH to cut the number of new and competing grants by 640 from last year if the grants were funded at the level of medical inflation. The Endocrine Society, along with a majority of the scientific community, has suggested to Congress that in order to maintain and translate the progress from the

NIH doubling period an appropriation of \$30.6 billion (a 10 percent increase) for FY 2005 is necessary.

## New Stem Cell Legislation Introduced

On June 9 2004, Congressman Gary Ackerman (D-NY) introduced H.R. 4531, The Ronald Reagan Memorial Stem Cell Research Act of 2004. Ackerman's legislation calls for the use of the stem cell research guidelines that the NIH created in August 2000. In addition, the bill provides an initial \$87 million in federal funds for this critical research. The guidelines treat research in an ethical manner, prohibiting human cloning and the creation of embryos solely to destroy them for stem cells. The legislation currently has two co-sponsors, Congressman Gene Green (D-TX) and Carolyn McCarthy (D-NY) and has been referred to the House Committee on Energy and Commerce.

## House Passes Steroid Abuse/Misuse Legislation

On June 3, 2004 the House of Representatives passed HR 3866, the Anabolic Steroid Control Act of 2004 by a vote of 408 to three. As passed the legislation would add several new steroid precursor substances to the list of banned substances and provide increased penalties for any individual who traffics in steroids within 1,000 feet of an athletic facility. Additionally, the legislation includes a requirement that the Department of Health and Human Services and the Department of Justice report to the House and Senate Committees on the Judiciary within two years regarding the need to add additional dangerous substances to the list. The bill now awaits action in the Senate. **EN**

*For more information about the Society's legislative activities, contact Chris Rorick, Manager, Government Relations, at [crorick@endo-society.org](mailto:crorick@endo-society.org)*

## Introducing Hershel Raff, Ph.D.

*Continued from page 8.*

helped drive the use of petrosal sinus sampling for adrenocorticotropic hormone (ACTH)—used to differentiate Cushing's syndrome—into the mainstream.

“My work has allowed me to gain an understanding of the thought processes and needs of the basic and clinical researcher as well as the physician-in-practice,” Dr. Raff notes. “Working at St. Luke's has provided me with a glimpse into the special role and needs of each constituency, which I plan to bring to each Council discussion.”

Not only does his current work embody the multidimensional nature of the Society, but it also

reflects the ENDO 2005 theme of “Pathways to Discovery and Practice” and the National Institutes of Health (NIH) Roadmap. Dr. Raff, along with the Society's leadership, realizes first hand the unique value of each constituency, but also understands the undeniable link between the basic researcher, the clinical researcher and the physician-in-practice.

As Secretary-Treasurer, Dr. Raff plans first to “listen.” His background and experience in both science and business allow him to bring a unique perspective to the table with the ability to look at the organization as a whole. He has served on many of the Society's committees including, the Development Committee, which he chaired, the Publications Committee, Performance and Compensation Steering Committee, Council and the

Finance Committee. With a global perspective in mind, Dr. Raff plans to “encourage programs and activities that maintain the overall efficiency of the Society and help preserve the balance by keeping the organization from over-extending itself.”

With no increase in subscriptions, dues, and registration rates for Society members in 2005, it seems that Dr. Raff has had a positive start. He emphasizes his plan to “help align the finances and budget by keeping costs down and creating programs that relate directly with the Society's mission and culture. This is an exciting time for members from all over the world. We have all the right tools to develop interactions for the three constituencies to grow and work together.” **EN**



# Highlights from ENDO 2004



## ENDO 2004 Quick Facts

**Total Attendance:** ENDO 2004 attracted almost 7,400 total attendees

**Scientific Attendance:** 5,818 scientific attendees were at ENDO 2004

**Diversity:** Attendees were from 70 countries

**Exhibitors:** 441 exhibit booths and 142 companies were represented

**Abstracts Submitted:** More than 2,100 abstracts were submitted

**New Members Joined: 460**

Attendees were also encouraged to get fit by walking the distance at ENDO 2004. Each morning of the annual meeting, Wake Up Walks were led by professional tour guides through the historic neighborhoods of New Orleans. Complimentary pedometers were provided to attendees by Takeda Pharmaceuticals North America to help attendees keep track of all of the miles walked to the meeting and surrounding sights.

### ENDO 2004 5K Walk/Run

Held in New Orleans' scenic Audubon Park, the race benefited The Hormone Foundation and was supported by GlaxoSmith-Kline. Over 50 enthusiastic members participated. Congratulations to the top finishers!

#### Men's Results

1. Steven King: 17:17
2. Rich Auchus: 19:15
3. Donald McDonnell: 19:20

#### Women's Results

1. Carolyn Humphrey: 24:12
2. Innling Eng: 25:02
3. Betty Eng: 25:15

### CMES Programs at ENDO 2004

In addition to the excellent scientific programming at ENDO 2004,

23 CME ancillary programs were presented—attracting an average attendance of 250 to 450 per program. These programs allowed attendees to gain additional CME credits while enhancing their overall ENDO experience.

CME enduring materials are being developed from several of the programs presented at the meeting. The format of these activities will either be a CD-ROM or a monograph.

Due to the continued efforts of the Special Programs Committee and the CME Advisory Committee as well as the support of corporate educational grants, the Society will continue to develop and deliver educational programs to the endocrine community.

For more information on CMES programs, contact Lisa Johnson at [ljohnson@endo-society.org](mailto:ljohnson@endo-society.org)

### History Exhibit Intrigued Attendees with Discovery, Honors and Artifacts

The ENDO 2004 History Exhibit featured information about the discovery and controversy surrounding parathyroid hormone (PTH), notable women in endocrinology and an array of historical endocrine texts and Society memorabilia. A



### Hundreds Get Fit-for-Life at ENDO 2004

As part of the ENDO 2004 focus on Obesity, attendees were able to take part in special Fit-for-Life activities that encouraged fitness. Almost 800 attendees visited the on-site check-up center comprised of various medical evaluations. The Fit-for-Life Health Check center, supported by Abbott Diagnostics, was manned by AREUFIT Health Services, Inc., of Malvern, PA.

timeline of PTH discovery was presented along with details of the controversy surrounding the discovery rights to PTH that ensued between Dr. Adolph Hanson and Dr. James B. Collip.

This was the first history exhibit to focus on the important role that the lesser known parathyroid gland plays in a person's daily life and metabolism. Constructive comments were offered from both researchers mentioned in the exhibit and attendees in the bone and mineral metabolism field.

The exhibit also honored notable women of The Endocrine Society including past and present Society officers, Koch Award winners, Nobel Laureate Dr. Rosalyn Yalow, and current members of the National Academy of Sciences and the Institute of Medicine.

Contributions to next year's history exhibit and the Society's ongoing efforts to expand the history archives are currently being sought. The Society is requesting donations of old texts, outdated endocrine-related medical equipment, personal documents and photographs. If you have an item of interest please contact Dr. Adolph Friedman at 1-301-941-0200 or [afriedman@endosociety.org](mailto:afriedman@endosociety.org)

### Corporate Liaison Board Hosts Successful Forum

Over 600 ENDO participants attended the Annual Corporate Liaison Board (CLB) Forum titled, "Addressing the Obesity Epidemic: From Bench to Bedside to Market." The exciting event was moderated by CLB Co-Chair, Dr. Andres Negro-Vilar. The CLB Forum featured viewpoints from industry, government and regulatory sectors which discussed each sector's approach towards addressing the issue of obesity. Each year, the CLB produces this insightful event to encourage and maintain dialogue between the Society and industry professionals within the

pharmaceutical and biotechnological industry. The evening's program featured presentations from the following expert speakers:

- *Framing the Challenges in Obesity Research & Our Progress Toward Solution*  
Dr. Robert Brackett, Center for Food Safety and Applied Nutrition, FDA
- *Impact of Obesity and Metabolic Syndrome on Human Health*  
Dr. Allen Spiegel, National Institutes of Diabetes & Digestive and Kidney Disease, National Institutes of Health
- *Emerging Concepts & Compounds in Obesity Therapeutics*  
Dr. Jose Caro, Lilly Research Laboratories, Eli Lilly & Company

Attendees received an overview of the CLB and its activities, along with an opportunity to network and converse with fellow peers and colleagues and interact with the evening's experts, one-on-one basis. For more information on the 2004 CLB Forum, please visit [www.endo-society.org/industry/clubforum.cfm](http://www.endo-society.org/industry/clubforum.cfm)

### ENDO 2004 Audio Tapes and CD's Now Available

Audio tapes and CD's from ENDO 2004 are now available online at The Endocrine Society Tape Store. Order a professionally recorded tape or CD of an individual session or purchase the complete audio or CD collection of 190 sessions presented at ENDO 2004. New this year are select sessions on MP3. For a complete listing of available products and ordering details, visit [www.CMEunlimited.org/es](http://www.CMEunlimited.org/es) or call 800-776-5454.

### Access ENDO 2004 Abstracts Online

All abstracts presented at ENDO 2004 are available for online viewing at the Abstracts2View™ site. You can search by session, author, title, keyword or category for all 2004 submitted abstracts. Access abstracts at [www.endo-society.org/scimeetings/endo2004/index.cfm](http://www.endo-society.org/scimeetings/endo2004/index.cfm) This product is supported by an unrestricted educational grant from Eli Lilly & Company.

### ENDO 2004 Web Casts

Did you miss a session at ENDO 2004? View the session on our Web site! A number of the sessions, symposia and plenary, were taped for an ENDO Web cast. The Web cast will be available by mid August, so keep checking our Web site for the launch of this program.

### Attendee Survey Winners

A special thank you goes out to all attendees who participated in the ENDO 2004 Meeting Attendee survey! The winners of a free registration to ENDO 2005 are:

**Ian Bird, PhD**

*University of Wisconsin*

**Wenyu Huang, MD,**

*Northwestern University*

**Min Li, MD/PhD**

*Tulane University*

**James Powell, MD**

*Hattiesburg Clinic*

**Susan Steiner, CRNP**

*Renal-Endo Associates EN*

### Make Plans Now for ENDO 2005 in San Diego!



Don't miss out on the excitement—mark your calendar now for The Endocrine Society's 87th Annual Meeting in San Diego, California, June 4-7 (Saturday-Tuesday), 2005.

# U

## Viewpoints on Polycystic Ovary Syndrome



*The following is a tri-point perspective from a basic scientist, a clinical researcher and a clinical practitioner on the following questions\*\*:*



Walter L. Miller, M.D.



John E. Nestler, M.D.



Walter Futterweit,  
M.D., F.A.C.P.,  
F.A.C.E.

- Should all women with PCOS receive metformin?
- Should metformin be continued throughout pregnancy?

*\*\* the perspective written by Walter Miller, M.D., focuses on what PCOS is (and isn't), and what its causes might be.*

## Basic Scientist

Walter L Miller, M.D., Department of Pediatrics,  
University of California, San Francisco

**Polycystic ovary syndrome (PCOS)—a group of hyperandrogenic disorders in search of mechanism-based therapies**

### SUMMARY

*The severe, apparently autosomal, dominant form of PCOS characterized by hyperandrogenemia and insulin resistance may be caused by gain-of-function mutations in a signal cascade leading to a serine kinase.*

While it is widely agreed that the polycystic ovary syndrome (PCOS) is the most common endocrine disorder, affecting up to 10 percent of reproductive age women, there is little agreement concerning the underlying molecular mechanisms of PCOS, hence precise mechanistically-based therapies are not available. Most investigators, including myself, agree that PCOS encompasses a group of several distinct disorders characterized by oligoanovulation and hyperandrogenism, generally associated with hyperandrogenemia, increased gonadotropins and ovarian cysts. Insulin resistance, metabolic syndrome X and obesity are common<sup>1</sup>. The past 20 years of clinical investigation have produced new insights. For many years, investigators debated whether the primary defect was in the hypothalamic-pituitary-gonadal (HPG) axis or in the ovary itself. Most now agree that hyperandrogenemia is primary and, in most patients, is of combined ovarian and adrenal origin.

Three lines of evidence support a primary disorder of androgen biosynthesis in PCOS. First, both ovarian and adrenal 19-carbon

(C19) steroid precursors of androgens are elevated in PCOS<sup>2</sup>. Suppression of either the adrenal with dexamethasone or the HPG axis with gonadotrophin-releasing hormone (GnRH) agonist fails to suppress the hyperandrogenemia, but the combination of both agents does; also, adrenal C19 steroids are increased in the presence of normal ACTH levels, suggesting a primary disorder of adrenal/gonadal steroidogenesis. Second, the hyperandrogenism is genetic. Multiple studies show familial clustering with probable autosomal dominant inheritance, with a male phenotype of elevated dehydroepiandrosterone sulfate (DHEAS) levels<sup>3</sup>.

Furthermore, studies with cultured theca cells show that the abnormal steroidogenesis persists

**Many PCOS women also have a heritable form of insulin resistance and secondary hyperinsulinemia, often associated with the metabolic syndrome, but independent of obesity.**

with multiple cell passages, indicating a primary disorder<sup>4</sup>. Third, the prenatal exposure of female fetuses with congenital adrenal hyperplasia to excess androgens or the exposure of fetal rhesus monkeys to exogenous androgens recapitulates many of the features of the disordered HPG axis seen in PCOS<sup>5</sup>.

Many PCOS women also have a heritable form of insulin resistance and secondary hyperinsulinemia, often associated with the metabolic syndrome, but independent of obesity. Insulin binding is normal,

but there is decreased downstream signal transduction<sup>6</sup>. A key breakthrough is the recognition that the hyperandrogenism and insulin resistance are early events, possibly originating in fetal life and manifesting clinically before the onset of puberty<sup>7</sup>. Thus, PCOS is a genetic developmental disorder in both sexes and not an acquired disease confined to adult women. A central challenge for scientists studying PCOS is to identify pathways that can account for both the hyperandrogenism and the insulin resistance through a molecular mechanism that will yield dominant inheritance. As PCOS is probably a group of disorders, no mechanism will explain all forms, however, the “serine phosphorylation hypothesis”<sup>8</sup>, which explains dominant adrenal/ovarian hyper-

androgenemia and insulin resistance, appears to be gaining support.

A single steroidogenic enzyme, P450c17, catalyzes both 17 $\alpha$ -hydroxylation (needed for cortisol synthesis) and 17,20 lyase activity (needed for C19 steroid synthesis) on its single active site, yet these two activities are differentially regulated, with cortisol secretion remaining fairly constant while adrenal C19 steroids rise 100-fold during adrenarche. Serine phosphorylation of P450c17 selectively

increases the 17, 20 lyase activity without affecting the hydrolyase activity<sup>8</sup>. Studies in the 1980's demonstrated that serine phosphorylation of the  $\beta$ -chain of the insulin receptor (IR $\beta$ ) inhibited the receptor's tyrosine phosphorylation and consequent downstream signal transduction. Zhang et al, suggested that a gain-of-function mutation in a single cAMP-in-

lidinedione drugs, only troglitazone, but not rosiglitazone or pioglitazone inhibits P450c17 at clinically-relevant concentrations<sup>10</sup>. Thus the mechanism by which metformin lowers circulating androgens is probably by lowering insulin; whether or not this drug is effective in patients with IR $\beta$  serine hyperphosphorylation remains unknown.

### Although metformin's actions are mediated by activation of AMP-activated protein kinase11, its precise molecular mechanism of action remains unclear.

ducible serine kinase might hyperphosphorylate both P450c17, causing hyperandrogenism, and IR $\beta$ , causing insulin resistance, providing a single autosomal dominant mechanism for the two cardinal features of PCOS<sup>8</sup>. Dunaif et al revealed serine phosphorylation of IR $\beta$  in multiple cell types from PCOS patients<sup>6</sup> and other studies have implicated a potential cascade of factors leading to the kinase, several of which might also cause a similar autosomal dominant phenotype<sup>9</sup>. Other mechanisms, notably the allosteric action of cytochrome b5, also foster the 17, 20 lyase activity of P450c17, but appear to be unconnected with insulin action. Thus, studies of the biochemistry, cell biology and genetics of androgen-producing tissues have begun to suggest the broad outlines of at least one mechanism likely to account for some, but not all forms of PCOS.

It has been suggested that various insulin-sensitizing drugs specifically inhibit the 17, 20 lyase activity of P450c17. While it is true that such drugs lower circulating concentrations of C19 steroids, metformin has no action on P450c17, and among the thiazolidinedione drugs, only troglitazone, but not rosiglitazone or pioglitazone inhibits P450c17 at clinically-relevant concentrations<sup>10</sup>.

Although metformin's actions are mediated by activation of AMP-activated protein kinase<sup>11</sup>, its precise molecular mechanism of action remains unclear. Therefore, it is premature to suggest that there is a scientific basis for clinical decisions about who should be treated with metformin, or whether it should be used during pregnancy. Metformin is a low-potency compound used in high doses. Data in rats show much higher concentrations in liver than in plasma; concentrations in the human fetus and placenta are not known. Metformin is listed as a Category B drug, meaning safety in pregnancy has not been established, but significant teratogenicity is not apparent, either. As it is clear that infants of hyperglycemic mothers have a higher incidence of congenital malformations, the desirability of glycemic control during pregnancy is clear. Thus conservative physicians generally manage pregnant type 2 diabetic patients with insulin rather than with oral agents; the same logic would seem to apply to pregnant women with PCOS. **EN**

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## Clinical Researcher

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The polycystic ovary syndrome (PCOS) affects five to 10 percent of reproductive age women, and is the most common cause of female infertility due to anovulation in the United States. Arguably, the most significant advance in our understanding of the syndrome during the past decade has been the appreciation that women with PCOS suffer from insulin resistance that is independent of obesity. Hence, lean women with PCOS possess a form of insulin resistance that is intrinsic to the syndrome and poorly understood. At the same time obese women with PCOS are markedly insulin resistant because they suffer from the combination of the insulin resistance intrinsic to PCOS and the insulin resistance of excess adiposity.

Treatment of PCOS can be divided into acute therapy to enhance fertility, and chronic therapy to address traditional therapeutic targets such as signs of androgen excess, oligomenorrhea and risk for endometrial hyperplasia/cancer. Because women with PCOS are at markedly increased risk for developing type 2 diabetes and, although more controversial, cardiovascular disease, novel targets for chronic therapy should likely also include prevention of diabetes and cardiovascular disease.

Space limitations and the nature of the two questions posed dictate that this review focus primarily on acute therapy for fertility. However, it should be noted that a cogent argument can be advanced for the use of Metformin as chronic therapy in most women with

PCOS. The basis for such a proposal includes, but is not limited to, the fact that 1) insulin resistance is highly prevalent among women with PCOS, 2) women with PCOS compose one of the groups at highest risk for the development of type 2 diabetes, and 3) the use of insulin sensitizing drugs in non-diabetic women at high risk for diabetes has been shown to decrease conversion to type 2 diabetes<sup>1,2</sup>. Insulin resistance may also play a role in the putative increased risk for cardiovascular disease in PCOS<sup>3-6</sup>, and emerging evidence suggests that insulin-sensitizing drugs may ameliorate this risk<sup>7-9</sup>. Insulin-sensitizing drug therapy should be coupled with lifestyle modification, a nonpharmacologic intervention for improving insulin sensitivity. The use of insulin-sensi-

effect of insulin resistance on ovulation, improving insulin sensitivity in PCOS, either through diet and exercise or administration of an insulin-sensitizing drug, has been reported to increase the frequency of ovulation, improve menstrual cyclicity, enhance the success rate of induction of ovulation with clomiphene citrate, and decrease ovarian androgen production<sup>11</sup>. These salutary effects have been observed in both lean and obese women with PCOS, and suggested guidelines for the use of Metformin to enhance pregnancy have been published<sup>12</sup>.

The insulin-sensitizing drug studied most widely in PCOS is Metformin. The efficacy of Metformin in enhancing fertility in PCOS was recently confirmed by a meta-analysis published by the

### **Treatment of PCOS can be divided into acute therapy to enhance fertility, and chronic therapy to address traditional therapeutic targets such as signs of androgen excess, oligomenorrhea and risk for endometrial hyperplasia/cancer.**

tizing drugs as chronic therapy for PCOS is a controversial and critical issue, and the reader is referred to an editorial that addresses the issue in greater detail<sup>10</sup>.

Insulin resistance and its compensatory hyperinsulinemia may hinder ovulation in PCOS through a variety of mechanisms, including but not limited to increased intraovarian androgens, altered gonadotropin secretory dynamics, or direct actions of insulin on the ovary. Consonant with the adverse

Cochrane Library<sup>13</sup>. This critical analysis of the world literature assessed 13 randomized trials involving 543 women with PCOS, and reported that Metformin significantly increased the frequency of ovulation compared to placebo (odds ratio of 3.9; CI 2.3-6.7). When Metformin was used in conjunction with clomiphene citrate it was superior to clomiphene alone in inducing an ovulation (odds ratio of 4.4; CI 2.4-8.2) and yielding a clinical pregnancy (odd ratio

of 4.4; CI 2.0-9.9). In fact, the number needed to treat (NNT) for Metformin monotherapy was only 4.4, and for Metformin plus clomiphene 3.0. In comparison to drugs administered for the treatment of hypertension, hyperlipi-

demia, or osteoporosis where the NNT is commonly between 15-25, the efficacy of Metformin appears dramatic. Moreover, these studies likely underestimated the true benefit of Metformin, since most were short-term (3-6 months), and Metformin treatment may require several months to achieve a full effect.

### **Although Metformin is a class B drug that appears to be safe during pregnancy, are there untoward effects of Metformin for ovulation induction that have not been identified?**

It is noteworthy that the majority of studies of Metformin in PCOS did not screen women for the presence of insulin resistance or use insulin resistance as an inclusion criterion. Moreover, studies involving lean women with PCOS have reported equally positive findings. No clear predictors of a positive response to Metformin have been identified, and even lean women with seemingly normal indices of insulin action respond to treatment with Metformin.

Given the demonstrated efficacy of Metformin in PCOS, the lack of confirmed predictors of positive response, and the limited risk of toxicity, a strong case can be made for an empiric trial of Metformin in all women with PCOS pursuing pregnancy.

Nonetheless, several questions remain. Is Metformin monotherapy superior to clomiphene citrate in the induction of ovulation? Should Metformin be added to clomiphene immediately, or only after demonstrated failure of

clomiphene alone? Although Metformin is a class B drug that appears to be safe during pregnancy, are there untoward effects of Metformin for ovulation induction that have not been identified?

An National Institutes of Health (NIH) trial, currently being conducted by the Reproductive Medicine Network (RMN) will soon answer many of these queries. The goal of the trial is to determine the optimal pharmacologic therapy for initial induction of ovulation in women with PCOS who are seeking pregnancy. Eligible women are randomized to one of three treatment arms (Metformin alone, clomiphene alone, or Metformin plus clomiphene), and the primary outcome measure is a live birth. Approximately 450 women have entered the trial thus far, and a total of 678 women will be studied. More information on the trial and participating sites can be found at <http://rmn.dcri.duke.edu>

### **No randomized controlled trial has been conducted to test the hypothesis that administration of Metformin during pregnancy decreases EPL in PCOS.**

Whether women with PCOS should remain on Metformin during pregnancy is a more difficult and controversial question. PCOS is associated with a 30 to 40 percent rate of early pregnancy loss (EPL), defined as miscarriage of a clinically recognized pregnancy during the first trimester. In most

cases no apparent cause can be identified but, in addition to defects in the developing embryo, adverse alterations in endometrial function may play a role.

In this regard, hyperinsulinemia has been identified as an independent risk factor for EPL. Studies in PCOS suggest that hyperinsulinemia suppresses endometrial expression of glycodeilin<sup>14</sup>, a protein whose circulating concentration may reflect endometrial function. Conversely, administration of Metformin to women with PCOS has been shown to increase circulating glycodeilin<sup>15</sup>. Glycodeilin is secreted by the endometrium, may inhibit the endometrial immune response to the embryo, and likely plays a critical role during implantation and in the maintenance of pregnancy. Moreover, both EPL and retarded endometrial development are associated with decreased secretion of glycodeilin from secretory endometrium.

Two retrospective studies have reported that continued administration of Metformin during pregnancy markedly decreased EPL in PCOS<sup>16,17</sup>. However, neither study identified the requisite duration of administration of Metformin, nor did they exclude the possibility that simply conceiving on Metformin might have conferred full benefit.

No randomized controlled trial has been conducted to test the hypothesis that administration of Metformin during pregnancy decreases EPL in PCOS.

With these caveats in mind, it may be reasonable to maintain a pregnant woman with PCOS on Metformin through the first



trimester if there is a history of prior miscarriage, and then discontinuing the Metformin since the period of greatest risk will have passed. What should we do with a woman with PCOS who is pregnant for the first time? My personal approach is to discuss with the woman our understanding of the literature to date, and to let her wishes help guide the decision process.

In summary, Metformin is an important and effective treatment of infertility in PCOS. Since predictors of response have not been identified, the response rate is high (as reflected by a low NNT), and risks are low, an empiric trial of Metformin in all women with PCOS seeking pregnancy seems reasonable. Guidelines for the use of Metformin for this purpose have been suggested. However, many questions regarding the treatment of infertility with Metformin remain outstanding, and we all await the findings of large-scale trials such as the RMN trial currently underway. **EN**

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## Clinical Practitioner

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The effectiveness of the biguanide metformin in the treatment of the polycystic ovary syndrome (PCOS) has been amply confirmed. It is generally preferred to insulin-sensitizing agents such as the available thiozolidinediones pioglitazone and rosiglitazone which may induce further weight gain, edema and rare hepatic laboratory abnormalities. Improved insulin resistance in PCOS is frequently associated with improved menstrual cyclicity and some anti-androgenic effect such as the reduction of hirsutism, acne and reduction of acanthosis nigricans secondary to the hyperinsulinism. In association with a modified carbohydrate diet, caloric restriction and exercise, a number of patients demonstrate weight reduction, which is associated with improved parameters of hyperinsulinism, increased sex-hormone binding globulin (SHBG), reduction of steroidogenic dysregulation and possible coincident decrease in luteinizing hormone (LH) secretion reducing ovarian androgen production.<sup>1</sup> The latter findings are more evident in women with higher insulin levels, lower androgen levels, and less severe menstrual abnormalities.<sup>2</sup>

The question of whom to treat with metformin is an important consideration in women with PCOS. Should all women with PCOS be treated with metformin? The fact that at least one in three show evidence of ovulatory cycles with the drug makes it, in my view and those of some other clinical researchers, the initial drug of choice in any woman with PCOS, particularly those desiring fertility.

In my experience with 600 PCOS patients treated with metformin, as the insulin level declines with or without significant weight loss, approximately 50 percent have improved menstrual cyclicity, often occurring as early as two months after initiation of therapy, and of these desiring fertility, nearly 30 to 40 percent become pregnant. The response rate is often better in nonobese patients with PCOS who are treated with metformin.<sup>3</sup> Parenthetically, the use of metformin in those with evidence of insulin resistance (IR) and/or

with PCOS. Although, a recent landmark study by Diamanti-Kandarakis et al of 59 women with PCOS of varying body weights, demonstrated a lack of correlation of the HOMA and QUICKI methodologies and insulin sensitivity as determined by the euglycemic-hyperinsulinemic clamp.<sup>6</sup> This study underscores a probable underestimation of published studies of IR in women with PCOS, who have a unique form of IR, and where mild IR may be present with borderline normal fasting glucose and insulin levels..

### **The question of whom to treat with metformin is an important consideration in women with PCOS. Should all women with PCOS be treated with metformin?**

impaired glucose tolerance (IGT) is clear, but what about those with normal glucose and insulin levels? In view of demonstrable changes in IR in lean and obese adolescents with PCOS aged 12 to 18 years<sup>4</sup> as well as older subjects<sup>5</sup> it is reasonable to start metformin in conjunction with caloric restriction and exercise in obese and nonobese patients at the time of diagnosis of PCOS.

Recently, data has shown the failure of the usual means of assessing IR with methodologies that only measure fasting glucose and insulin levels including homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) in assessing insulin sensitivity.<sup>6</sup> These had not been specifically assessed in women

Perhaps other hormonal factors, as well as ethnicity, may influence the degree of IR, and yield conflicting reports of the incidence of IR in women with PCOS. Thus the use of metformin in most women with PCOS appears to be a desirable treatment option.

Contraindications to the use of metformin include women with impairment of renal function, namely a serum creatinine level of 1.4 mg percent or greater, significant hepatic dysfunction, alcohol binge drinkers, and inability to tolerate some of the side effects of the drug. Initial side effects are common including, nausea, bloating, flatulence, occasional vomiting and frequent bowel movements. Most are significantly reduced after the first four to eight weeks, but bowel

frequency often remains an intermittently annoying symptom. The patient is advised to take the drugs with food, and to plan a snack between breakfast and lunch, in the afternoon and before bedtime, to avoid symptoms of postprandial hypoglycemia (tiredness, lack of concentration, possible tremulousness, sleepiness, hunger and irritability). The latter is unlikely to be related to metformin and usually due to reactive hyperinsulinism particularly after a carbohydrate-rich meal. It is standard practice to stop the drug at the time of an iodine-contrast study, intercurrent infection, and prior to major surgery. Most patients are able to tolerate the drug when given in slow increments (500 mg with a meal per 10 to 14 day intervals) to a desired level of at least 1500 mg/day in divided doses, with a view to increasing this to 2000-2500 mg daily as necessary. The use of supplementing these patients with folic acid and vitamin B12 is also recommended due to a reduction in their intestinal absorption with metformin.

Improvement of mental status and energy is noted in most patients treated with the drug. The frequent sense of well-being and a reduction of depression encourage many to improve their lifestyle and thus reduce potential cardiovascular risks inherent in PCOS. Parenthetically, combined systematic weight loss and exercise may be more effective than metformin alone in women with PCOS and IR. The addition of nonandrogenic oral contraceptive formulations in association with antiandrogens are used in conjunction with metformin in those seeking relief from common symptoms of persistent acne, hirsutism and alopecia noted in this syndrome.<sup>7</sup> These drugs are effective in buffering the effects of some of the factors involved in the pathophysiology of PCOS.

Recent data confirm earlier studies suggesting the use of metformin

in PCOS women with recurrent miscarriages.<sup>8</sup> Jakubowicz et al conducted a retrospective study of 36 pregnancies in women with PCOS with a prior history of miscarriage and compared the results obtained with the use of metformin to those in a control group of 12 pregnant women.<sup>9</sup> Four of the 36 PCOS treated women miscarried (11.1 percent) as compared with seven of 12 pregnancies in the control group (58.3 percent). The hypothesis that hyperinsulinemic IR contributes to the high frequency of first-trimester pregnancy loss appears tenable, and administration of metformin during the first trimester of pregnancy to these women may be a reasonable option. The experience in my practice supports this conclusion in six women with PCOS and a history of one or two early miscarriages, with four achieving full-term pregnancies with no maternal complications or birth defects following use of metformin during the entire course of the pregnancy. In PCOS patients with no prior history of early pregnancy loss, I routinely discontinue metformin once pregnancy is established.

In conclusion, my view as a clinical practitioner, is that most women with PCOS should be on metformin as initial monotherapy for infertility and if unsuccessful have concomitant treatment with clomiphene citrate. Women with symptoms related to the pilosebaceous unit should be treated conjointly with antiandrogens (usually spironolactone, and sometimes flutamide) and oral contraceptives. What I call, "triple therapy," in association with lifestyle modifications, is the preferred treatment for PCOS patients with skin manifestations and/or menstrual dysfunction. Long-term use for PCOS patients, awaits longitudinal or cross-sectional studies demonstrating a reduced incidence of cardiovascular disease and diabetes mellitus in this heterogeneous entity. **EN**

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## Society's International Program, A Huge Success!

The International Endocrine Scholars Program (IESP) was established by The Endocrine Society in 2003 to facilitate the career development of young endocrinologists from around the globe. Coordinated by the International Relations Committee along with Dr. Richard Santen and Terry Jacobson, Director of Membership & Professional Affairs, the goal of the IESP is to identify talented people and offer them an exceptional training experience that will positively impact their career in endocrinology.

Committees consisting of the country's current endocrine society president and four senior endocrinologists select the candidates for this unique program after a thorough evaluation process. Ideal prospects are young post-doctoral endocrinologists who demonstrate outstanding promise and exude strong leadership skills in their home countries. The candidates must be willing to receive training in another country under the guidance of an Endocrine Society member and are asked to indicate a preferred laboratory to conduct their research.

The pilot phase of the IESP took off in 2003 and was a tremendous success. Six scholars were chosen from Brazil and went through the review and placement process without a hitch. Led by Dr. Valeria Guimaraes, President of The Brazilian Endocrine Society, the majority of the fellows have successfully begun their training.

Highly anticipated by both mentors and scholars, the 2004 IESP achieved a remarkable attendance. The international outreach expanded to include three scholars from both Brazil and Finland, six from Poland and two each from Hungary and the Czech Republic. In addition, over 50 interviews



*During ENDO 2004, several of the scholars and mentors gathered for dinner. Staggered from left to right: Adam Kretowski, Agnieszka Siejka, Risto Lapatto, Luciani de Carvalho, Dr. Richard Santen (IESP Program Coordinator), Anna Gruszka and Taneli Raivio*

were conducted between the 16 candidates and their potential Society mentor during ENDO 2004, the Society's annual meeting. The majority of scholars were offered positions in the laboratories of their choice and offers from other laboratories are still pending. **EN**

*For more information about the International Endocrine Scholars Program (IESP), contact Terry*

*Jacobson, Membership Director, by phone 1-301-941-0211 or by email [tjacobson@endo-society.org](mailto:tjacobson@endo-society.org)*

### Congratulations and Good Luck to the 2004 Scholars!

#### Brazil

Gustavo Barra, Melissa Premaor, Luciani de Carvalho

#### Czech Republic

Sona Stanicka, Katerina Zajickova

#### Finland

Risto Lapatto, Taneli Raivio, Virpi Tervonen-Ylitalo

#### Hungary

Attila Patocs, Emma Varga

#### Poland

Marek Demissie, Anna Gruszka, Daria Handkiewicz Junak, Adam Kretowski, Agnieszka Siejka, Malgorzata Wiench **EN**

### Thanks to:

The Presidents and Selection Committee Chairs of the Participating Endocrine Societies:

#### Brazil

Valeria Cunha Guimaraes

#### Czech Republic

Vojtech Hainer  
Josef Marek

#### Finland

Olli Janne  
Reijo Vihko

#### Hungary

Ida Gerendai

#### Poland

Stefan Zgliczynski

### And to The Endocrine Society Mentors:

Carolyn Becker  
William Crowley, Jr.  
John Funder  
Valeria Cunha Guimaraes  
Janet Hall  
Pamela Mellon  
Marcella Motta  
Richard Santen  
Hironobu Sasano  
Evan Simpson **EN**

## An Eventful Evening for Women in Endocrinology!

The Women in Endocrinology Annual Dinner meeting was held on Wednesday, June 16, 2004, in conjunction with ENDO 2004, in New Orleans, Louisiana. During the dinner, WE President Carole Mendelson, Ph.D. acknowledged the female Society members who have been elected to office and have received prestigious awards from the Society during the current year. Endocrine Society Past-President, Chip Ridgway, and 2004-2005 President, Anthony Means, Ph.D., thanked WE for its efforts in providing them with suggestions of outstanding candidates for awards and for elected positions in leadership.

The keynote speaker for the evening was Dr. Kathie Olsen, Associate Director for Science, Office of Science and Technology Policy who presented a lecture entitled, "From a Science Degree to the White House..." Dr. Olsen advises the President and others within the Executive Office regarding the implementation of scientific and educational policy in the sciences.

Also during the dinner, Rebecca Sokol, M.D. presented Jo Anne Brasel, M.D., Chief, Division of Pediatric Endocrinology in the Department of Pediatrics, Harbor-UCLA Medical Center, with the Women In Endocrinology Mentor Award. The award is supported by a grant from Pfizer. Dr. Brasel is an outstanding academic pediatric endocrinologist and teacher who has made major contributions to the mentorship and career advancement of women and men in the field of endocrinology.

### Finally we announced new leadership:

- Dr. Synthia Mellon, WE President
- Andrea Gore, M.D, WE Secretary-Treasurer,

- Ursula Kaiser, M.D., Chair of the Awards Committee
- Sally Radovick, M.D. Chair of the Nominating Committee,
- Carolyn Smith, Ph.D. Chair of the Communications Committee. **EN**

## Hormone Foundation Director Receives Award from FDA

Congratulations to Hormone Foundation Director Molly H. Wade for recently receiving the Commissioner's Special Citation from the Food and Drug Administration (FDA). The award was presented to

Ms. Wade on May 7th at the FDA Honor Awards Ceremony in Gaithersburg, Maryland. She received the award in honor of her outstanding performance on the "Menopause and Hormones Information Campaign," which resulted in the launch of a national public awareness outreach campaign by the FDA. **EN**



Molly H. Wade,  
Director, Hormone  
Foundation

### IN MEMORIAM

#### Judson J. Van Wyk

Kenan Professor of Pediatrics and Biology Emeritus  
University of North Carolina, Chapel Hill  
June 10, 1921 – June 22, 2004

It is with great sadness that we announce the passing of Judson J. Van Wyk, M.D.

Dr. Van Wyk was a member of The Endocrine Society for 50 years and was the 1989 recipient of the Society's highest award, the Fred Conrad Koch award. During his membership he served on the Society's Council as well as Awards and Publications committees. Dr. Van Wyk is known worldwide for work that led to advances in the diagnosis and treatment of growth abnormalities in children and adults, specifically research in peptide growth factor. He was most proud of training over 57 physician/scientists in the field of endocrinology, "the training program has been the number one joy of my professional life," he once said.

He is survived by his wife of 60 years, Persis, and three children, Judson, Jr., Peter and Judith. **EN**

## DONATE YOUR JOURNALS NOW!

This month we are highlighting three journals that are needed to pursue our online Legacy Data Project. We are seeking donations for the following journals:

- *Molecular Endocrinology*, Volume 1, 1987
- *Molecular Endocrinology*, Volume 2, 1988
- *Molecular Endocrinology*, Volume 4, 1990 (Jan., June, and Dec.)

If you have and are willing to donate the requested issues or volumes, please contact Adrienne Weber, Journals Publication Coordinator, at 1-301-941-0238 or [aweber@endo-society.org](mailto: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](http://www.endo-society.org/journals/legacy.pdf).



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(levothyroxine sodium, USP)

# LEVOXYL® (levothyroxine sodium tablets, USP)

Brief Summary (for full prescribing information see package insert). For Oral Administration

**CONTRAINDICATIONS**  
Levothyroxine is contraindicated in patients with untreated subclinical (suppressed serum TSH level with normal T<sub>4</sub> and T<sub>3</sub> levels) or overt thyrotoxicosis of any etiology and in patients with acute myocardial infarction. Levothyroxine is contraindicated in patients with uncorrected adrenal insufficiency since thyroid hormones may precipitate an adrenal crisis by increasing the metabolic clearance of glucocorticoids (see **PRECAUTIONS**). LEVOXYL® is contraindicated in patients with hypersensitivity to any of the inactive ingredients in LEVOXYL® tablets (see **DESCRIPTION**, **Inactive Ingredients**).

**WARNINGS**  
**Warning:** Thyroid hormones, including LEVOXYL®, either alone or with other therapeutic agents, should not be used for the treatment of obesity or weight loss. In euthyroid patients, doses within the range of daily hormonal requirements are ineffective for weight reduction. Larger doses may produce serious or even life threatening manifestations of toxicity, particularly when given in association with sympathomimetic amines such as those used for their anorectic effects.

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 thyrotoxicosis.

**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 not receiving adequate calcium or vitamin D. Therefore, it is recommended that patients receiving levothyroxine sodium be given the minimum dose necessary to achieve the desired clinical and biochemical responses.

**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. In patients without cardiac disease (see **WARNINGS**, **PRECAUTIONS**, **Geriatric Use**, and **DOSE 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. Over-treatment with levothyroxine sodium may have adverse cardiovascular effects such as an increase in heart rate, cardiac 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 thyroid disease of this type. In patients with nontoxic diffuse goiter, prevention of 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**, **Autism spectrum polyendocrine syndrome**) for additional deficiency.

**Autism spectrum polyendocrine 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, aortic septal defect, and ventricular septal defect), being the most common association.

**Information for Patients**

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 if 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. 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**).
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 doses of levothyroxine are sufficient to correct 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 any of the following symptoms occur: 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, itching or skin rash, or any other unusual medical effect.
8. Notify your physician if you become pregnant while taking LEVOXYL®. It is likely that your dose of LEVOXYL® will need to be increased during pregnancy.
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**  
**Serum TSH**  
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<sub>4</sub>.

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 appropriate replacement dose of LEVOXYL® may be evidence of inadequate absorption, poor compliance, drug interactions, or decreased T<sub>4</sub> 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 and is recommended as follows: 4-6 week 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 annually in patients receiving LEVOXYL® (see **WARNINGS**, **PRECAUTIONS**, and **DOSE 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- and free- T<sub>4</sub>. During the first three years of life, the serum total- or free- T<sub>4</sub> 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 an *in utero* hypothyroidism. Failure of the serum T<sub>4</sub> 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- and free- T<sub>4</sub> 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 compliance is suspected or abnormal values are observed. It is recommended that TSH and T<sub>4</sub> levels, and a physical examination, if indicated, be performed 2 weeks after any change in LEVOXYL® drug. Routine clinical examination, including assessment of mental and physical growth and development, and compliance monitoring, should be performed at regular intervals (see **PRECAUTIONS**, **Pediatric Use** and **DOSE AND ADMINISTRATION**).

**Secondary (pituitary) and tertiary (hypothalamic) hypothyroidism**  
Adequacy of therapy should be assessed by measuring serum free-T<sub>4</sub> 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-thyroid axis interactions is contained in Table 2.

The list of drug-thyroid axis interactions in Table 2 may not be comprehensive due to the introduction of new drugs that interact with the thyroid 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.

Drugs that alter thyroid hormone secretion	
<b>Drugs that may decrease thyroid hormone secretion, which may result in hypothyroidism</b>	
Amiodolone Amiodolone iodide (including iodine-containing contrast agents) Lithium Methazolamide 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 radioactive iodine or surgery) are among those individuals who are particularly susceptible to iodine-induced hypothyroidism. Amiodolone, amiodolone iodide, and amiodolone are slow acting, producing more prolonged hypothyroidism than parenterally administered iodinated contrast agents. Amiodolone iodide and amiodolone may minimally decrease T <sub>4</sub> and T <sub>3</sub> levels and increase TSH, although all values remain within normal limits in most patients.
<b>Drugs that may increase thyroid hormone secretion, which may result in hyperthyroidism</b>	
Amiodolone iodide (including iodine-containing contrast agents) Radioiodine 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. Amiodolone may induce hyperthyroidism by causing thyrotoxicosis.
<b>Drugs that may decrease T<sub>4</sub> absorption, which may result in hypothyroidism</b>	
Antacids - Aluminum and 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 ferrous-thyroxine complex. Administer levothyroxine at least 4 hours apart from these agents.
<b>Drugs that may alter T<sub>4</sub> and T<sub>3</sub> serum transport – but FT<sub>4</sub> concentration remains normal; and, therefore, the patient remains euthyroid</b>	
<b>Drugs that may increase serum TBC concentration</b> <b>Drugs that may decrease serum TBC concentration</b>	
Clofibrate Ethinone-containing oral contraceptives Estrogens (oral) - Ethinone - 5-Fluorouracil Mifentane Tamoxifen	Androgens / Anabolic Steroids Aromatase Inhibitors Glucocorticoids Slow Release Nicotinic Acid
<b>Drugs that may cause protein-binding site displacement</b>	
Furosemide (> 80 mg IV) Heparin Hydantoin Non Steroidal Anti-inflammatory Drugs - Fenamates - Phenytoin - Propylthiouracil Salicylates (> 2 g/day)	Administration of these agents with levothyroxine results in an initial transient increase in FT <sub>4</sub> . Continued administration results in a decrease in serum T <sub>4</sub> and normal FT <sub>4</sub> and TSH concentrations and, therefore, patients are clinically euthyroid. Salicylates inhibit binding of T <sub>4</sub> and T <sub>3</sub> to TBG and thyroxine. An initial increase in serum FT <sub>4</sub> is followed by return of FT <sub>4</sub> to normal levels with sustained therapeutic serum salicylate concentrations, although total-T <sub>4</sub> levels may decrease by as much as 30%.
<b>Drugs that may alter T<sub>4</sub> and T<sub>3</sub> metabolism</b>	
<b>Drugs that may increase hepatic metabolism, which may result in hypothyroidism</b>	
Carbamazepine Cytarabine Phenobarbital Rifampin	Stimulation of hepatic microsomal drug-metabolizing enzyme activity may cause increased hepatic degradation of levothyroxine, resulting in decreased levothyroxine responses. Phenytoin and carbamazepine reduce serum protein binding of levothyroxine, and total- and free-T <sub>4</sub> may be reduced by 20% to 40% but most patients have normal serum TSH levels and are clinically euthyroid.
<b>Drugs that may decrease T<sub>4</sub> 5'-deiodinase activity</b>	
Amiodolone 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 <sub>4</sub> to T <sub>3</sub> , leading to decreased T <sub>3</sub> levels. However, serum T <sub>4</sub> levels are usually normal but may occasionally be slightly increased. In patients treated with large doses of propranolol (> 160 mg/day), T <sub>4</sub> and T <sub>3</sub> 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 <sub>4</sub> concentrations by 30% with minimal change in serum T <sub>3</sub> levels. However, long-term glucocorticoid therapy may result in slightly decreased T <sub>4</sub> and T <sub>3</sub> levels due to the decreased TBG production (see above).
<b>Miscellaneous</b>	
Anticoagulants (oral) - Coumatin 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., Meprobamate) - Selective Serotonin Reuptake Inhibitors (SSRIs; e.g., Sertraline)	Concurrent use of tricyclic 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. Simultaneous administration of sertraline in patients stabilized on levothyroxine may result in increased levothyroxine requirements.
Antidiabetic Agents - Biguanides - Meglitinides - Sulfonylureas - Thiazolidinediones - 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 Glucosides	Serum digoxin glycoside levels may be reduced in hyperthyroidism or when the hypothyroid patient is converted to the euthyroid state. Therapeutic effect of digoxin glycosides may be reduced.
Oxytocins - Interferon-α - Interleukin-2	Therapy with interferon-α has been associated with the development of antibody microsome antibodies in 20% of patients and some have transient hypothyroidism, hyperthyroidism, or both. Patients who have antibody microsome before treatment are at higher risk for thyroid dysfunction during treatment. Interleukin-2 has been associated with transient painful thyroiditis in 20% of patients. Interleukin-2 has not been reported to cause thyroid dysfunction.

Ketamine	Concurrent use may produce marked hypertension and tachycardia; cautious administration to patients receiving thyroid hormone therapy is recommended.
Methoxyanthine 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 <sup>131</sup> I, <sup>125</sup> I, and <sup>123</sup> I.
Sympathomimetics	Concurrent use may increase the effects of sympathomimetic or thyroid hormones. Thyroid hormones may increase the risk of coronary insufficiency when sympathomimetic agents are administered to patients with coronary artery disease.
Chloral Hydrate Diazepam Ethinone Lorazepam Meclozamine 6-Mercaptopurine Nitrofurantoin Paracetamol Perphenazine Resorcinol (excessive topical use) Thiazide Diuretics	These agents have been associated with thyroid hormone and/or TSH level alterations by various mechanisms.

**Oral Anticoagulant Therapy** – 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 digoxin glycoside levels may be decreased when a hypothyroid patient becomes euthyroid, necessitating an increase in the dose of digitalis glycosides (see **Table 2**).

**Drug-Drug Interactions** – Consumption of certain foods may affect levothyroxine absorption therapy necessitating adjustments in dosing. Soybean flour (infant formula), cotton seed meal, walnuts, and dietary fiber may bind and decrease the absorption of levothyroxine sodium (see **Table 2**).

**Drug-Laboratory Test Interactions** – Changes in TBG concentration must be considered when interpreting T<sub>4</sub> and T<sub>3</sub> values, which necessitates measurement and evaluation of unbound (free) hormone and/or determination of the free T<sub>4</sub> index (FT<sub>4</sub>). Pregnancy, infectious hepatitis, estrogens, estrogen-containing oral contraceptives, and acute intermittent porphyria increase TBG concentrations. Decreases in TBG concentrations are observed in nephrosis, severe hypothyroidism, severe liver disease, acromegaly, and after androgen or corticosteroid therapy (see also **Table 2**). Familial hypoproteinemia or hypo-thyroxine binding globulinemia 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<sub>4</sub> 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. Levothyroxine should be discontinued during pregnancy and hyperthyroidism 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<sub>4</sub> levels may decrease and serum TSH levels increase to values above 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 athyroidic fetuses being approximately one-third maternal levels. Transfer of thyroid hormones from the mother to the fetus, however, may not be adequate to prevent fetal goiter 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 **DOSE 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 hypothyroidism is established, and levothyroxine therapy should be reinitiated. If the T<sub>4</sub> 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. If the results of the levothyroxine withdrawal test are inconclusive, careful follow-up and subsequent testing will be necessary.

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.

**Equivalent 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 mental 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 **DOSE AND ADMINISTRATION**).

**ADVERSE REACTIONS**  
Adverse reactions associated with levothyroxine therapy are primarily those of hyperthyroidism due to excessive replacement. They include the following:

**General:** fatigue, nervousness, 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, hives, antralgia, serum sickness and wheezing. Hypersensitivity to levothyroxine itself is not known to occur.

**MANUFACTURER**  
JONES PHARMA INCORPORATED  
(a wholly owned subsidiary of King Pharmaceuticals, Inc.)  
St. Louis, MO 63146

Prescribing Information as of August 2003.

\*The thyroid shape is a registered trademark.

Table 2: Drug – Thyroid Axis Interactions

Drug or Drug Class	Effect
<b>Drugs that may reduce TSH secretion – the reduction is not sustained; therefore, hypothyroidism does not occur</b>	
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).



**Reference:** 1. Price-Check PC® January 2004.  
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# Hormone Abuse/Misuse: Altering the Tale

**How The Endocrine Society & The Hormone Foundation are Working to Educate the Public & Congress**

**D**r. Linn Goldberg maintains a file of consumer product advertisements that use the phrase “on steroids,” such as the 3M Corporation’s advertisement for its self-sticking easel pad “Think of it as a Post-it® Note on steroids”.

“Do a Google search and you will get an endless list of products that are touted as being ‘on steroids.’ In effect, you learn that bigger means better,” he says.

“On steroids’ has entered our vernacular as something that is good,” observes Dr. Goldberg, a member of The Hormone Foundation’s Hormone Abuse Program Advisory Council.

The positive perception of steroids largely stems from their association with the winning and record setting ways of high-profile Olympic and professional athletes, among whom steroid use is

believed to be common, he notes.

However, despite the trend of buzz phrases and star athletes, anabolic-androgenic steroids and other performance-enhancing substances present a variety of serious health risks to their users, especially adolescents, according to a report in progress, by Dr. Goldberg and fellow Endocrine Society and Hormone Foundation members, written in conjunction with the American Medical Association’s Council on Scientific Affairs.

The report which will soon be published in a major medical journal, lays the scientific groundwork for an ongoing, collaborative effort by The Endocrine Society and The Hormone Foundation to educate the public—most notably teens—about hormone abuse and its dangers.

“Young developing bodies are likely more sensitive to the adverse health effects of steroids, some of which can be irreversible such as the stunting of height in males and voice and body/facial hair changes in females,” says Dr. Goldberg.

In addition to writing a definitive report on hormone abuse

**BY: NICHOLAS MULCAHY**

among teens, The Endocrine Society and The Hormone Foundation have successfully spearheaded the legislative effort to pass federal laws to add “precursors” to anabolic steroids such as androstenedione and boldione to the substances list regulated under the Controlled Substances Act, which would thus ban their over-the-counter sales.

In fall of 2002, both The Endocrine Society and The Hormone Foundation worked with the United States Anti-Doping Agency (USADA) to co-found The Coalition for Anabolic Steroid Precursor and Ephedra Regulation (CASPER). This advocacy group, comprised of the nation's leading medical, public health and sport organizations, is focused on supporting efforts to regulate products containing steroid precursors and products containing ephedra.

On Thursday, June 3, 2004, these efforts resulted in the passage of the Anabolic Steroid Control Act (ASCA) in the United States House of Representatives. The law was passed by the House in an overwhelming victory of 408 to three. The bill now awaits action in the U.S. Senate. The ASCA is co-sponsored by Senator Joseph Biden (D-DE) in the Senate and Congressmen John Sweeney (R-NY) and Tom Osborne (R-NE) in the House of Representatives. The bill includes funding for the Department of Health and Human Services (HHS) to carry out science-based education programs in elementary and secondary schools to highlight the harmful effects of anabolic steroids.

On the issue of steroid abuse, "The Endocrine Society has a unique voice to offer everyone from patients to national legislators in Congress. There is no organization quite as strong in both the clinical and basic science issues of hormones. So we should be leaders," says Dr. Dan Spratt, Chair of the Government Relations Committee, for The Endocrine Society and member of The Hormone Foundations, Hormone Abuse Advisory Council.

Part of that clinical and basic science expertise relates to the question of the precursors of anabolic steroids, often referred to as "supplements."

Defenders of the "supplements," including the supplement industry, which produces them, say they are not as powerful as anabolic steroids and are sufficiently regulated under the Dietary Supplement Health and Education Act (DSHEA) law. Dr. Goldberg begs to differ about both the effects of steroid precursors such as androstenediol, boldione and dehydroepiandrosterone and their regulations.

"With these supplements, we are not talking about food additives such as proteins, minerals, vitamins and carbohydrates. These supplements are metabolically active, impact the metabolic milieu and have powerful effects. They must be held up to the standards of

products sold as dietary supplements containing andro unless they were able to prove their safety.

Unable to prove otherwise, the companies were banned from selling those products by the Food and Drug Administration's (FDA), on April 12, 2004.

### **The Rise Among Our Youth**

Use of hormone-based dietary supplements has been growing among teens.

"These substances do enhance athletic prowess. Plus, the media and athlete-role models play a large role [in creating their appeal]," says Dr. Goldberg.

Performance-enhancing anabolic steroids are the only drugs that

**These supplements are metabolically active, impact the metabolic milieu and have powerful effects.**

**They must be held up to the standards of drugs—namely, be proven to be safe and effective.**

drugs—namely, be proven to be safe and effective," he says.

By allowing steroid precursors to be regulated under the DSHEA, the federal government has made the "buyer beware," says Dr. Goldberg, because DSHEA does not require manufacturers to prove safety and efficacy.

Realizing the growing usage among teens and the lack of protection from the government the Society's Government Relations Committee identified hormone abuse as a legislative priority in 2004 and took several steps to help prevent abuse through legislative and regulatory advocacy. As a result, in early March, the Department of Health & Human Services (HHS) launched a proactive "crackdown" on products containing androstenedione (andro). Companies were asked to cease distribution of prod-

are increasing in use among American teens. The use of most other illegal drugs has leveled off or declined, according to the new report.

"More and more, users are young women and non-athletes," says Dr. Lisa Fish, Chair of the Foundation's, Hormone Abuse Program. Anabolic steroids and their precursors may be even more damaging to young women because some of the effects among females, such as deepening of the voice, growth of facial and body hair and enlarged genitalia, can be permanent.

Dr. Fish notes that hormones are not only used to enhance athletic performance. Increasingly, among both young men and women, they are used to change physical appearance due to altered perceptions of body image.

After seeing growing numbers of patients in her clinic with hormone-related medical problems, Dr. Fish brought hormone abuse to the top of The Hormone Foundation's agenda and formed the Hormone Abuse Program Advisory Council Committee in 2001.

In November 2002, The Hormone Foundation convened a meeting of a diverse group of experts to address adolescent hormone abuse and discuss comprehensive solutions to the problem. Participants included the National Institute on Drug Abuse, the National Youth Anti-Drug Media Campaign of the Office of National Drug Control Policy and Blue Cross/Blue Shield Association's Healthy Competition Program. The meeting was funded by the U.S. Anti-Doping Agency, the watchdog agency that monitors Olympic athlete's use of steroids and other substances.

After this meeting, The Endocrine Society and The Hormone Foundation began their initiative to get hormone abuse and misuse legislation written and passed. Part of the proposed legislation would direct the U.S. Sentencing Commission to review federal sentencing guidelines for crimes involving anabolic steroids such as selling them without a prescription and consider strengthening them.

Despite being controlled substances, anabolic-androgenic steroids are available on the Internet without a prescription and are often illegally imported and manufactured, according to The Hormone Foundation. Gyms and sports training centers are believed to be a major point of purchase for many users.

"I have seen patients who are taking either steroids or steroid precursors and say that they don't know about the harmful effects of these substances. Often their coaches or trainers tell them it's a

protein powder and that they should take it. In some cases, this may be true [that it is a protein powder]—but in other cases they are unaware of the other ingredients and the many harmful side effects," says Dr. Fish.

Improved legislation would cut down on the problem of illegal steroid use, she says, and reduce the availability of these products to teens.

The effects of anabolic steroids include acute acne, balding undesirable body changes such as the development of breasts (gynecomastia) and shrinking testicles in men and, as previously mentioned, masculinization in women. Use may increase the risk of heart attacks and strokes by elevating blood pressure and cholesterol levels. Oral steroids have been linked to liver disease and evidence exists for increased risk of prostate, liver and kidney cancer. There is also evidence that abuse of steroids can increase aggressive behavior in males, also known as "Roid Rage."

Despite the body of analysis and evidence about the effects of steroids and their precursors, the

**Oral steroids have been linked to liver disease and evidence exists for increased risk of prostate, liver and kidney cancer. There is also evidence that abuse of steroids can increase aggressive behavior in males, also known as "Roid Rage."**

scientific data is not abundant, explains Dr. Fish. "Steroids are hard to study for a variety of reasons, including the fact that people often use them in methods such as stacking and cycling. You could never get such a study approved by a review board," she says. Stacking refers to taking more than one compound at once and cycling is an on-again, off-again pattern of use. "The studies of steroids that we do have are often at some small

fraction of the amounts that athletes and other people actually use. So our conclusions about effects are probably conservative," she adds.

The prevalence of hormone abuse among teens has been assessed by a number of national studies, including the National Institutes on Drug Abuse's Monitoring the Future (MTF), which is a confidential assessment of about 50,000 kids in the eighth, tenth and 12th grades. During 2001, lifetime use of anabolic steroids was at a new high of 3.7 percent among 12th graders and since 1993, lifetime use had doubled among tenth graders. Overall, lifetime use of steroids was higher than abuse of PCP, the well-publicized hallucinogenic also known as angel dust.

Most young anabolic steroid users participate in organized athletics, says the new report, and the influence of high-profile athletes has a powerful influence on teen steroid use. The Kaiser Family Foundation recently found that 73 percent of surveyed youth admire and want to emulate famous athletes; 52 percent of the kids

believed that famous athletes commonly use steroids and other banned substances to win.

Educating teens about their health and nutrition options in pursuing their ideal body or top physical condition is the essential to solving this problem of hormone abuse, says Dr. Spratt.

"Teens don't need to resort to drugs to enhance their bodies and athleticism. With good nutrition, weight lifting and training, they

will naturally develop. So, we need to tell them: ‘You can get bigger, stronger and faster without drugs,’” says Dr. Diane Eliot, Principal Investigator, for Athletes Targeting Healthy Exercise & Nutrition (ATHENA), co-author

Avoid Steroids (ATLAS) and Dr. Eliot’s ATHENA are designed to effectively discourage drug use by providing appealing options.

The story of performance-enhancing drugs in American society is ongoing, says Dr. Spratt.

efforts, a quote from Dr. Linn Goldberg will also now appear in the story and the effects of hormone abuse in teens will not be ignored,” he says, “we are the ones who are looking out for the kids—help us, help them.” **EN**

**The story of performance-enhancing drugs in American society is ongoing, says Dr. Spratt. However, the efforts of The Endocrine Society and The Hormone Foundation have begun to alter the tale.**

*For more information about The Hormone Foundation and the Hormone Abuse Program please visit [www.hormone.org](http://www.hormone.org) or contact Paula Correa, Program Manager, The Hormone Foundation at [pcorrea@endo-society.org](mailto:pcorrea@endo-society.org) or by phone 1-301-951-2604.*

of the report, “Hormone Abuse in Young Adults: A Review of Current Knowledge,” and member of The Endocrine Society. Programs such as Dr. Goldberg’s Athletes Training & Learning to

However, the efforts of The Endocrine Society and The Hormone Foundation have begun to alter the tale. “Barry Bonds and Marion Jones will always get the headlines, but thanks to our

*For more information regarding The Endocrine Society’s Legislative activities, please contact Chris Rorick, Manager, Government Relations by email [crorick@endo-society.org](mailto:crorick@endo-society.org) or by phone 1-301-941-0254.*

**A Rewarding Year**

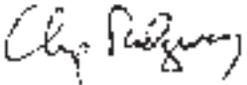
*Continued from page 4.*

tees for both basic and clinical research), the Clinical Affairs Committee (with a new Clinical Guidelines Subcommittee), and the plans for a new Publication Committee structure are all examples of revitalizing and enriching our society. I was also very proud to witness the implementation of the first major public relations campaign in the Society’s history.

But, when all is “said and done,” I have learned from all of you a few key ingredients to success. They can be remembered by the abbreviation E.N.D.O.

- E** Expand and enrich your vision (ie The Strategic Plan)
- N** Be Nimble in your approach to new opportunities (i.e., It’s a very complex world)
- D** Diversify members and programs

**O** Maintain your Optimism—particularly about each other. Thank you for the privilege of serving you. It, indeed, has been a pleasure.

Sincerely,  
  
 Chip Ridgway

**Don’t Miss the Testosterone In Women Audioconference!**

Stay tuned for an upcoming audioconference in mid-September, sponsored by The Endocrine Society. Leading experts will discuss the latest research and findings regarding testosterone use in treating women. Participants will receive CME credit. **EN**

*For more information contact Chanel George by email [cgeorge@endo-society.org](mailto:cgeorge@endo-society.org) or by phone 1-301-941-0223.*

# SPOTLIGHT ON...

## The Nuclear Receptor Signaling Atlas [www.nursa.org](http://www.nursa.org)

Ronald N. Margolis, NIDDK/NIH, Ronald M. Evans, Salk Institute, Bert W. O'Malley, Baylor College of Medicine

The Nuclear Receptor Signaling Atlas (Nursa) was created to develop a comprehensive understanding of the structure, function and role in disease of nuclear hormone receptors.

The 'Atlas' began as an initiative from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in recognition of the emerging roles of Orphan Nuclear Receptors as morphogens, intracellular regulators of metabolism and key intermediates in biochemical pathways. With important cofunding from the National Institute on Aging (NIA) and the National Cancer Institute (NCI), the 'Atlas' has expanded to include all Nuclear Receptors and represents a consortium between the NIH and five institutions (Baylor College of Medicine, Salk Institute, Duke University, University of Pennsylvania, UT Southwestern).

Members of the 'Atlas' work as a team to approach research questions that require complex technologies which are not easily performed in an individual investigator's laboratory, and in an interdisciplinary mode. In order to catalyze progress in understanding the complex interplay between and among the NR superfamily and associated coregulators, the 'Atlas': 1) Executes research strategies designed to rapidly and efficiently elucidate those facets of NR biology most critical to its understanding; 2) Facilitates the generation of hypotheses, design of experiments and communication of results by scientists active in this field. The ultimate goal is to expedite the translation of basic findings into tools that can find clinical applications, particularly in the areas of obesity, type 2 diabetes, osteoporosis, processes of aging and hormone-dependent cancers.

While the 'Atlas' strives to use state-of-the-art strategies to elucidate function, the key to broad dissemination of validated datasets revolves around development of a Web accessible bioinformatics resource in which current and emerging information on NRs will be organized into more accessible and "user-mineable" forms. Through the Nursa Web site [www.Nursa.org](http://www.Nursa.org) the 'Atlas' can reach out to all interested members of the Nuclear Receptor research community to provide highlight new findings, provide access to new reagents, large validated data sets, a library of annotated prior publications in the field, and the *Nursa e-journal*, a venue for commentaries, reviews and technical reports relevant to NR biology. **EN**

For further information access the Web site at [www.Nursa.org](http://www.Nursa.org) or contact the NIDDK Project Scientist for the Nursa, Ron Margolis [margolisr@extra.niddk.nih.gov](mailto:margolisr@extra.niddk.nih.gov)

**T**ranslational research in endocrinology is an essential step in bringing the discoveries emerging from the basic and clinical research laboratory to daily use in the clinical practice setting. This teaching scenario and companion commentary, prepared by the founding Ethics Advisory Committee Chair, Dr. Stan Korenman, explores a range of conflict of interests that may arise during the process of translational research.

The Ethics Advisory Committee invites you to use this case to stimulate discussion on these important professional issues—we encourage you to share these questions (and develop your own answers) with your students, fellows and colleagues!

*Joan M. Lakoski, Ph.D., Chair, Ethics Advisory Committee*

*The conflicts of interest guideline document Ethical Aspects of Conflicts of Interests can be obtained by visiting <http://www.endo-society.org/pubrelations/ethics.cfm>*

## An ethics case from the Ethics Advisory Committee

### **Sleek or slippery? A problem in translational endocrinology**

Jones, a translational researcher in Metabolism in a major academic department of medicine has developed a small molecule that traverses the blood-brain barrier and activates the satiety center. This anorexigenic agent has safely reduced appetite and weight in genetically obese mice as well as normal animals. Jones calls the product “Sleek.” Jones gets Sleek patented by the university and founds a biotech company “ANOREX” to complete the clinical trials and market the product as

effects and allow the establishment of a dosage schedule adequate for a large Phase 3 clinical trial.

ANOREX engages a clinical trials company to conduct the trial on Jones’ design in consultation with the FDA. Sleek is to be given at two doses versus control to 500 extremely obese individuals for 12 weeks in a double blinded randomized manner. DEXA scans, weights, BP, and chemistry are to be done every two weeks. After completion, all participants are to be placed on Sleek in an open label extension for a further six months. Jones plans to enrol 100 participants from his own clinic with the remainder to be

During the course of the 12 week trial, participants lose an average of two pounds weekly, are never hungry, and are delighted. A participant who works at a local newspaper asks Jones for an interview and graciously an upbeat one is given in which the interviewer is cautioned that the trial remains in progress and is not conclusive. The article appears in a prominent place in the newspaper and is quickly taken up by the popular press. During the open label portion of the trial, two participants from the metabolic clinic become ill. They have developed congestive heart failure and, on hospitalization are found to have idiopathic dilational cardiomyopathy. Sleek is stopped in both cases and the serious adverse event (SAE) is reported to the IRB and the FDA. However, the report claims that the drug was “probably” not the cause of the event since there have been no reports of trouble at the other sites and in any case idiopathic cardiomyopathy is not all that uncommon in this population group. One of the two patients improves rapidly, but the other deteriorates to the point where his doctors are considering a heart transplant.

### **During the course of the 12 week trial, participants lose an average of two pounds weekly, are never hungry, and are delighted.**

well as to develop even better agents. Jones became CEO of the company and takes an allocation of 25% of the stock. Obtaining venture capital funding is a snap. Phase 1 and 2 clinical trials on obese patients in Jones’ metabolism clinic go according to plan. They do not demonstrate any adverse

enrolled at 20 cooperating sites. Since Sleek is a new drug Jones arranges a Data and Safety Monitoring Board consisting of the leadership of ANOREX and three other Principal Investigators, each of whom receives consulting fees from ANOREX. All participating IRBs approve the trial expeditiously.

**An ethics case***Continued.***Some questions**

1. You were a member of one of the IRBs considering this project. Given the information provided, would there have been any questions you might have wanted to put to Jones prior to approval of the protocol? Do you think approval of the protocol in this form was justified? Would you have recommended—or insisted on—any changes?
2. You are an IRB chair reading the SAE report. Would you require any further steps to be taken? Should the extension trial be allowed to proceed at your site? Is there any other action you would take?
3. You are a member of the Data and Safety Monitoring Board. What would you do at this point? It is scheduled to meet semi-annually: would you suggest that it meets earlier? Are you comfortable with the generous fee you receive?
4. You are a venture capitalist looking for somewhere to put your money. Would you buy shares in ANOREX?

*(Case prepared by Stan Korenman)*

## Conflicts of Interest—Case Study Analysis

*Stan Korenman, M.D., and the Ethics Advisory Committee of The Endocrine Society*

**W**e design teaching scenarios to be flawed so that the discussion participants can elucidate the dynamics of ethical decision making. Many IRBs would not have approved this proposal as submitted.

The main problems with the protocol are the conflicts of interest of the Principal Investigator (PI), whether or not they are acknowledged on the informed consent form. Jones is conflicted between personal financial gain and research quality and between professional recognition and research quality. Jones has a lot to gain if this trial succeeds and a lot to lose if it does not.

The conflicts of interest lie in the situation—not in anyone's behavior. Nevertheless, humans have an infinite capacity for self-deception. That's why any statement a PI might make about not compromising responsibility toward the research participants could be suspect. In fact, the credibility of the research would be enhanced if Jones were not

involved in the clinical trial. Jones' colleagues, who are getting consulting funds from ANOREX while conducting the trial, also have serious conflicts of interest.

In its recent report on individual conflicts of interest, the American Association of Medical Colleges (AAMC) <http://www.aamc.org/members/coitf/firstreport.pdf> indicated that having equity or receiving funds from a sponsor should rule

**The conflicts of interest lie in the situation—not in anyone's behavior. Nevertheless, humans have an infinite capacity for self-deception.**

out participation in a clinical trial of the sponsor's drug except with monitoring and under very limited circumstances.

Exception has been taken to the drastic nature of the AAMC restrictions, asserting that the pharmaceutical or device company sponsor should have the benefit of

the best expertise in designing a trial. Some feel that being a consultant, where only a minute portion of one's income is derived from the function, does not convey a sufficient conflict of interest to preclude participation. The most recent Department of Health and Human Services guidance on financial conflicts of interest in human research <http://obrp.osophs.dhhs.gov/humansubjects/finreletn/>

*finalguid.pdf* requires that IRBs and institutions develop strong systems to make conflicts of interest transparent, manage significant conflicts of interest and make sure that research participants are provided appropriate information about the interests of the investigators.

*Continued on page 32.*

### Conflicts of Interest—Case Study Analysis

*Continued from page 31.*

The IRBs in this case might have raised questions about the composition of the Data and Safety Monitoring Board (DSMB). DSMBs are recent phenomena, initially derived from the need to monitor studies such as this, in which the investigators are blinded to the treatment. Large therapeutic trials require a DSMB. DSMBs are supposed to protect the research participants. They have the power to stop a trial for efficacy or safety. If the drug provides either a clear benefit or is statistically sure to be ineffective, the trial can be stopped. If an excess of adverse events or a few serious adverse events can be attributed to the therapy, the trial may also be stopped. For example, in endocrinology, DSMBs have acted in the Diabetes Control and Complications Trial (DCCT) and twice in the Women's Health Initiative (WHI).

There are no established standards for DSMBs. These boards should review the protocol at onset, determine what events to analyze regularly, and monitor trials conscientiously. At least some of the members of the boards are expected to be entirely independent of the drug company sponsor and the investigators, that is, to have no conflicts of interest. However, no systematic approach to vetting members of DSMBs exists. In this case, the DSMB was poorly constituted, as all of the DSMB members were financially connected to ANOREX. The DSMB should have met prior to starting the trial to ensure the appropriateness of the protocol

and to develop the tools to evaluate efficacy and safety.

Jones gave an upbeat interview prior to completion of the study. In this study, it would have been hard to remain blinded because it might have been possible to tell which participants were on the drug from their changing appearance. However, the data had not been properly analyzed. It is premature to speak to the public before presenting the data and results to the profession. Thus, presenting at The Endocrine Society meeting would

**Any adverse event that leads to hospitalization or death is considered a serious adverse event (SAE). SAEs can be related or unrelated to the study intervention.**

permit media interviews. However, in this case, Jones could report ethically only that the study was underway and perhaps when data would become available. The PI has a responsibility not to “hype” studies either before the profession—where at least some experts could express skepticism—or to the public, where the media may seek a compelling story more than truth.

Any adverse event that leads to hospitalization or death is considered a serious adverse event (SAE). SAEs can be related or unrelated to the study intervention. SAEs must be reported to the IRB, sponsor and DSMB as soon as possible, i.e., no more than seven days after learning of it. Some IRBs require

earlier notification, e.g. within 48 hours. Jones wrongly did not report to the DSMB. The sponsor must report an SAE forthwith to the FDA. In this case, the opinion of the sponsor and the PI that these were not drug-related would be viewed with skepticism. The study could be closed down forthwith by the DSMB or the IRB, but that might be a shame if indeed the PI was right.

Perhaps the best approach would be for a group of independent cardiologists to evaluate the situation. When I presented a similar scenario to cardiologists, they suggested that cardiomyopathy was

not particularly rare and that a good sample of the remaining participants should have a diagnostic evaluation for subclinical congestive heart failure at sponsor cost. If evidence of heart failure was present in a significant percent of the population, then the study should be stopped and the drug abandoned. If, on the other hand, there was no further evidence of cardiac damage, the study could be continued. The consent form would have to be amended to indicate the possibility of cardiomyopathy, and the participants would have to be reconsented. After all, they have a right to know changes in the risk/benefit equation. **EN**

*For more information about the Ethics Advisory Committee please contact Jeanie Dow, 1-301-951-2612 or email [jdow@endo-society.org](mailto:jdow@endo-society.org)*

# BECOME A MEMBER OF THE ENDOCRINE SOCIETY

The Endocrine Society welcomes you to apply for membership if you have a commitment to endocrine research, practice and/or education. Membership in the Society will provide you with an extraordinary opportunity to network with more than 11,000 scientists and clinicians worldwide who are involved in all disciplines of endocrinology. You will also benefit from the variety of programs and services that the Society offers to foster and enhance your professional development, including:

- Discounted registration rates to the Society's scientific meetings including ENDO and Clinical Endocrinology Update
- Discounted subscription rates to the Society journals: *The Journal of Clinical Endocrinology and Metabolism*, *Endocrinology*, *Molecular Endocrinology*, *Endocrine Reviews*
- Eligibility to sponsor abstracts that are submitted for ENDO
- Preferential consideration for ENDO travel grants and Summer Research Fellowships
- Exclusive access to the online Member Directory with search capabilities to quickly locate colleagues
- Access to career services including a resume database, job opportunities database and the ENDO Job Fair
- Participation in the reorganization of NIH endocrine-related study sections
- Professional representation in Washington, D.C. on legislation and regulations affecting endocrinologists including: funding issues, healthcare reform, medical research and clinical investigation

## MEMBERSHIP INFORMATION REQUEST

To receive an application form, please complete the information below and mail or fax it to 1-301-941-0259. You may also access a membership application online by visiting the Society's web site at <https://www.endo-society.org/membership/become.cfm>

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ATT: MEMBERSHIP DEPARTMENT FAX: 1-301-941-0259

- I am not currently a member, and I would like to receive information regarding membership.  
 My membership has lapsed, and I would like to reinstate it.

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EN

**QUESTIONS?** Contact the Membership Department by email at [membership@endo-society.com](mailto:membership@endo-society.com) by phone at 1-888-363-6762 ext. 207 or 388; or by fax at 1-301-941-0259.

## 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.*

### Thyroid Treatment

On June 24 for the first time, the U.S. Food and Drug Administration (FDA) approved generic levothyroxine sodium for the treatment of hypothyroidism. The American Thyroid Association (ATA), The Endocrine Society (TES), and the American Association of Clinical Endocrinologists (AACE), are concerned that the FDA has moved to approve generic levothyroxine preparations as equivalent to branded preparations without seeking the input of the expert clinicians treating thyroid disease. The current recommendation by the FDA, ATA, TES and AACE, for patients switching between branded levothyroxine products is to have **repeat thyroid function testing** to allow for dose retitration if the therapeutic target is not

being achieved with the new preparation. **EN**

For more information visit [http://www.endo-society.org/publications/fda\\_thyroid.cfm](http://www.endo-society.org/publications/fda_thyroid.cfm)

### Obesity & Erectile Dysfunction

Obese men with erectile dysfunction may be able to improve their sexual function with exercise and weight loss, according to a study in the June 23rd issue of *The Journal of the American Medical Association* (JAMA). Katherine Esposito, M.D., of the Center for Obesity Management, Second University of Naples, Italy, and colleagues found that lifestyle changes, including a reduced calorie diet and increased exercise, improved erectile function in obese men and resulted in about one-third of men

with erectile dysfunction regaining sexual function after treatment. **EN**

For more information visit <http://www.jama-assn.org>

### Polycystic Ovary Syndrome

Women who suffer from polycystic ovary syndrome (PCOS), one of the most common reproductive abnormalities in women, have a higher chance of developing cardiovascular disease (CVD), according to two studies published in the May issue of *The Journal of Clinical Endocrinology & Metabolism* (JCEM). Dr. Zeev Blumenfeld and researchers at Rambam Medical Center confirmed that women who suffer from PCOS should be closely monitored for CVD risk factors. Dr. Saara Taponen and researchers at the University of Oulu concluded that self-reported symptoms of PCOS are a feasible screening tool for CVD among women. **EN**

For more information visit <http://jcem.endojournals.org>

## WHAT CAN A NEW LOOK DO FOR YOU?

Find out at [www.endo-society.org/new\\_design.cfm](http://www.endo-society.org/new_design.cfm)



Log on to preview the new look coming this fall to The Endocrine Society Web site. And catch a glimpse of the enhanced features designed to make finding information more convenient than ever before!

### Highlights of the new Society site include:

- Expanded search options that allow you to quickly access topic-specific information
- Customized member tools such as personalized pages and online membership management



THE HORMONE  
FOUNDATION

www.hormone.org

# HORMONES & YOU

## Patient Information Page

# Anabolic Steroids and Young Adults

### What are anabolic steroids?

Anabolic steroids are drugs that are forms of the hormone testosterone. They are known for their effects on muscle. However, they also have effects like growth of facial hair, deepening of the voice, and changes in behavior.

Anabolic steroids are occasionally prescribed to help AIDS patients gain weight and to treat some types of severe anemia. These drugs are also used illegally by some athletes to improve performance, and by others to get a more muscular appearance.

### Anabolic Steroids

- Anadrol (oxymetholone)
- Dianabol (methandrostenolone)
- Winstrol (stanozolol)
- Deca-Durabolin (nandrolone)
- Oxandrin (Oxandrolone)
- Depot-Testosterone

Anabolic steroids come in various forms including pills, creams, patches, tablet or drops placed under the tongue, and injectables. Veterinary steroids often contain the same components as human steroids, but are not as pure. People are sometimes using these as well.

### Who is using anabolic steroids?

Both adults and children use anabolic steroids. Since 1996, use in children has increased 39% among 8th graders, 67% among 10th graders and 84% among seniors in high school. A recent survey

reported that one of every 16 high school students has used anabolic steroids. Use among girls as well as boys is rising.

Steroid use by college athletes has increased in recent years as well, and some professional athletes continue to use these drugs. Anabolic steroids are also used by young people who are not athletes, but who take them to get a more muscular appearance.

### Why care about anabolic steroids?

Anabolic steroids have dangerous physical and psychological side effects. These may be more dangerous in young adults because they can stop growth, and in females they can cause permanent changes in the voice and genitals.

After stopping these drugs, people can experience severe depression and moodiness.

Injections of anabolic steroids carry the risk for infection with AIDS or hepatitis if needles are shared. Anabolic steroids obtained without a prescription are unreliable and may contain additional substances, and may not even contain the steroids.

### What can you do with this information?

If you are using anabolic steroids without a doctor's prescription, stop. You could be causing irreversible damage to your body. If you have used anabolic steroids and are experiencing health problems, see your doctor. If you are a parent, teacher or coach and know of kids who are using steroids, talk to them about the risks and counsel them on healthy nutrition and exercise alternatives.

### Resources

Find-an-Endocrinologist (physician referral):  
[www.hormone.org](http://www.hormone.org)

ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives):  
[www.obsu.edu/hpsm/athena.html](http://www.obsu.edu/hpsm/athena.html)

ATLAS (Athletes Training and Learning to Avoid Steroids):  
[www.obsu.edu/hpsm/atlas.html](http://www.obsu.edu/hpsm/atlas.html)

MedlinePlus: [www.medlineplus.org/](http://www.medlineplus.org/)

National Institute on Drug Abuse:  
[www.steroidabuse.org/](http://www.steroidabuse.org/)

United States Anti-Doping Agency:  
[www.usantidoping.org/](http://www.usantidoping.org/)

### Side Effects of Anabolic Steroid Use

#### For Girls:

- Facial hair
- Deep voice
- Increased body hair
- Irregular periods
- Increased appetite
- Enlarged clitoris

#### For Boys:

- Breasts
- Shrunken testicles

#### For Both:

- Severe acne
- Baldness
- Liver abnormalities and tumors
- Angry outbursts ("roid rage") or aggressive behavior
- Paranoia
- Hallucinations
- Psychosis
- Blood clots

PLEASE TEAR HERE

ANABOLIC STEROIDS

**EDITORS:**  
Lisa Fish, MD  
Linn Goldberg, MD  
Daniel Spratt, MD  
August 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](http://www.hormone.org/bilingual) or call 1-800-HORMONE. The Hormone Foundation, the public education affiliate of The Endocrine Society ([www.endo-society.org](http://www.endo-society.org)), serves as a resource for the public by promoting the prevention, treatment, and cure of hormone-related conditions. This page may be reproduced non-commercially by health care professionals and health educators to share with patients and students. Translation by MEDI-FLAG Corp. © The Hormone Foundation 2004



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# LAS HORMONAS Y USTED

## Página de información para pacientes

# Los Esteroides Anabólicos y los Jóvenes

LOS ESTEROIDES ANABÓLICOS

### ¿Que son los esteroides anabólicos?

Los esteroides anabólicos son drogas derivadas de la hormona testosterona que son conocidas por el efecto que tienen en los músculos. Sin embargo, también tienen otros efectos, tales como el crecimiento del vello facial, engrosamiento de la voz y cambios de comportamiento.

En ciertas ocasiones, los esteroides anabólicos se recetan para ayudar a los pacientes que tienen el SIDA a aumentar peso y a tratar unas formas de anemia severa. Estas drogas también están siendo usadas ilegalmente por algunos atletas para mejorar su desempeño y por otras personas para adquirir una apariencia física más muscular.

#### Esteroides anabólicos

- Anadrol (Oximetolona)
- Dianabol (Metandrostenoilona)
- Winstrol (Estanozolol)
- Deca-Durabolin (Nandrolona)
- Oxandrin (Oxandrolona)
- Depot-Testosterona

Los esteroides anabólicos vienen en diversas formas, incluso pastillas, cremas, parches, tabletas o gotas colocadas debajo de la lengua, e inyectables. Los esteroides veterinarios muchas veces incluyen los mismos componentes que los esteroides humanos pero no son tan puros. Hay gente que está usando esteroides veterinarios también.

### ¿Quién está usando los esteroides anabólicos?

Los esteroides anabólicos están siendo usados por adultos y jóvenes. Desde 1996, el uso juvenil ha aumentado un 39% entre estudiantes del 8º grado, un 67% entre estudiantes del 10º grado y un 84% entre

estudiantes del último año de secundaria. Una encuesta reciente descubrió que uno de cada 16 estudiantes ha usado esteroides anabólicos. El uso está aumentando tanto entre muchachas como en muchachos.

El uso de esteroides entre los atletas universitarios también ha aumentado en los últimos años, a la vez que algunos atletas profesionales continúan usándolos. Los esteroides anabólicos también son empleados por jóvenes que no son atletas pero que los toman para adquirir una apariencia más muscular.

### ¿Por qué preocuparse por los esteroides anabólicos?

Los esteroides anabólicos tienen efectos secundarios peligrosos, tanto físicos como psicológicos. Estos pueden ser más peligrosos en los jóvenes porque interrumpen el crecimiento, y en las mujeres pueden causar cambios permanentes en la voz y los órganos genitales.

Después de dejar de tomar estas drogas, las personas pueden sufrir una depresión severa.

El uso de las inyecciones de esteroides anabólicos corren el riesgo de contagio con el SIDA o hepatitis si se comparten las agujas. Los esteroides anabólicos que se obtienen sin receta

no son confiables y pueden contener otras sustancias, y es posible que ni siquiera contengan esteroides.

### ¿Qué puede hacer con esta información?

Si usted está usando esteroides anabólicos sin receta médica, pare. Puede estarle causando un mal irreversible a su cuerpo. Si ha usado esteroides anabólicos y está teniendo problemas de salud, visite a su médico. Si usted es un padre, un maestro o entrenador y conoce a jóvenes que están usando esteroides, hábleles sobre los riesgos y aconsejeles sobre alternativas como una nutrición y ejercicio saludable.

### Recursos

Encuentre un endocrinólogo:  
[www.hormone.org](http://www.hormone.org)

ATHENA (Atletas Encaminados hacia Alternativas de Ejercicio Saludable y Nutrición): [www.ohsu.edu/hpsm/athena.html](http://www.ohsu.edu/hpsm/athena.html)

ATLAS (Atletas Entrenándose y Aprendiendo a Evitar Esteroides): [www.ohsu.edu/hpsm/atlas.html](http://www.ohsu.edu/hpsm/atlas.html)

Instituto Nacional Contra el Abuso de Drogas: [www.nida.nih.gov/Infofax/Steroids-Sp.html](http://www.nida.nih.gov/Infofax/Steroids-Sp.html)

MedlinePlus:  
<http://medlineplus.gov/spanish/>

### Efectos secundarios del uso de esteroides anabólicos

#### En las jóvenes:

- Vello facial
- Engrosamiento de la voz
- Aumento de vello en el cuerpo
- Periodos irregulares
- Aumento de apetito
- Crecimiento del clítoris

#### En los jóvenes:

- Senos
- Testículos reducidos

#### En ambos:

- Acne severo
- Calvicie
- Anormalidades y tumores en el hígado
- Explosiones de ira ("rabia de esteroide") o comportamiento agresivo
- Paranoia
- Alucinaciones
- Psicosis
- Coágulos de sangre

#### EDITORES:

Lisa Fish, MD  
Linn Goldberg, MD  
Daniel Spratt, MD

Agosto 2004

Para más información sobre cómo encontrar un endocrinólogo, obtener publicaciones gratis de la Internet, traducir esta página de datos a otros idiomas, o para hacer una contribución a la Fundación de Hormonas, visite a [www.hormone.org/bilingual](http://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](http://www.endo-society.org)), sirve de recurso al público para promover la prevención, tratamiento y cura de condiciones hormonales. Esta página puede ser reproducida para fines no comerciales por los profesionales e instructores médicos que deseen compartirla con sus pacientes y estudiantes. Traducción hecha por MEDI-FLAG Corp. © La Fundación de Hormonas 2004

## Endocrine Society Presents Awards at International Science and Engineering Fair

In May 2004, The Endocrine Society presented awards to seven students at the Intel International Science and Engineering Fair held in Portland, Oregon. The fair hosted over 1,300 high school students from

Ellacott, Linda Lester and Kristine Wiren volunteered to serve as judges and were given the task of choosing the top endocrine-related projects for two cash prizes and 12 honorable mentions. Although the projects varied tremendously, the

from Southridge High School in Beaverton, Oregon. Her project was titled, "The Effects of the Relaxin Hormone on the Laxity of Male and Female Anterior Cruciate Ligament Tissue, in vitro."

Two **Finalist Awards** were presented in the amount of \$500. Eighteen-year old Shamita Chaudhuri received a finalist award for her project titled, "Microarray Analysis Reveals Glucocorticoid-regulated Survival Genes that are Associated with Inhibition of Apoptosis in Breast Epithelial Cells." Ms. Chaudhuri attends Lincoln Park High School in Chicago, Illinois. Seventeen-year old Jason S. Pellegrino also received a Finalist award for his project titled, "Analysis of Metaformin's Effect on Brain Insulin Receptors." Mr. Pellegrino attends Manhasset High School in Manhasset, New York.

**Honorable Mentions** were given to Tristan Gonzalez-Sanz (Florida), John Z. Luo (Rhode Island), Cesar Marquez (Illinois) and Rebecca Vitale (Kentucky).

### Judges Needed!

The 2005 Fair will be held May 8-14, 2005 in Phoenix, Arizona. Society members in that area are asked to serve as judges. For additional information or to volunteer to serve as a judge, please contact Colleen Gorman at [cgorman@endo-society.org](mailto:cgorman@endo-society.org) or 1-301-951-2611. **EN**



*Award winners (front row from left to right) Dr. Dennis Chia (Judge); Allison Landstrom (1st Place); Shamita Chandhuri (Finalist); Jason Pellegrino (Finalist). (Back row from left to right) Honorable Mention: Tristan Gonzalez-Sanz; Rebecca Vitale; John Luo; Cesar Marquez*

40 countries to compete for over three million dollars in awards and scholarships. The students were all top winners in local, state, or national science fairs. Society members Drs. Dennis Chia, Kate

students were equally excited and dedicated to the science. Congratulations to all!

The Society presented the **First Place Award** of \$1,000 to Allison J. Landstrom, a Seventeen-year old

### 2004 Medical Student Achievement Award Nominations Still Available

The Endocrine Society has announced the winners of the 2004 Medical Student Achievement Award (see page 39). If your institution has not yet submitted a nomination for 2004, the Society will accept your nomination through the end of the year. To nominate a student from your institution, please refer to the list of participating institutions on the Society's Web site at <http://www.endo-society.org/about/medical.cfm>. A contact person has been established at most institutions. Please contact that person directly to submit your nomination. If your institution or a contact is not listed and you would like more information about participating, please contact Colleen Gorman at [cgorman@endo-society.org](mailto:cgorman@endo-society.org) or 1-301-951-2611. **EN**

## Clinical Research Award Winners Announced

The Endocrine Society is pleased to announce the award winners for the **2004 Endocrine Society/Pfizer, Inc. International Award for Excellence** for published clinical research in *The Journal of Clinical Endocrinology & Metabolism*. Awardees were selected from papers accepted for publication from January 1 to December 31 of the previous year. You can view the full-text articles online at <http://jcem.endojournals.org/misc/awards.shtml>

### FIRST PRIZE:

**Anne B. Loucks and Jean R. Thuma**  
“Luteinizing Hormone Pulsatility Is Disrupted at a Threshold of

Energy Availability in Regularly Menstruating Woman,” Vol. 88, No. 1, 2003, p. 297-311.

### FINALIST:

**Daniel Aeschbach, Leo Sher, Teodor T. Postolache, Jeffery R. Matthews, Michael A. Jackson, and Thomas A. Wehr**  
“A Longer Biological Night in Long Sleepers Than in Short Sleepers,” Vol. 88, No. 1, p. 26-30

### FINALIST:

**Stephen M. Shalet, Elena Shavrikova, Morris Cromer, Christopher J. Child, Eberhard Keller, Jirina Zapletalova, Thomas Moshang, Werner F. Blum, John**

**J. Chipman, Charmian A. Quigley, and Andrea F. Attanasio**  
“Effect of Growth Hormone (GH) Treatment on Bone in Postpubertal GH-Deficient Patients: A 2-Year Randomized, Controlled, Dose-Ranging Study,” Vol. 88, No. 9, p. 4124-4129.

### FINALIST:

**Staffan Enoksson, Sonia K. Caprio, Frances Rife, Gerald I. Shulman, William V. Tamborlane, and Robert S. Sherwin**  
“Defective Activation of Skeletal Muscle and Adipose Tissue Lipolysis in Type 1 Diabetes Mellitus during Hypoglycemia,” Vol. 88, No. 4, p. 1503-1511. **EN**

## Shortcourse Participants Awarded Travel Grants to Attend ENDO 2004

The Minority Affairs Committee awarded the following travel grants to students and faculty who participated in the Shortcourse Program during Fall 2003 and Spring/Summer 2004 academic year to attend the ENDO 2004 Annual Meeting recently held in New Orleans, LA. The Program is supported by a grant from the National Institute of General Medical Sciences (NIGMS) to foster interest in the science of endocrinology.

*For more information about the Shortcourse Program contact Veronica Parcan at 1-301-951-2601 or by email [vparcan@endo-society.org](mailto:vparcan@endo-society.org)*

### Faculty

Joseph Cameron, Jackson State University  
Malak Kolta, Florida A&M University  
Monica Converse, Lincoln University

Evangeline Motley, Meharry Medical College  
Timothy Turner, Tuskegee University  
Kennedy Wekesa, Alabama State University  
Sara Young, Montana State University

### Students

Donna Alcantara, TexasA&M Corpus Christi  
Alicia Armstead, Alabama State University  
Shana Augustin, University of Virgin Islands St. Croix  
Joseph Braud, Meharry Medical College  
Sarah Brokenleg, Haskell University  
Temesha Buckley, University of Virgin Islands, St. Thomas  
Travis Chipp, Albany State University  
Ana Costa, Hunter College

Alesha Crawford, Johnson C. Smith University  
Charnita Davidson, Tuskegee University  
Nina Davis, Tennessee State University  
Roman Fisher, Montana State University  
Natalia Garcia, South Mountain Community College  
Heather Germain, Medgar Evers College  
Megan Gillespie, Fond Du Lac Community College  
Isadora Gonzalez, University of Puerto Rico Cayey  
Terrance Green, Kentucky State University  
LePercival Griffin, Jackson State University  
Syleena Guilford, Virginia State University

*Continued on page 41.*

# Endocrine Society Announces Winners of Medical Student Achievement Award

The Endocrine Society established the Medical Student Achievement Award in 1997 to recognize and encourage students in their pursuit of careers in endocrinology. The Society presents these awards to each senior medical school student who show exceptional ability and interest in endocrinology.

Faculty from each participating institution selects and nominates their award recipient. Each recipient receives a one-year complimentary Fellow/Student Associate membership in the Society, a one-year subscription to *Endocrine Reviews*, and an award certificate which is presented to them by their institution during their school's awards ceremony. The Society is pleased to award the following students who have been nominated by their faculty in 2004:

## Canada

*Memorial University of Newfoundland*  
Christopher Sharpe

*Queen's University School of Medicine*  
Melanie Spring

*University of Alberta Faculty of Medicine & Dentistry*  
Jeremy Man

*University of Toronto*  
Rajan Sah

## Germany

*Medizinische Poliklinik*  
Katharina Laubner

## Israel

*Joyce and Irving Goldman School of Medicine*  
Ran Schwarzkopf

## Italy

*Brescia University Faculty of Medicine & Surgery*  
Monica Nezzo

*University of Bari School of Medicine*  
Cristiana Lattanzio

*University of Pisa*  
Letizia Fornari

## Sweden

*Umea University Hospital*  
Magnus Strand

## United Arab Emirates

*Faculty of Medicine & Health Sciences, U.A.E. Univ*  
Faisal Abdulla Al Shamsi

## United States

*Brody School of Medicine at East Carolina University*  
Jennifer Locklear

*Columbia University College of Physicians & Surgeons*  
Tamim M. Nazif

*Drexel University College of Medicine*  
David Speicher

*Duke University School of Medicine*  
Christina E. Barkauskas

*Medical College of Ohio*  
Melissa A. Frederick

*Medical College of Wisconsin*  
Susan L. Goldsmith  
Allison I. Ziff (Shared)

*Mount Sinai School of Medicine of NYU*  
Amy Dosoretz

*Northeastern Ohio Universities College of Medicine*  
Scott Soleimanpour

*Pennsylvania State University College of Medicine*  
Molly Caldwell-McMillan

*Saint Louis University School of Medicine*  
Staci Niemoth

*Tulane University Health Science Center*  
Trang Le

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Erica Schipper

*University of Texas Southwestern Medical School*  
Allison L. Smith

*Washington University School of Medicine*  
Amy Slansky

*Yale University School of Medicine*  
Rina Garcia **EN**

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# Coding Online Medical Evaluations; Helping the Society with Coding and Valuation

*Richard A Dickey, MD, FACP, FACE, Chair, Clinical Affairs Committee, Endocrine Society's CPT advisor and RUC advisor*

## Coding Online Medical Evaluations

As was described briefly in the April 2004 Coding News column, the Current Procedural Terminology (CPT) Editorial Panel of the American Medical Association (AMA) has created a new code set called "Category III CPT codes." Some of the most important aspects of our field begin as what the panel classifies as "new technology." The new category III code 0074T is a code that should be of interest to members for several reasons. The use of this technology is rapidly growing and it is sometimes able to get paid for the service by the payer, especially when it is a way to improve care or for the payer to save money. So be careful but be aware of this code and decide if it is appropriate for your practice. If so, give the payer reasons why it is cost-effective for them to do so and ask the payer to compensate for it.

The currently available Category III CPT code for Online Medical Evaluation is:

**0074T: Online evaluation & management service, per encounter, provided by a physician, using the Internet or similar electronic communications network, in response to a patient's request; established patient**

This Category III CPT code is intended to be used for data collection purposes to substantiate widespread usage and since payment for these services/procedures is deter-

mined by the policies of payers, they may not be payable. This long-awaited code, must be provided by a physician or qualified health care professional to a patient using Internet resources in response to the patient's online inquiry. Reportable services involve the physician's personal timely response to the patient's inquiry and must involve permanent storage (electronic or hard copy) of the encounter. This service should not be reported for patient contacts (e.g. telephone calls) considered to be pre-service or post-service work for other evaluation and management (E&M) or non E&M services. A reportable service would encompass the sum of communication (e.g. related telephone calls, prescription provision, laboratory orders) pertaining to the online patient encounter or problem(s).



*Richard A Dickey, MD, FACP, FACE*

warded to the RUC for determination of physician work, administrative, practice expense, and medical liability relative value units (RVUs) for payment.

## Helping Society with Coding and Valuation Processes

Since much of the work of the endocrinologist is done behind the scenes, so-to-speak, that is, not face-to-face with the patient, the importance of recognizing and fairly valuing this work is especially important to the endocrinologist. This is one reason the Society's active monitoring and participation in the CPT and RUC process is so important. Unless one understands, analyzes, and responds appropriately and proactively to

the values assigned and the codes available for work and expenses, one can be at a great and increasing

**To date, the Society has been represented by volunteers with the support of the staff, but more help is needed.**

Use this code to help the coding system collect data on its use and help substantiate its consideration for a Category I code in the future. Particularly important as well, this will help justify a request for the CPT Editorial panel to create of one or more Category I CPT codes which, in turn, will be for-

disadvantage to others whose professional organizations are doing this.

To date, the Society has been represented by volunteers with the support of the staff, but more help is needed. Recently, the Society added personnel with considerable expertise to create a more effective

advocate in the socioeconomic and reimbursement field. All that is needed now are additional members who will become familiar with pertinent systems of coding, valuation and reimbursement, members who are able to do the background study and work on these topics, formulate strong positions to present the Society's recommendations for changes, and attend those meetings where the changes can be formulated and presented (i.e. CPT and RUC meetings and meetings for planning prior to those meetings) to advocate for the endocrinologist's needs and to help correct inequitable values.

### Volunteers Needed!

The Clinical Affairs Committee (CAC) recently created a workgroup to focus on coding and reimbursement issues, a critical part of becoming more aware and effective in the process. This workgroup now needs volunteer members. Any Society member who is interested in assisting with this aspect of professional contribution is invited to join the workgroup. Please contact Janet Kreizman by phone 1-301-941-0252 or email [jkreizman@endo-society.org](mailto:jkreizman@endo-society.org) if you are willing to join this workgroup or contribute in any other way on CPT and RUC matters. **EN**

### REFERENCES:

- <sup>1</sup> *HCPCS Level II Codes 2004 Available from the AMA (discount for AMA member) or other suppliers.*
- <sup>2</sup> *Current Procedural Terminology, CPT 2004 Available from the AMA or other licensees. AMA order phone number is (800) 621-8335. Discount for AMA member.*
- <sup>3</sup> *International Classification of Diseases ICD-9-CM 2004. Available from the AMA (discount for AMA member) or other suppliers.*
- <sup>4</sup> *cpt changes: An Insider's View Available from the AMA. AMA order phone number is (800) 621-8335. Discount for AMA member.*
- <sup>5</sup> *CPT Assistant. A quarterly publication available by subscription from the*

*AMA. Articles explain in detail complex coding issues. Citations of these articles are provided in Current Procedural Terminology, CPT 2004.*

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### Shortcourse Travel Grant Awards

*Continued from page 38.*

- Charles Hall, Florida A&M University
- Alexis Hand, Jackson State University
- Nicholas Harrell, University of Arizona
- Jason Harris, Albany State University
- Larry Harris, Tuskegee University
- Tamara F. Hinton, Medgar Evers College
- Jennifer Hughes, Southern University Baton Rouge
- Linda Hunt, Albany State University
- Latoya Jenkins, Benedict College
- George Jules, Meharry Medical College
- Harriett King, Savannah State University
- Vashti Lachhman, Hunter College
- Lesley Lara, Contra Costa Community College
- Maria Loy, Contra Costa Community College
- Jennifer C. Miller, Claflin University
- Larry Minor, Southern University Baton Rouge
- Norma Moreno, Texas A&M University Corpus Christi
- Charity Morgan, Southern University Baton Rouge
- Peter Mukweho, Voorhees College
- Maliaka Nance, Tennessee State University
- Theresa Okeyo-Owuor, Prairie View A&M University

- Zaira Perez, Santa Monica College
- Renee Peterkin, Lincoln University
- Danielle Rascoe, Kentucky State University
- Lorina Reed, Meharry Medical College
- Kyrishia Reid, Savannah State University
- Ryon Sun Rhodes, Montana State University
- Erika Richardson, Claflin University
- Cheryl Robertson, Alabama State University
- Asha Robinson-Parks, Meharry Medical College
- Jazmine Robinson, Florida A&M University
- Melvin Rodriguez, University of Puerto Rico Cayey
- Faith Rowland, Xavier University
- Dominica Scott, Virginia State University
- La Shaundra Taylor, Florida A&M University
- Jamie Tuura, Fond Du Lac Community College
- Jane Ullah, Lincoln University
- Eneida Villanueva, University of Puerto Rico Mayaguez
- Gladys Varela, University of Puerto Rico Mayaguez
- Foncia Webb, Meharry Medical College
- Stephanie Wiley, Johnson C Smith University
- Montica Wilson, Jackson State University **EN**



SEPTEMBER / OCTOBER

**September 20 – 22, 2004: 15th National Conference on Women's Health Care**, Las Vegas, NV. For more information visit <http://www.symposiamedicus.org/calendar.asp>

**September 23 – 25, 2004: 18th Annual Fall Conference on High Risk Obstetrics**, New Orleans, LA. For more information visit <http://www.symposiamedicus.org/calendar.asp>

**September 23 – 24, 2004: Nigerian Society for Endocrinology and Metabolism Scientific Conference and AGM**, Lagos, Nigeria. For more information contact Dr. Tonia Ogbera or Dr. Fasanmade by phone 1-23-480-330-081-27 or email [ofasanmade@yahoo.com](mailto:ofasanmade@yahoo.com)

**September 23 – 26, 2004: JPGM GOLD CON: 50 years of Medical Writing - International Conference on Journal Writing and Publishing**, Mumbai, India. For more information visit <http://www.jpgmonline.com/goldcon.asp> or call 91-22-25032398 [goldcon@jpgmonline.com](mailto:goldcon@jpgmonline.com)

**September 23 – 25, 2004: 17th Quebec CME Programme**, Quebec, Canada. For more information visit [http://sogc.medical.org/conferences/quebec/index\\_e.shtml](http://sogc.medical.org/conferences/quebec/index_e.shtml)

**September 24 – 26, 2004: SoCRA 2004 Annual Conference**, Montreal, Quebec, Canada. For more information visit [http://www.socra.org/2004\\_conference.htm](http://www.socra.org/2004_conference.htm)

**September 24 – 26, 2004: APPES (Asia Pacific Pediatric Endocrine Society) 3rd Scientific Meeting**, (in association with the Japanese Society of Pediatric Endocrinology) Kobe, Japan. For more information please visit <http://www.appes.org/>

**September 25 – 29, 2004: The Placenta Association of the Americas (PAA) 2004 on Signaling and the Placenta, 10th IFP**, Asilomar, CA. For more information visit <http://www.paa2004.org> or contact by phone +44 (0)186-584-3297 fax +44 (0)186-584-3958 or email [n.woods@elsevier.com](mailto:n.woods@elsevier.com)

**September 29 – October 3, 2004: 76th Annual Meeting of the American Thyroid Association (ATA)**, Vancouver, British Columbia, Canada. For more information visit <http://www.thyroid.org> call 1-703-998-8890, fax 1-703-998-8893 or email [admin@thyroid.org](mailto:admin@thyroid.org)

**September 30 – October 3, 2004: Colon Cancer in Murine Models and Humans**, Bar Harbor, ME. For more information visit <http://www.jax.org/courses/events/coursedetails.do?id=38> or contact Judi Alexander by phone 1-207-288-6326, fax 1-207-288-6080 or email [judih@jax.org](mailto:judih@jax.org)

**September 30 – October 3, 2004: The American College of Nutrition Annual Meeting**, Long Beach, CA. For more information visit <http://am-coll-nutr.org/>

**October 1 – 5, 2004: 26th Annual Meeting—American Society for Bone and Mineral Research**, Seattle, WA. For more information visit <http://www.asbmr.org/meeting/index.cfm>

**October 2 – 4, 2004: EFES Postgraduate Courses in Molecular and Cellular Endocrinology**, Berlin, Germany. For more information visit <http://www.euro-endo.org/courses.htm> call 1-49-30-450-524922 or email [elke.abdelkarim@charite.de](mailto:elke.abdelkarim@charite.de)

**October 3 – 6, 2004: 129th American Neurological Association Annual Meeting**, Toronto, Canada. For more information visit <http://www.aneuroa.org/>

**October 3 – 6, 2004: Clinical Endocrinology Update (CEU) 2004**, Baltimore, MD. For more information visit <http://www.endo-society.org/scimeetings/index.cfm>

**October 8 – 13, 2004: Neuroendocrine-Immune Interactions—EuroConference on Cytokines in the Brain: Expression and Action of Cytokines in the Brain and Pathophysiological Implications**, Giens (near Toulon), France. For more information visit <http://www.esf.org/euresco/04/mc04140> or contact Mrs. Sally Lewis-Ford by phone 1-33-388-76-71-35, fax 1-33-388-36-69-87 or email [slewis@esf.org](mailto:slewis@esf.org)

**October 9 – 12, 2004: 58th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research in association with the Council on the Kidney in Cardiovascular Disease**, Chicago, IL. For more information visit <http://www.americanheart.org> **EN**

## Worldwide Endocrine Events Calendar

Your online resource for endocrinology meetings around the globe.  
Search by sponsoring organization, date, topic, location, and beyond.  
Post your event on the calendar or search the database.

[www.endo-society.org](http://www.endo-society.org)

# Type 1 Diabetes

*An Accurate  
Diagnosis Requires  
The Right Tools*

**GAD, IA-2 and  
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*The Immunologic Markers of Choice  
for the Differential Diagnosis &  
Management of Type 1 Diabetes*



**GADAb and  
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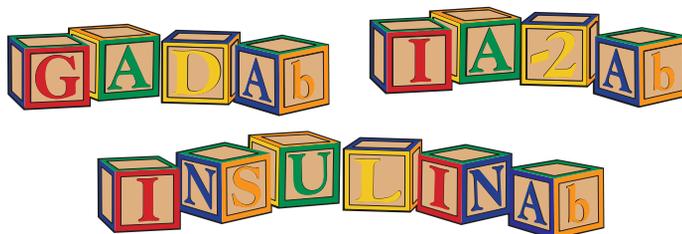
## Tools of the Past...

For many years, the physician has had to rely on the measurement of **cytoplasmic islet cell antibodies** (ICA) measured via indirect immunofluorescence test (IFA) to aid in the diagnosis and management of diabetes. While useful, the IFA method is labor intensive and difficult to standardize, making it challenging to obtain consistent, objective results.

## Tools of the Present...

KRONUS now offers test kits for the measurement of autoantibodies to the **three key autoantigens**— glutamic acid decarboxylase (GAD), IA-2 and insulin — for assessment of the immune process associated with Type 1 diabetes, resulting in improved sensitivity, specificity and positive predictive value. Generally present and measurable several years **prior to the clinical onset of disease**, the measurement of **GAD, IA-2 and insulin autoantibodies** can help identify individuals at-risk and provide vital information with regards to the autoimmune progression of diabetes.

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## Update on Clinical Advances in Endocrinology

- Keep up with changes in clinical practice based on new research
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- Improve your practice skills
- Prepare for Board Exams
- Earn up to 24.5 hours of Category 1 CME credits

## Focus on Diagnosis and Management of Endocrine Disorders

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- Cutting-edge plenary lectures
- Taught by experts
- Format offers opportunity to interact with faculty and ask questions on case management
- Covers seven major endocrine areas: thyroid, pituitary, calcium/bone, reproduction, diabetes, obesity/lipids, adrenal/hypertension

Register by August 6th and save!

Final Advance Registration Deadline: August 27th

**For online registration and more information, visit**  
[www.endo-society.org/scimeetings/ceu2004/index.cfm](http://www.endo-society.org/scimeetings/ceu2004/index.cfm)



## Board Review Session

October 1–2, 2004

*A separate optional course preceding CEU 2004 presents eight 90-minute modules with a specific focus: pituitary, diabetes, lipids, thyroid, calcium/bone, reproduction, adrenal, pediatric.*



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