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Trends and Insights for the Endocrine Community

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Andrea Dunaif, M.D.

The past five years have been a period of intense reflection for The Endocrine Society. We have developed and implemented a Strategic Plan, which has resulted in substantial changes in governance to recognize the Society's three constituencies: basic scientists, clinical scientists and physicians-in-practice. Conversations with these constituencies have brought fundamental issues into sharp relief. Who are we and what should we become? How can we retain our diverse membership, given the powerful competition from other societies and meetings? How can we improve the care of patients with endocrine disorders? How can we increase funding for endocrine research?

Our diversity is perhaps the Society's greatest strength, because we span the field from basic science through integrative physiology to clinical practice. In this era when the bench-to-bedside gap has become an issue of national concern, no society is better positioned to bridge this gap. Indeed, our Annual Meeting has just presented elegant examples of these "pathways to discovery." The overarching theme of my presidency will be to define the unique strengths of The Endocrine Society to our public, including patients and Congress, as well as the broader scientific and medical communities. If we have a clear identity and focus, we can best serve all of our constituencies.

A looming issue is the return of record federal deficits, which affect our scientists by flattening the NIH budget and our physicians-in-practice via constraints on healthcare spending. Thus, a major initiative will be forceful government advocacy. Not only will we continue to be active in the Federation of American Societies for Experimental Biology (FASEB), but we will also increase our independent advocacy efforts. How the reorganization of the NIH study sections affects the success of endocrine grants will be a priority for the Research Affairs Committee and the possibility of developing independent tracking systems will be explored. The Minority Affairs Committee will consider a plan to collaborate with endocrine training programs on the recruitment and retention of minority trainees. The Society will begin to set the standard for the diagnosis and treatment of endocrine disorders through the promulgation of our clinical guidelines. A new initiative before Council will be the development of criteria for hormone assay quality. Finally, the Society will aggressively define itself through outreach to the public and the media. We plan to continue the *Obesity in America* campaign and to sponsor our first conference for science writers to educate them on cutting-edge issues in the field, such as hormone abuse.

The 2006 annual meeting in Boston will have a number of enhancements in response to input from our constituencies via task forces and focus groups. Instead of a single theme, there will be four special emphasis areas: the endocrine brain; metabolic syndrome and growth factor signaling; controversies in endocrinology; and stem cells and transplantation. Each will be the focus of a day of the meeting. This change will allow us to bring forward themes from previous meetings, such as obesity and cardiovascular endocrinology as part of the metabolic syndrome, while identifying novel areas for emphasis. Many of the endocrine controversies will have a debate format, while the stem cells and transplantation program will include sessions on state-of-the-art technology. There will also be the opportunity at the end of these sessions for informal interactions with the speakers and colleagues. This structure will permit us to create the focus, scientific depth and intimacy of a smaller meeting within the already superb larger meeting. We believe that these programs will also attract nonmembers from the Boston area, who will be able to register for single days of the meeting. As always, there will be an outstanding program of general scientific sessions and plenary lectures of interest to all our constituencies on each day of the meeting.

In closing, there are no words adequate to express my thanks for the great honor that you have bestowed on me by electing me as your President. I will do my utmost to be deserving of your trust. ■

Sincerely,

Andrea Dunaif
President, The Endocrine Society

Thanks to Mrs. Sheldon (Jackie) Waldstein for permission to reprint the cartoon, a copy of which she received from cartoonist Ned Riddle.

Introducing The Endocrine Society's New President, Andrea Dunaif

Andrea's first passion in life was horseback riding, which she began at the age of three during a family vacation to Cape Cod. Throughout her childhood and adolescence — mostly spent in Ossining, New York — she rode competitively. Riding, she says, taught her many skills that proved useful for pursuing a career in science, including how to compete, how to be coached, and how to win and lose. "All my free time was spent on training, so hard work never really fazed me," she says. The toughest lesson of all came at the age of 15, when she realized that, as good as she was, she lacked the special talent to earn a place on the U.S. Equestrian Team.

Andrea redirected her energy into school work and blossomed as a scientist. She became intrigued with endocrinology while earning her M.D. degree at Columbia University in New York City. "I was attracted to the fact that it was so logical. You could understand the biologic basis of endocrine diseases, and diagnose and treat conditions based on these principles."

She completed her residency training in Internal Medicine at the Presbyterian Hospital in New York City and her fellowship in Endocrinology and Metabolism at the Massachusetts General Hospital in Boston. She then worked at the Mount Sinai School of Medicine in New York City, the Pennsylvania State University College of Medicine in Hershey and Harvard Medical School in Boston. She became the first Director of Women's Health at Brigham and Women's Hospital, Boston, and in 2001 became the Charles F. Kettering Professor and Chief, Division of Endocrinology, Metabolism and Molecular Medicine at the Feinberg School of Medicine, Northwestern University in Chicago.

Apart from her academic appointments, Andrea spent a year with the pharmaceutical company, Parke Davis, overseeing the clinical development of an insulin-sensitizing diabetes drug that also showed promise for the treatment of polycystic ovary syndrome (PCOS). She notes that clinical investigators are often intrigued by opportunities in the pharmaceutical industry. "It completes the chain from fundamental science to its practical application to the actual treatment of human disease," she says. "Drug development is the last link in this chain and it is rarely done in an academic environment." Overall, her work in industry was a valuable experience, she says. "But I missed running my own research program and returned to academia."

Andrea says her proudest scientific achievement was the discovery, almost 20 years ago, that women with PCOS were profoundly insulin-resistant and at markedly increased risk for type 2 diabetes mellitus. This discovery indicated that the syndrome was not only a reproductive disorder, but could also have serious metabolic implications throughout a woman's lifespan. She continues to study PCOS at Northwestern, where her lab is now focused on identifying PCOS-susceptibility genes and investigating the possible fetal origins of the disorder.

Her proudest professional achievement is to have been elected as President of The Endocrine Society, an organization that has drawn her extensive involvement since the early 1990s and that she hopes to continue to serve throughout her career. "In science and medicine, we are judged by our peers and their approbation is perhaps the greatest honor that one can receive. My challenge now is to serve them well," she says. ■

Endocrine news

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Widely Used Pesticide May Affect Human Reproduction, Mouse Study Suggests

➤ A common pesticide used against insects and on food crops, methoxychlor (MXC), has a lasting effect in mice on the expression of a particular gene. This gene is required for reproductive tract development and function, a finding that may be similar in humans, according to a study to be published in ***Endocrinology*** later in 2005.*

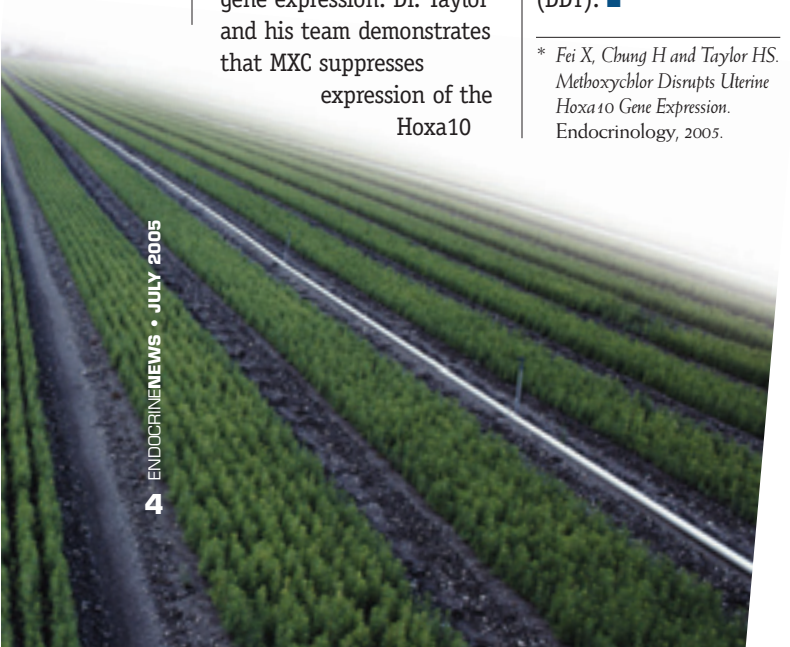
The mouse study, led by Hugh S. Taylor, M.D., of Yale University, shows how MXC and its metabolites bind the estrogen receptor and function as endocrine disruptors, diminishing the uterine decidual cell response necessary to support embryo implantation. One common mechanism by which endocrine-disrupting chemicals produce lasting reproductive tract defects is through permanent alteration of developmental gene expression. Dr. Taylor and his team demonstrates that MXC suppresses expression of the Hoxa10 estrogen-regulated gene.

Previous studies show that diethylstilbestrol (DES) exposure in mothers affects offspring by altering the spatial pattern and level of Hox gene expression. Hox genes impart developmental identity to multiple vertebrate embryonic axes, including the central nervous system, vertebrae, limb and the reproductive tract.

"The effect of MXC exposure in humans is not well-characterized and, like the effects of DES exposure, may be subtle," the authors write. "As MXC and DES have similar effects on developmental gene expression in exposed animals, the effect of human exposure to either of these two endocrine disruptors may be similar."

MXC is a man-made organochloride pesticide used to kill flies, mosquitoes, cockroaches and other insects, and is applied directly to food crops, livestock, home gardens and pets. It was developed as an alternative to dichlorodiphenyltrichloroethane (DDT). ■

* *Fei X, Chung H and Taylor HS. Methoxychlor Disrupts Uterine Hoxa10 Gene Expression.* Endocrinology, 2005.



How to Prevent and Identify Scientific Misconduct

➤ Unethical conduct exists in science, as in any profession, but scientists running a study or lab can take several steps to prevent or identify research misconduct in an effective way, according to a presentation at an ethics workshop in conjunction with **ENDO 2005**.

The presentation, authored by Peter Abbrecht, M.D., Ph.D., of the U.S. government's Office of Research Integrity, listed the following 12 guidelines to help prevent misconduct:

- Establish a lab climate that stresses the need and reasons for scientific integrity.
- Thoroughly train all staff in integrity principles and in conducting their portions of the protocol.
- Maintain strong communication between supervisors and staff, and ensure a supervising "presence" in the study setting, such as verifying a sample of the research records.
- Require that any data forms are altered by strike-through, rather than eliminating the original. Changes should have initials and date.
- Question staff about data alterations in the research record.
- Design protocols with realistic requirements for staff and patients.
- Keep staff workloads reasonable.
- Make protocol research forms simple and clear.
- In interview studies, require patients to be re-contacted for quality-control reasons.
- In continuing studies, train more than one staff member for follow-up, if possible.
- Retain copies of all laboratory reports (and spot check on routine and special audits).
- Avoid having protocol sponsors pay bonuses based on how many patients are enrolled.

The workshop was titled "Enhancing Integrity in Clinical Research." More highlights from the workshop will appear in upcoming issues of ***Endocrine News***. ■

Workshop supported by ORI/AAMC, Eli Lilly & Co., Novo Nordisk Pharmaceuticals and Wyeth. Report contents do not reflect views of sponsors.

Taking Folic Acid Is Good for a Woman's Heart

➤ Postmenopausal women who take folic acid supplements have lower plasma homocysteine (Hcy) levels, and better insulin and lipid metabolism, thereby reducing their risk of cardiovascular disease, according to findings to be published in ***The Journal of Clinical Endocrinology & Metabolism*** later this year.*

Too high a level of Hcy—an amino acid that naturally increases with a woman's age—is related to a greater risk of coronary heart disease, stroke and peripheral vascular disease. Folic acid is known to help break down homocysteine. However, studies have produced conflicting evidence about the relationship between Hcy and glucose, insulin and lipidic metabolism.

Aiming to clarify the beneficial effects of folic acid, Antonio Lanzone, M.D., of Catholic University of Sacred Heart in Rome, Italy and his team conducted a randomized, but not double-blind placebo trial with 20 healthy postmenopausal women, ages 48 to 61. In particular, they examined the complex relationship between Hcy metabolism and carbohydrate and lipid metabolism. For eight weeks, the women took either 7.5 mg/day of folic acid (L-isomer) or a placebo. The researchers found that women taking the L-folic acid had significantly reduced total basal homocysteine concentration and plasma post-methionine loading Hcy values. Furthermore, L-folic acid intake resulted in a significant improvement of the carbohydrate metabolism through an increase of fractional hepatic insulin extraction and peripheral insulin sensitivity in normoinsulinemic women. HDL levels rose considerably, inducing an improvement of other atherosclerotic indexes such as the cholesterol/HDL and LDL/HDL ratios. ■

* *Villa P, Perri C, Suriano R, Cucinelli F, Panunzi S, Ranieri M, Mele C and Lanzone A. L-Folic Acid Supplementation in Healthy Postmenopausal Women: Effect on Homocysteine and Glycolipid Metabolism.* JCE&M *2005.*

House Votes on Stem Cell Issue

➤ On May 22, 2005, the U.S. House of Representatives voted 238-194 to support legislation that would expand embryonic stem cell research. The Stem Cell Research Enhancement Act (H.R. 810), co-sponsored by Representatives Mike Castle (R-DE) and Diana DeGette (D-CO) would allow federally-funded researchers to use all stem cell lines derived from embryos originally created for in vitro fertilization that would otherwise be discarded, regardless of the date they were derived. Donors would need to provide written informed consent and would not receive any compensation. The bill now heads to the Senate where supporters are optimistic about its chances for passage. The Senate companion bill, S. 471, is sponsored by Senator Arlen Specter (R-PA). Before the House vote, President Bush threatened to veto the legislation should it reach his desk. He said the current policy of limited research on existing lines is a sufficient balance between both those who support and oppose embryonic stem cell research.

At the request of the bill's sponsors, The Endocrine Society circulated a member alert requesting that Society members encourage their members of Congress to support this legislation. Also in the Senate, Senator Orrin Hatch (R-UT) and Senator Dianne Feinstein (D-CA) introduced legislation that would provide federal funding for somatic cell nuclear transplantation (SCNT). The bill, The Human Cloning Ban and Stem Cell Research Protection Act (S.876), would provide for limited SCNT research, while banning human cloning.

To view periodic updates on stem cell research legislation, see **Endocrine Insider** at *http://www.endo-society.org/publicpolicy/insider/index.cfm.* ■

Scientists Find Marker for Differentiated Thyroid Cancer

➤ Differentiated thyroid cancers, the most common endocrine cancers, lack a reliable molecular marker for prognosis. Tackling this problem, Chris J. McCabe, Ph.D., at the University of Birmingham in England and his team investigated PTTG Binding Factor (PBF). Their study will be published in ***The Journal of Clinical Endocrinology & Metabolism*** later in 2005.*

The scientists found PBF to be a novel transforming and tumorigenic gene in thyroid cancer and that its expression correlates with tumor recurrence. They propose that up-regulated PBF augments PTTG's established roles in both thyroid tumor initiation (via chromosomal instability) and progression (via growth factor upregulation), resulting in tumor growth and development. Based on these findings, the authors suggest PBF is an additional prognostic indicator in differentiated thyroid cancers. ■

* *Stratford AL, Boelaert K, Tannahill LA, Kim DS, Warfield A, Eggo MC, Gittoes NJL, Young LS, Franklyn JA and McCabe CJ. PTTG Binding Factor (PBF): A Novel Transforming Gene in Thyroid Tumorigenesis.* JCE&M, *2005.*

New Fertility Impact Seen from CYP17 Deficiency in Male Mice

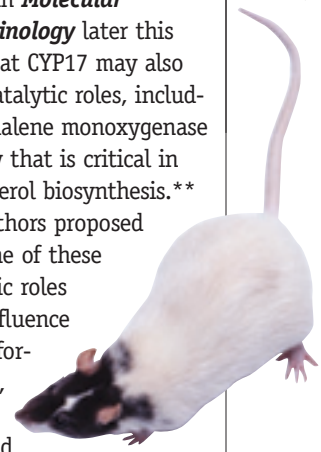
➤ Mice lacking the gene that encodes cytochrome P450 17-hydroxylase/17, 20-lyase (CYP17), a blend of two enzymes needed for cortisol and sex steroid synthesis, become infertile by an unexpected mechanism, according to a study to be published in ***Molecular Endocrinology*** later in 2005.*

Earlier studies suggested that animals lacking the CYP17 gene would have insufficient testosterone levels to maintain fertility. However, this study led by Vassilios Papadopoulos, Ph.D., of Georgetown University, raised the prospect that infertility might be caused primarily by factors other than an androgen imbalance caused by CYP17's absence, even if the androgen imbalance has a secondary impact by depressing sexual interest. Experiments showed that mice lacking the CYP17 gene failed to produce offspring, due to altered sperm structure and function linked to the absence of the CYP17 gene in the affected sperm. This suggest that either germ cells or sperm have the ability to form androgens from pregnenolone or progesterone, or else CYP17 may have alternative functions affecting sperm formation. Indeed, the authors noted, there is evidence that germ cells express CYP17 and metabolize androgens to estrogens.

Moreover, the same group recently suggested in another study to be published in ***Molecular Endocrinology*** later this year that CYP17 may also have catalytic roles, including squalene monoxygenase activity that is critical in cholesterol biosynthesis.** The authors proposed that one of these catalytic roles may influence sperm formation, function and fertility. The authors noted evidence that appropriate amounts of cholesterol must be present in sperm to help sperm structure and function. ■

* *Liu Y, Yao Z-X, Bendavid C, Borgmeyer C, Han Z, Cavallli LR, Chan W-Y, Folmer J, Zirkin BR, Haddad BR, Gallicano I and Papadopoulos V. Haploinsufficiency of Cytochrome P450 17-hydroxylase/17,20-lyase (CYP17) Causes Infertility in Male Mice.* Mol Endocrinol, *2005.*

** *Liu Y, Yao ZX, Papadopoulos V. Cytochrome P450 17α hydroxylase/17,20 lyase (CYP17) function in cholesterol biosynthesis: identification of squalene monooxygenase activity associated with CYP17 in Leydig cells.* Mol Endocrinol, *in press.*



SMART MOVES

developments in the endocrinology world

Andrea Dunaif, M.D., has been appointed by the NIH Director to a four-year term as a member of the Advisory Committee on Research on Women's Health.

Daniel Einhorn, M.D., F.A.C.E., has been promoted to Clinical Professor at the University of California – San Diego School of Medicine, and has been awarded the Yank Coble Distinguished Service Award of the American College of Endocrinology.

Jeffrey S. Flier, M.D., received the Banting Medal from the American Diabetes Association during its 65th Annual meeting in San Diego.

Alan M. Miller, M.D., recently completed law school and received a J.D. (Doctor of Jurisprudence) degree from Concord Law School, Los Angeles.

Manuel Neves-e-Castro, M.D., was elected Honorary Member of the European Menopause and Andropause Society. He was also elected Honorary Founding President of the Portuguese Menopause Society.

Hershel Raff, Ph.D., The Endocrine Society's Secretary-Treasurer, has been elected to join the Alpha Omega Alpha (AOA) – Medical College of Wisconsin, Beta Chapter of the National Honor Medical Society.

Arlan Rosenbloom, M.D., was awarded the International Society for Pediatric and Adolescent Diabetes (ISPAD) Prize for Achievement in Science, Education, and Advocacy on Behalf of Young People with Diabetes.

Charles R. Rosenfeld, M.D., received the Southern Society for Pediatric Research's 2005 Founders Award.

Philipp E. Scherer, Ph.D., is the recipient of the Lilly Award from the American Diabetes Association.

Judith Vaitukaitis, M.D., will step down as Director of the NIH's National Center for Research Resources (NCRR) to become Senior Adviser to the NIH Director on scientific infrastructure and resources. **Barbara L. Alving, M.D.**, Deputy Director of the National Heart, Lung, and Blood Institute, will serve as acting director of NCRR.

STAT

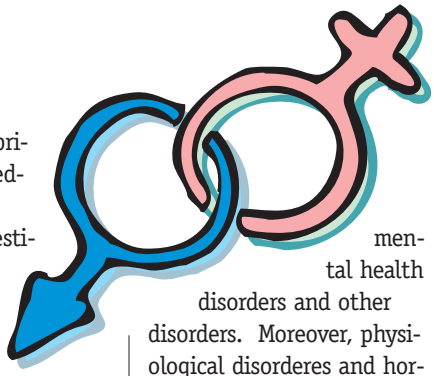
In 30% to 50% of male infertility, the cause is unknown.

Source: The Hormone Foundation

Report Reveals Low NIH Support for Sex Difference Research

➤ Research grants awarded to study biological differences between males and females averaged only about 3 percent of all grants awarded by the National Institutes of Health (NIH) between 2000 and 2003, according to a recent report by the nonprofit Society for Women's Health Research.*

The authors reviewed abstracts from successful grant applications for four years and determined the percentage of NIH grants awarded to study male–female differences.



The NIH, as the primary source of federal support for independent investigator-initiated biomedical research in the United States, also influences many private research funders, the report noted.

"Women are not small men," the report states, noting that until the 1990s biomedical research was firmly rooted in the male model. It cites several recent studies showing that sex differences in disease susceptibility, prevalence, time of onset and severity are evident in cancer, obesity, coronary heart disease, autoimmune disorders, mental health disorders and other disorders. Moreover, physiological disorderes and hormonal fluctuations may also play a role in the rate of drug metabolism and effectiveness of response in females and males, the report notes.

The study reports that some branches of the NIH, such as the National Institute on Drug Abuse, support hypothesis-driven research designed to study both sexes and have mechanisms in place to foster such research. However, the institutes with the largest budgets appear to be supporting very little or no such research.

"NIH research guidelines must be updated and modified once again to actively promote sex differences' research at all levels, including basic research in cell and tissue culture, the development and study of appropriate animal models early-stage clinical research, as called for by the IOM (Institute of Medicine)," the report states. ■

* *Simon VR, Hai T, Williams SK, Adams E, Ricchetti K and Marts SA. National Institutes of Health: Intramural and Extramural Support for Research on Sex Differences, 2000 – 2003.*

Estrogen May Be Factor in Obsessive Compulsive Disorder

➤ Estrogen appears to play a role in the development of obsessive compulsive disorder (OCD), especially in males, according to first-time findings of a study on mice presented at **ENDO 2005**.* Researchers say these findings may eventually lead to treatment for this debilitating disorder, which affects 2 to 3 percent of the U.S. population.

Compared with women sufferers, men with OCD exhibit signs of the disorder at a younger age, have more tics and have a worse outcome, studies have shown. To investigate estrogen's role in the development of OCD, Rachel A. Hill, Ph.D., of Prince Henry's Institute of Medical Research and Monash University in Melbourne, Australia, and colleagues did an experiment using an estrogen-deficient mouse model. Aromatase knockout (ArKO) mice are unable to convert androgens to estrogens. When the mice were six months old, the researchers sprayed water on each knockout and regular male and female mouse and watched for OCD-type behavior. In the 20 minutes after the spraying, the researchers recorded the time and frequency of grooming activity. They found that the male ArKO mice groomed significantly more than normal mice, but this level of grooming decreased after the mice received three weeks of estrogen replacement. There was no difference in the behavior of female mice, whether ArKO or normal.

To determine the molecular basis behind this behavioral phenomenon, the researchers studied the catechol-o-methyl-transferase (COMT) gene, which is often absent in male humans with OCD. They found that COMT protein levels in the brains of male ArKO mice were significantly lower than in normal mice, but that estrogen treatment of the ArKO mice restored COMT levels to normal. Again, the researchers observed no differences between female ArKO and normal female mice, although both had significantly lower COMT levels than males.

The research indicates that a lack of estrogen in the male mouse leads to a decrease in COMT levels in the brain, which in turn is associated with extreme grooming behavior — a characteristic of OCD. This effect of estrogen deletion appeared only in the male ArKO mice, further suggesting a sex difference in how estrogen affects the brain. ■

* *Hill RA, McInnes KJ, Gong ECH, Jones MEE, Simpson ER and Boon WC. Estrogen Deficiency May Be Linked with Obsessive Compulsive Disorder in the Male but Not Female Mouse.*

Book Review: Viewpoints belong to the authors and not The Endocrine Society.

Bioidentical Hormone Replacement: MYTHS & FACTS

Do Natural Bioidentical Hormones Help Women Stay **Younger?**

BY Leslie Salomone, M.D., and Richard J. Santen, M.D.

Through the ages, humans have sought to cling to disappearing youth — and that quest continues today, with an apparently new tool: bioidentical hormones. Such hormones have a similar chemical structure to hormones produced by the human body. Among widely prescribed bioidentical substances are levothyroxine for thyroid hormone and various estradiols for estrogen. But as soldiers in the battle against aging, various bioidentical hormones are grabbing the attention of the public and media, mostly because of two recent books on the topic by the popular author and actress Suzanne Somers: *The Sexy Years* and *Slim and Sexy Forever.*

Ms. Somers writes about her experience taking bioidentical hormones to relieve her menopause symptoms, the positive effect she observed on her general health and her plans to take them for the rest of her life. However, many medical professionals question the accuracy of Ms. Somers' claims. Leslie Salomone, M.D., and Richard J. Santen M.D., both members of The Endocrine Society and physicians at the University of Virginia Health System in Charlottesville, Virginia, took a close look at Ms. Somers' latest book, *Slim and Sexy Forever*, and made the following assessment:

The Review:

Ms. Somers claims that the key to emotional and physical well-being in the second half of life is through hormonal balance with natural, bioidentical hormones. She observes that her previous approach to fitness and health ("Somersizing" program), which kept her looking and feeling great, failed when she reached menopause. According to Ms. Somers, no weight-loss program will work for you at or beyond this phase of life if your hormones remain unbalanced. She admits that menopause is a natural process of hormonal decline and offers bioidentical hormone replacement therapy (BHRT), along with compliance with her fitness and dietary recommendations, as the solution to "controlling weight," "avoiding diseases of aging," and restoring "energy, vitality, a youthful glow, sexuality, a slim figure, a good attitude, healthier bones, a healthier heart and ... a healthier brain" (p.14). She says BHRT is the answer to the problems plaguing so many middle-aged women.

Ms. Somers begins her chapter on hormonal balance by criticizing the pharmaceutical industry's "one-pill-fits-all" approach to menopause with synthetic hormones. She repeatedly emphasizes that those drugs are harmful to your health, in contrast to non-drug, natural replicas of human hormones, or BHRT. She theorizes that because synthetic hormone replacement therapy (i.e. Prempro, Premarin and Provera) mimics pregnancy, it causes a high-insulin state, which is dangerous to a woman's health. A recent report from the Women's Health Initiative, in fact, shows the contrary. Prempro use was associated with a decreased incidence of new diabetes and decreased insulin levels, while increasing insulin sensitivity. Ms. Somers goes on to claim that this is one of many reasons that the Women's Health Initiative (WHI) advised women to stop taking these drugs.

This is simply not true. This theory was generated and stated by Ms. Somers' personal endocrinologist, Dr. Diane Schwarzbein, in *The Sexy Years* (Ms. Somers' first book about BHRT) from observations in her own patients who were on continuous/combined synthetic hormones and developed type 2 diabetes and obesity. Dr. Schwarzbein concludes that continuous/combined hormone use, whether synthetic or bioidentical, promotes a constant high-insulin state that causes type 2 diabetes, heart attack, stroke, pulmonary embolus and high blood pressure — to name a few. Although the WHI clearly demonstrated increased risks for certain events (primary endpoints), a high-insulin state was not one of them.

In the Bioidentical vs. Synthetic Hormone section of her book, Ms. Somers correctly differentiates between "synthetic" hormones and "synthesized" hormones, stating, BHRT is "synthesized in a lab (from yam and soy extract) to exactly replicate the hormones we make in our own bodies." She further clarifies that eating those foods will not replenish lost hormones, because our bodies cannot convert these foods into usable hormones.

This information is true, as is her statement that estrogen (17-beta-estradiol, E2) maintains bone health.

However, in this same section, Ms. Somers proceeds to pronounce boldly that the hormonal imbalance of menopause, either from the natural process itself or the use of synthetic hormones to treat symptoms, directly causes weight gain. Once again, this claim has no scientific foundation; however, she credits BHRT with her own ability to maintain perfect weight. Based solely on this personal experience, Ms. Somers goes on to say that not only should perimenopausal/menopausal women with weight gain have their hormones analyzed, but even young women "would be well-served to have a blood and/or saliva tests to get a clear picture of their hormone levels." Her explanation for hormonal imbalance in otherwise healthy young women is stress. This, too, is not supported by valid evidence. Ms. Somers advocates expensive, unnecessary testing based on no science. No data exist regarding weight loss as a primary endpoint of BHRT or synthetic hormone replacement therapy in any age group.

Ms. Somers makes these statements based on her reasoning that that proper eating and regular exercise, even the "Somersize" way, are not enough if your hormones are unbalanced. In her opinion, BHRT is the answer to your weight and the key to optimal living!

"There just is not any evidence that adjusting BHRT, or even being on it, has a direct impact on a person's weight. This is strictly Ms. Somers' opinion."

Although her opinion is not grounded in evidence-based medicine, Ms. Somers' support of regular blood testing for women taking BHRT is sound advice, on a conceptual basis. Validated assays for blood levels of various hormones are widely available and frequently used by physicians. Normal ranges of hormones for age and sex have been established. It has long been the practice of many endocrinologists to adjust BHRT based on blood levels.

However, Ms. Somers' belief that BHRT should be adjusted either because you experience increased stress in your life or you gain weight, is just not true. If a patient re-develops hot flashes, checking blood hormone levels and adjusting for low levels is legitimate. But if adjustments are made based on symptoms alone, with no objective guidance, then what is the purpose of testing?

This is where Ms. Somers' misunderstanding of hormones comes into play. She attests that hormones are not drugs and therefore cannot be harmful and have no consequences. To her, if something is natural, it cannot hurt you, so more is better if you are having symptoms. Substantial scientific evidence exists that hormonal excess of any hormone, either exogenously or endogenously, can be harmful and cause increased morbidity and mortality (thyroid storm, hypoglycemic coma, severe Cushing's Syndrome, pheochromocytoma and ovarian hyperstimulation syndrome, to name a few). In her book, Ms. Somers emphasizes that in her eight years of BHRT use, the symptom of weight gain, usually associated with increased stress in her life, is the most common reason she seeks an adjustment in her BHRT dose. There just is not any evidence that adjusting BHRT, or even being on it, has a direct impact on a person's weight. This is strictly Ms. Somers' opinion.

We concur with Ms. Somers, however, that any woman with the classic symptoms of perimenopause/menopause, such as hot flashes, menstrual irregularity, pain with sexual intercourse, vaginal itching and/or mood lability (notice that weight gain is not mentioned here) should seek advice from her medical provider about BHRT. Even if the provider is not comfortable with compounded formulations, prescription E2 (e.g. Estrace, Gynodiol) — the most potent form of estrogen clinically proven to alleviate the symptoms of menopause and available in several modes of delivery, and progesterone (e.g. Prometrium) are available and approved by the Food and Drug Administration. Frequently it takes several months to get the dosages

exactly tailored to the individual's needs. This way, the "one-pill-fits-all" approach is avoided entirely.

We agree with Ms. Somers that part of this tailoring includes the person's own choice about cyclic or combined therapy (i.e. continuing to have periods, versus inducing uterine atrophy and maintaining amenorrhea). Either way is acceptable. It is entirely up to the woman. However, Ms. Somers, under the care of Dr. Schwarzbein, has made the decision to menstruate the remainder of her life, maintaining continued E2 exposure and putting herself at higher risk for breast cancer recurrence. That is her choice. Contrary to Ms. Somers' philosophy, even natural hormones have potential side effects. There is no doubt that with E2 as part of the replacement regimen, vasomotor instability and symptoms of vaginal atrophy, plus the indirect effects of both, will be alleviated, likely improving overall quality of life.

However, to encourage women to take BHRT to lose weight, as Ms. Somers does, is giving false hope to millions of perimenopausal/menopausal women. There is no proof that BHRT are weight-loss pills, but it is well documented that hormone replacement therapy of any form can smooth out the menopausal transition.

In light of the media-hyped results of the WHI, which dissuaded many women from all hormone replacement therapy, we applaud Suzanne Somers for encouraging women in the second half of life to discuss BHRT with their medical providers. Risk assessment at the time of this discussion is strongly encouraged. There is no reason to suffer through the severe symptoms of perimenopause/menopause. Whether the preparations are compounded or commercially formulated, BHRT can help women maintain physical and emotional well-being through this transition. However, it is good medicine to dismiss as false advertising Ms. Somers' claims that BHRT is the key to helping women lose weight and remain young the rest of their lives, without any adverse side effects. The claims are grounded only in her personal experience and a few testimonials, with no scientific support.

Scientific Interpretation of Bioidentical Hormone Administration Concept:

The thesis proposed by Ms. Somers is that patients should be given the hormone that is normally made in the body, rather than alternatives, and that measurements of those hormones should be made to guide therapy. She emphasizes the use of 17-beta-estradiol and progesterone, as bioidentical hormones, rather than Premarin as an estrogen alternative or synthetic progestins as progesterone alternatives. This concept is sound, although not yet proven by compelling data from clinical trials.

To endocrinologists, the concept of synthetic, bioidentical hormones is appealing, because it is analogous to the approaches that are now uniformly taken with respect to thyroid hormone replacement. Endocrinologists no longer use desiccated thyroid, but now uniformly use synthetic l-thyroxine, the bioidentical thyroid hormone. Further, it is a uniform practice among endocrinologists to measure free thyroxine as well as TSH to adjust dosages to the needs of individual patients. This is exactly what Ms. Somers proposes in her book, with respect to the estrogens and progestins.

What bioidentical estrogen and progesterone preparations are available to patients? Forms of 17-beta-estradiol approved by the Food and Drug Administration include: Estrace, given orally; transdermal estradiol patches for skin absorption; alcoholic gels with estradiol (Estrodose); vaginal tablets (Vagifem) for local use; vaginal cream (Estrace) for local use; and vaginal silastic rings (Estring). Rarely, estradiol may be administered by injection (17-beta-estradiol cypionate). Estradiol administered via any one of these methods can be measured in plasma. Progesterone preparations include Prometrium, a crystalline form taken orally, as well as intra-vaginal and IM formulations. Like estradiol, natural progesterone can be measured in plasma.

Ms. Somers recommends using compounding pharmacies to obtain 17-beta-estradiol or progesterone. This is to be discouraged, because the compounding pharmacies have less stringent quality-control methods than FDA regulations require for prescription drugs.

What data suggest that use of synthetic, bioidentical 17-beta-estradiol and progesterone is preferable to Premarin and other synthetic estrogens, such as mestranol or ethynylestradiol, or that Prometrium is superior to synthetic progestins? The data here are largely lacking. There are exceptions. Recent studies have carefully examined the dose response effect of 17-beta-estradiol on bone. These studies indicate that very low treatment doses (i.e., as low as 15 micrograms per day) will increase bone density and prevent bone loss. No studies have examined the relationship between blood levels of estradiol and relief of hot flashes.

Regarding progesterone, there are no systematic data from controlled studies suggesting that progesterone is preferable to the synthetic progestins. However, a very recent study in the French literature finds an increase in breast cancer risk with use of estrogen plus synthetic progestins, but not with estrogen plus crystalline progesterone (Fournier A, Berrino F, Riboli E, Avenel V and Clavel-capelon F. Breast Cancer Risk in Relation to Different Types of Hormone Replacement Therapy in the E3N-EPIC Cohort. *International Journal of Cancer*, 2005; 114:448-454).

Based upon this analysis, while the concept of bioidentical hormone replacement is sound, the data to convincingly demonstrate its superiority to usual methods are lacking.

Myth or Fact: Ms. Somers' Recommendations:

Ms. Somers' statements are in italics

MYTH:

- *Weight loss programs will not work in menopausal women unless hormone replacement is given.*

- *Bioidentical hormone replacement, BHRT, along with compliance with her fitness and dietary recommendations, are the solution to "controlling weight, avoiding diseases of aging, and restoring energy, vitality, a youthful glow, sexuality, a slim figure, a good attitude, healthier bones, a healthier heart and a healthier brain."*
  (This statement is partially correct, but her claim is all inclusive and, at least for heart disease, probably incorrect.)

- *Synthetic alternatives to 17-beta-estradiol (Premarin, Prempro) are uniformly harmful, because they are not bioidentical.*
  (Many of the deleterious effects of hormone replacement are due to the class of the biological nature of estrogen and progesterone.)

- *Prempro is harmful because it causes a high insulin state.*
  (In fact, the WHI (randomized, controlled study of 16,608 women) showed that Prempro reduced the incidence of diabetes, when compared to placebo, and caused no change in insulin level, but it reduced the level of insulin resistance, as determined by HOMA-IR. (Morgolis KL et al. Effect of oestrogen plus progestin on the incidence of diabetes in post-menopausal women: results from the WHI Hormone trial. *Diabetologia*, 2004;47:1175–1187.) Another smaller study on fewer than 105 women showed a minor decrease in insulin sensitivity of 17 percent at two years. (Cites CK et al. The effect of hormone replacement therapy on body composition, body fat distribution, and insulin sensitivity in menopausal women: a randomized, double blind, placebo-controlled trial. *JCE&M*, 2005;90:2701–2707.)

- *Weight gain at menopause is due to estrogen deficiency.*
  (Actually, Prempro did not significantly change body mass index after one year of use and slightly increased this parameter after three years of use of Premarin and Provera in the WHI study, in the *Diabetologia* study cited above.)

- *Bioidentical hormones are not drugs and therefore cannot have harmful effects.*
  (The harmful effects of 17-beta-estradiol are universal, regardless of whether the preparation is bioidentical or synthesized.)

- *Adjustments in BHRT doses are symptom-driven, not necessarily based on the actual level of hormones.*
  (Normal ranges for estradiol and progesterone have been established for post-menopausal women, but the optimal blood level of these hormones during replacement therapy to enhance benefit and reduce risk has not.)

FACT:

- *Women should be encouraged to discuss bioidentical hormone replacement therapy and voice questions concerns about the menopause with their medical providers.*

- *Tailoring of therapy to the individual patient is appropriate.*
  (It is true that some women may only need local vaginal estrogens to alleviate dyspareunia and need not be subjected to the risks of systemic estrogen.)

- *The "one-pill-fits-all approach" is not the best way to manage menopause.*

- *Bioidentical hormones are synthesized in the laboratory and are "natural" compounds, exact replicas of the hormones produced by a woman's ovaries.*

- *Monitoring of blood levels of administered estradiol is beneficial in the patients who are not responding well to therapy.* ■

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Diabetes care for patients, including those in the hospital, should be managed by a team and tackled aggressively from the outset, according to two experts from the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK). They spoke in Grand Rounds presentations in May at the Bethesda campus of the National Institutes of Health.

NIH EXPERTS Present Latest Best Ways to Manage DIABETES

By Cathy Kristiansen

"Aggressive management of any patient with diabetes is very beneficial," said David Harlan, M.D., Chief, NIDDK's Islet and Autoimmunity Branch. "Physicians and patients should strive to achieve tight control early and maintain it…It is not acceptable to have blood glucose of 180 (mg/dl), measurable day after day."

Speaking more specifically about treatment options available for optimal blood sugar control was Kristina I. Rother, M.D., Senior Staff Clinical Investigator in NIDDK's Islet and Autoimmunity Branch, whose theme was: "Don't shy away from using insulin."

Dr. Harlan based his comments on three landmark studies, each a prospective, randomized intervention trial with at least 1,000 patients. The first was: The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *NEJM*, 1993; 329:977-986.

In this study, the researchers examined whether intensive treatment to maintain blood glucose concentrations close to the normal range could decrease the frequency and severity of long-term microvascular and neurologic complications in patients. The trial involved 1,441 patients with type 1 diabetes divided into two groups: those with retinopathy and those without. Within each group, half the subjects received conventional therapy of one to two insulin injections per day and daily self-blood glucose monitoring, and the other half received intensive insulin therapy of three or more daily injections (or insulin via a pump), more frequent self monitoring of their blood glucose, hospitalization to teach the intensive regimen and monthly clinical visits.

In the intensive treatment group, about 70 percent of patients attained good glycemic control. The closer the blood glucose was to normal, the more likely retinopathy progression was avoided, and the more delayed and diminished was the risk of microalbuminuria and other end points. "After this study, it was no longer acceptable to have anything less than the best glycemic control possible for any patient," Dr. Harlan said, although he acknowledged that delivery of the proper care remains difficult for both the patient and the care-delivery team. "Still today, the health care system is not well suited to manage patients with type 1 diabetes," he said.

Looking at care of type 2 diabetes, Dr. Harlan cited a British study (U.K. Prospective Diabetes Study, *Lancet*. 1998;352:837-853) involving about 5,000 patients, investigating whether intensive treatment could help control blood sugar levels. For this study, patients who were not hyperglycemic and needed immediate treatment were given time to control their blood sugar with diet. Then these patients received either conventional treatment or "intensive" treatment, the latter consisting of a sulfonylurea or insulin. Although the treatment was considered intensive at the time, by current standards the blood glucose control was not optimal. The study showed that type 2 diabetes is a progressive disease, in that sugar levels tended to increase over time in both the conventional and intensive treatment arms. Even so, those under intensive treatment attained better blood sugar levels compared with those in the conventional group, which resulted in better kidney function and fewer microvascular complications.

Dr. Harlan cited a third study that focused on 1,548 patients admitted to the University of Leuven, Belgium, intensive care unit: Van den Bergh et al. Intensive insulin therapy in critically ill patients. *NEJM*, 2001;345:1359-1367. The study enrolled ICU patients who were on mechanical ventilation; most were in the ICU after cardiac surgery. Dr. Harlan noted there are ample data showing that individuals with diabetes have a two to four times greater chance than the general population of requiring hospitalization and that, if hospitalized, their stays average about 30 percent longer. Moreover, hospitalized patients with diabetes are two to three times more likely to die than patients without diabetes.

In the study, only 13 percent of patients had a history of diabetes. Patients were randomized to intensive treatment and were started on intravenous insulin if their fasting blood sugar level was greater than 110 mg/dl. Patients randomized to more conventional treatment were not started on insulin unless their blood glucose was higher than 215 mg/dl. Under intensive treatment, patients maintained an average blood sugar level of 102 mg/dl, while those conventionally treated had blood sugars that Dr. Harlan noted would not alarm too many intensive care unit physicians, 152 mg/dl on average.

The intensively treated patients had a marked decrease in mortality, whether they had a history of diabetes or not. These patients also had fewer bacteremia incidents, required antibiotics less often, had shorter requirements for mechanical ventilation, suffered less critical illness polyneuropathy, received fewer blood transfusions and had shorter intensive care unit stays. "You start seeing significant improvements in survival, based on how well glycemia was controlled," Dr. Harlan said. He stressed that it is much easier to achieve glycemia control in an intensive care setting than in a general hospital setting.

"Individuals with diabetes have a two to four times greater chance than the general population of requiring hospitalization. If hospitalized, their stays average about 30 percent longer. Moreover, patients with diabetes are two to three times more likely to die once hospitalized than patients without diabetes."

He made an additional point: Early studies suggest that such intensive treatment is cost-effective. For instance, data from the University of Wisconsin Diabetes Management Service suggest that patients with diabetes coming in for coronary artery bypass grafting have shorter hospital stays and much less expensive hospitalizations if they receive specialized diabetes service team care. "We need a specialized team approach so we can properly care for the patients who are hyperglycemic," Dr. Harlan said.

Elaborating on the benefits of using insulin in diabetes care, Dr. Rother said she supports the use of insulin pumps very early after the diagnosis of type 1 diabetes in both children and adults. She mentioned other convenient and patient-friendly devices for the administration of insulin, such as insulin pens, and listed indications for the use of insulin in patients with type 2 diabetes. For example, people whose blood sugar is totally out of control should receive insulin at the beginning.

In deciding which type of insulin to give, Dr. Rother favored fast-acting insulins, such as lispro and aspart. The patient can inject, then eat right away, which improves compliance.

Dr. Rother analyzed the various diabetes drugs available:

- Sulfonylureas, introduced in the 1950s, work by binding to a small protein on the surface of insulin-

producing beta cells, called ATP sensitive potassium channel. However, potassium channels are also present in the heart and play an important role in cardiac functions such as adaptation to stress. It is quite reassuring that large studies (for example, the UK Prospective Diabetes Study) have shown no increased cardiovascular risk from sulfonylureas, although some smaller trials still suggest negative effects, she noted.

- Agents that inhibit carbohydrate absorption, such as acarbose and miglitol, are less effective than some other drugs and are rarely used as monotherapy.
- Agents that reduce hepatic output: Metformin is a great drug, but there are certain circumstances, such as reduced kidney function, when it cannot be given.
- Insulin sensitizers or thiazolidinediones are successful in patients with type 2 diabetes. They have a positive effect not only on blood sugar control, but also on lipids, and may help lower blood pressure. However, contraindications include conditions such as congestive heart failure, and prescribing doctors need to take into account the drugs slow onset of action and their somewhat higher costs compared with other drugs, such as sulfonylureas.

Dr. Rother noted that by treating other illnesses more effectively, we have "created" new types of diabetes, such as in patients who have received a transplanted organ and in patients with HIV. Regarding alternative medications, she urged physicians to ask patients whether they are taking any, specifically some that may have a glucose-lowering effect. These include bitter melon, cinnamon, fenugreek, ginseng, ivy gourd, and l-carnitine. Another supplement, ginkgo biloba, may actually increase blood sugar, she said, referring to a small study done in 20 patients with type 2 diabetes.

Regarding newly available drugs, Dr. Rother discussed pramlintide acetate, which was approved in March for patients with type 1 and 2 diabetes who take insulin. It is to be injected before meals. It delays gastric emptying and lowers the glucose rise associated with meals. Exenatide, another injectable medication, available for patients with type 2 diabetes, increases insulin secretion and lowers glucagon levels. The NIH team is conducting a clinical trial in which it uses exenatide for another reason and in a different patient population; to test whether it can stimulate beta cell growth and differentiation in people with type 1 diabetes.

Dr. Rother concluded with her recommendation that physicians should always treat patients immediately and take an individualized approach based on factors such as whether the patient is sick and hospitalized, the patient's liver and kidney function, and whether the patient is likely to comply well by taking medicine. "Don't focus on just glucose," she said. Last, she noted, physicians should make extensive use of the teaching capacity available from nursing staff, dieticians, pharmacists and social workers. ■

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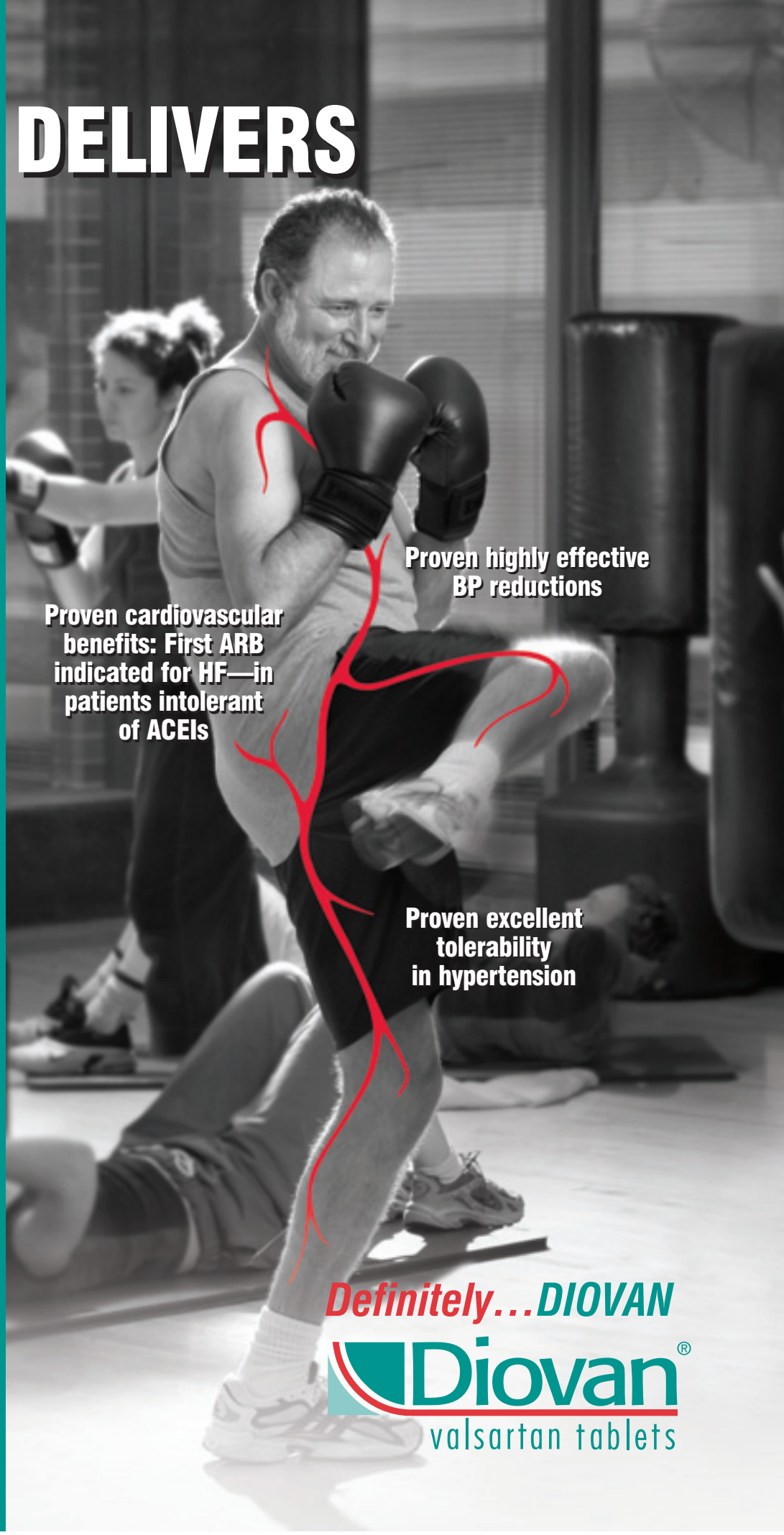

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, DIOVAN should be discontinued as soon as possible. See **WARNINGS** in brief summary of complete Prescribing Information on next page.

DIOVAN is contraindicated in patients who are hypersensitive to any component of this product.

Because of the risk of hypotension, caution should be observed when initiating therapy in HF patients. Evaluation of HF patients should always include assessment of renal function. In patients with Heart Failure, concomitant use of DIOVAN, an ACE inhibitor, and a beta-blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable Heart Failure outcome.

In Val-HeFT, discontinuation due to adverse events was 10% for valsartan vs 7% for placebo; most common side effects were: dizziness (17% vs 9%), hypotension (7% vs 2%), and diarrhea (5% vs 4%).

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USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.
See ***WARNINGS: Fetal/Neonatal Morbidity and Mortality.***

INDICATIONS AND USAGE: Hypertension: Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Heart Failure: Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. *(See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information for details.)*

CONTRAINDICATIONS: Diovan® (valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS: Fetal/Neonatal Morbidity and Mortality: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan® (valsartan) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hypotension: Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hypotension in Heart Failure Patients: Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients.

PRECAUTIONS: General: ***Impaired Hepatic Function:*** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan® (valsartan) to these patients.

Impaired Renal Function - Hypertension: In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Impaired Renal Function - Heart Failure: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). Evaluation of patients with heart failure should always include assessment of renal function.

Concomitant Therapy in Patients with Heart Failure: In patients with heart failure, concomitant use of Diovan, an ACE inhibitor, and a beta blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable heart failure outcome *(see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information).*

Information for Patients: ***Pregnancy:*** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli;* a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Pregnancy: ***Pregnancy Categories C (first trimester) and D (second and third trimesters):*** *See WARNINGS, Fetal/Neonatal Morbidity and Mortality.*

Nursing Mothers: It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.

ADVERSE REACTIONS: Hypertension: Diovan® (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole: Allergic reaction and asthenia; ***Cardiovascular:*** Palpitations; ***Dermatologic:*** Pruritus and rash; ***Digestive:*** Constipation, dry mouth, dyspepsia, and flatulence; ***Musculoskeletal:*** Back pain, muscle cramps, and myalgia; ***Neurologic and Psychiatric:*** Anxiety, insomnia, paresthesia, and somnolence; ***Respiratory:*** Dyspnea; ***Special Senses:*** Vertigo; ***Urogenital:*** Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Heart Failure: The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse events vs. 7% of placebo patients.

The table shows adverse events in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)		Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%	Back Pain	3%	2%
Hypotension	7%	2%	Dizziness, postural	2%	1%
Diarrhea	5%	4%	Hyperkalemia	2%	1%
Arthralgia	3%	2%	Hypotension, postural	2%	1%
Fatigue	3%	2%			

Other adverse events with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.

Post-Marketing Experience: The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: There are rare reports of angioedema; ***Digestive:*** Elevated liver enzymes and very rare reports of hepatitis; ***Renal:*** Impaired renal function; ***Clinical Laboratory Tests:*** Hyperkalemia; ***Dermatologic:*** Alopecia.

Clinical Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan-treated patients compared to 0.9% of placebo-treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan-treated patients compared to 6.3% of placebo-treated patients.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

[see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

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Spotlight On…
Free Public Access to Research: Who Really Pays?

By Endocrine News staff

The debate over free access to science has raised many issues, including that of government encroachment on private enterprise and copyright infringement. But it also begs one important question: If it's a free lunch, who pays the cook?

In May, the National Institutes of Health (NIH) instituted a policy requesting researchers who receive NIH funding to submit their resulting reports to the agency's online repository, PubMed Central (PMC), upon peer review and acceptance by a publisher.

The author designates when the uncopy-edited manuscript may be posted at PMC for open access to the public.

According to Elias Zerhouni, NIH Director, "For the first time, the public will have access to peer-reviewed research publications that result from studies funded by NIH, and scientists will have a new pathway to make their NIH-funded research known to the public that funded it. … The policy creates a permanent archive to preserve vital research findings, which will be a searchable compendium of these research publications."

While agreeing with the overall goals of the NIH policy, many in the scientific publishing industry view its implementation as poorly planned and as usurping the scientific publisher's role. For more than a century, biomedical specialty organizations have been the outlet for scientists publishing research. Publishers pay for rigorous peer review to select the best papers, then to copy-edit, compose, code electronically, and distribute them in print and online versions.

Why has the NIH Assumed the Role of Quasi-Publisher?

Much of the impetus for open access has come from Capitol Hill, with patient advocacy constituents complaining about the perceived high cost of accessing medical information. Also exerting pressure are libraries, academic institutions and hospitals — the traditional purveyors of scientific content to physicians, researchers and students.

> **"The cost of producing an article … is closer to $3,000, not $1,500."**
>
> **Lenne Miller, The Endocrine Society**

Then, 2004 saw another shift in the publishing industry, when a relatively small but vocal group of scientists, claiming the scientific publishing model was a rampant monopoly, established a new publishing venture, the Public Library of Science (PLoS). Aided by a private $9 million grant, the PLoS eschews traditional "user pays" subscription-based publishing and instead advocates a model in which content is free to the public, but authors pay $1,500.

In heralding the PLoS launch, the media tarred all publishers, commercial as well as not-for-profit, with the same brush, failing to distinguish between increasingly expensive for-profit publications and historically low-priced not-for-profit publications from organizations that use publishing revenues to further science.

The viability of the "author pays" model remains unproven, and once the grant runs out, authors' fees may not be enough to sustain it. According to Lenne P. Miller, Senior Director of Publications at The Endocrine Society, the cost of producing an article, including peer review, copy-editing, and online production tasks, such as searching and linking tools, "is closer to $3,000 per article, not $1,500."

If nonprofit publishers like The Endocrine Society, The American Physiological Society and the American Association for Cancer Research cannot recoup what they spend adding significant value to research papers, one can envision that they might compensate by publishing fewer papers, discontinuing their journals, or, ultimately, leaving the publishing business. And without the revenue generated by publications, many scientific society programs could disappear.

When the NIH announced its public access plan, a host of not-for-profit society publishers publicly supported its goals, while attempting to dissuade the NIH from spending vast sums to "reinvent the wheel."

According to Stanford University's Director of Academic Information Resources, Michael Keller, "HighWire Press is a high-quality, successful, and not-for-profit Internet publishing service part of the Stanford University Libraries. The nearly 120 not-for-profit publishers associated with HighWire Press offer the largest free collection of articles in the world in the life sciences and medicine, currently almost 900,000 free articles. Abstracts of all articles from these

publishers are free on HighWire." Access to an additional 14 million articles from 4,500 journals is available as pay-per-view for a typical price of $10 to $30.

The Endocrine Society's Role

The Endocrine Society, which has four peer-reviewed publications, has led the way in providing unrestricted access to content. Papers are posted free to the world on the Society's *Journals Online* Web site, immediately upon acceptance for publication. These uncopyedited manuscripts remain free, even after the final version is published. Then all edited content is free after 12 months. The Society spends $5 million per year to publish its four journals, recouping the costs through subscriptions.

Says Miller, "In essence, The Endocrine Society has been doing for years what the NIH is trying to accomplish via Federal mandate. We have been working with the NIH to persuade them to tap into the existing resources that we and other society publishers already provide to accomplish its goals. We are concerned about the burdens placed on our authors, but we must protect the asset without which the Society could not function financially — our content."

Some experts in the publishing industry have also construed the NIH open access policy as a dangerous encroachment into copyright ownership. The NIH has cited the "Federal Purpose" statute to justify open publication of copyrighted content.

Publishers like The Endocrine Society say they can continue to exist only if they continue to own the content they invest many millions of dollars to publish. "The universal elixir has always been the wrong goal," Keller has said. The key to this issue may yet be found in continued dialogue between the NIH and scientific publishers.

Authors' Guidelines for NIH Articles

By The Endocrine Society Publishing Oversight Committee

April 26, 2005

Dear Authors of The Endocrine Society Journals:

The United States National Institutes of Health will soon implement a new policy that will affect some of our authors. For articles published on or after May 2, 2005, that report original research (not

reviews), supported in whole or part by the NIH, the NIH requests that the authors provide it with an electronic copy of the manuscript accepted for publication. This is not a requirement, but a request intended by the NIH to do the following:

1. Replace reporting requirements for NIH grantees previously fulfilled by submitting manuscripts as part of the annual grant renewal process.

2. Be a part of a central resource through which the public may view publicly funded research.

The Endocrine Society appreciates that our authors are our journals' greatest resource. This letter is intended to help our authors become familiar with NIH's new reporting request, details of which are to be posted by the NIH at *http://nihms.nih.gov*.

How Authors May Comply with the NIH Policy

- The manuscript provided by authors must be in its "preprint" form. It is the accepted, unedited manuscript, exactly like what The Endocrine Society publishes online and free of charge as a "Rapid Electronic Publication."
- As the author-grantee principal investigator, you must submit your accepted manuscript at a secure Web site, following the NIH file format requirements (a wide range of electronic word processing formats or PDF). For a full description of the submission procedures, please visit the PubMedCentral (PMC) Web site at *http://nihms.nih.gov*. After you submit your manuscript to PMC, PMC will reconfigure it to comply with a standard PMC format (i.e., on PMC it is likely to look different from your accepted manuscript on The Endocrine Society Rapid Electronic Publications site).
- When you submit manuscripts to PMC, the NIH requests that you (only the principal investigator may do this) designate when your accepted, unedited manuscript may be posted on PMC for public access. This designation will be in the form of a delay period from final publication by the publisher, for example, a delay of up to 12 months after print (final) publication of the article by the publisher. The Endocrine Society permits, and requests, that you designate no delay after the date of print (final) publication by The Endocrine Society. Note that PMC will be able to determine the date of print (final) publication. The author need not do anything after submitting the preprint manuscript.
- The Endocrine Society will be

unable to submit manuscripts on the author's behalf. Therefore, the author must fulfill his/her reporting requirements with PMC. However, The Endocrine Society will be allowed and may choose later to replace the author's unedited manuscript in PMC with The Endocrine Society's final version of the article or, preferably, a link back to the author's article on The Endocrine Society Web site. You, as the author, may not submit the final, copyedited article to PMC.

- Copyright remains with The Endocrine Society, which invests time and effort in reviewing the accepted manuscript, printing and posting online the final edited version of the manuscript, and archiving your research findings.

Author Instructions from Endocrine Society Journals Regarding Compliance With the NIH Policy

It is important for our authors to recognize that, once your manuscript is accepted, it will be prepared for online distribution. This final accepted article cannot be modified when you submit to PubMedCentral. Therefore, we ask that you prepare this manuscript in the understanding that it will appear unaltered after submission and acceptance. You will also be provided with instructions from the editor-in-chief to include a statement on the title page indicating that this is not a copy-edited version of the manuscript.

If the work described in your manuscript has been supported in whole or in part by the U.S. National Institutes of Health, in the editor-in-chief's letter to you requesting any revision, you will be *required* to insert the following phrase on the title page of all articles, typed immediately after the authors' affiliations: "This is an uncopy-edited author manuscript, copyright The Endocrine Society. Cite this article as appearing in (name of Journal, publication year). This may not be duplicated or reproduced, other than for personal use or within the rule of "Fair Use of Copyrighted Materials" (section 107, Title 17, U.S. Code) without permission of the copyright owner, The Endocrine Society.

From the time of acceptance after peer review, the full text of this manuscript is made freely available by The Endocrine Society at *http://www.endojournals.org*. The final copy-edited article can be found at *http://www.endojournals.org*. The Endocrine Society disclaims any responsibility or liability for errors or omissions in this version of the manuscript or in any version derived from it by the National Institutes of Health or other parties."

> **"It is important for our authors to recognize that, once your manuscript is accepted, it will be prepared for online distribution. This final accepted article cannot be modified when you submit to PubMedCentral."**

There are several important reasons we ask you to do this. Most important to you, as an author, is that we want the citations to your article to be accurately recorded and counted. Also, we believe it is essential that the reader at the PMC site know that your accepted manuscript is not the final version of record (after the copyediting and your corrections) and that the reader be directed to the final version of your article on The Endocrine Society journals online Web site with all of the reference linking, advanced searching, and other tools that make your article an integral part of the scientific record.

The Endocrine Society Supports Sustainable Open Access

The Endocrine Society supports the widest possible dissemination of science. Under current practice, accepted manuscripts are posted immediately after acceptance and free of charge as Rapid Electronic Publications at our Journals' online Web site. Your published manuscripts therefore already are openly available to the research community and to the public at The Endocrine Society journals online Web site, independent of any dissemination through PMC.

Our own Open Access policy was implemented only after a decade of considerable planning, effort and financial cost. It represents a publication model now being tested.

We continue to monitor any effect that model may have on the continued success and viability of The Endocrine Society and its journals. As such, even though The Endocrine Society operationally supports Open Access more than most other publishers, we fully support the right of our fellow publishers to decide when publications can be made available.

This is the policy as of this writing. We will keep you apprised of any changes in the NIH policy or procedures. If you have questions about the specific NIH submission requirements, please see *http://nihms.nih.gov*. For questions regarding The Endocrine Society policies, please contact the editorial office of the journal to which you are submitting. ■

Coding News: Society Volunteers Participate in the RUC and CPT* Processes

By Richard A Dickey, MD, FACP, FACE

The Endocrine Society needs to increase its involvement in the Resource-Based Relative Value Scale Update Committee (RUC) and Current Procedural Terminology (CPT) processes, which are essential for determining the proper descriptions and valuation of services that clinical practice members provide. This will be possible only when an adequate number of Society members volunteer to do the work involved. The support and presence of staff members at RUC and RUC-related group meetings has been helpful, but physician RUC advisory positions need filling. Anyone seeking to take over the Society's CPT and RUC adviser roles, or anyone who volunteers as an alternate RUC adviser volunteer, will receive ample help from me. Recently, Richard A Guthrie, MD, volunteered to be the Society's alternate CPT physician adviser.

Coding and Reimbursement Workgroup Formed

The Society has formed a coding and reimbursement workgroup composed of members and coordinated by the Clinical Affairs Committee (CAC), but it needs additional volunteers. The workgroup includes several CAC member volunteers, the RUC and CPT advisers, and CAC staff.

RUC Activities

In the current five-year review process, the Society has joined a group of more than two dozen so-called 'cognitive' specialty societies (non-surgical specialty societies), in requesting that the Centers for Medicare and Medicaid (CMS) reassess the physician work values for most evaluation and management (E/M) codes. Participation in the RUC survey of valuation of services by Society members is growing, reflecting well on the Society's involvement in the RUC process. The cognitive specialties are now involved in analyzing survey results and the developing recommendations for new values in this five-year review cycle—the third cycle. Society members' participation in the required surveys was critical to accumulating the data. The financial impact of changes in the value of these services will be of major importance to our field, which heavily uses the E/M codes (including those for office visits, hospital care and consultations). Revisions in values will appear in the physician fee schedule, beginning in 2007.

CPT Activities

The unreasonably low reimbursement for blood sampling/venipuncture (CPT codes 36400 and following) for laboratory tests has not been rectified, even though the actual practice expenses for this work were presented to the RUC by our Society. An old agreement between CMS and clinical laboratories is suspected of restraining fair reimbursement for this service. This was recently brought to the attention of the RUC and CMS.

A three-member Society panel (Howard Baum, MD, Ted Bransome, MD, and Richard Dickey, MD) recently identified outdated/obsolete CPT codes. The American Medical Association (AMA) now requests that detailed forms to explain the reasons for proposing deletion of these codes from the CPT list be completed and presented to the CPT Editorial Panel. Society volunteers are needed for this work.

Last year The Endocrine Society proposed changes in the multidisciplinary team conference codes (CPT codes 99361 & 99362). A workgroup was convened at the annual CPT advisers meeting, chaired by a member of the CPT Editorial Panel (Helene Fearon, PT) and Dr. Dickey. The assistance of another CPT Editorial Panel member (Peter Hollman, MD) was very helpful. The workgroup, of a consortium of professional society representatives, has developed a comprehensive proposal for a series of new codes, which are being presented to the CPT panel this year.

When the panel recently decided against accepting the Society's proposed editorial changes for laboratory result interpretation and reports (CPT codes 80500 & 80502), the Society appealed to the panel, which invited a more detailed proposal. The goal is to allow the clinical endocrinologist and others performing similar interpretations and reports to use these codes (e.g., for evocative and suppression test panels). The current code description mentions only pathologists as performing this service. The Society is seeking members willing to assist with the development of a detailed proposal on this topic.

Members interested in assisting as volunteers for the RUC or CPT activities should contact Janet Kreizman at *jkreizman@endo-society.org*. ■

* *CPT is a trademark of the American Medical Association. All Current Procedural Terminology (CPT) five digit numeric codes, descriptions, numeric modifiers, instructions, guidelines, and other material are Copyright 2003 American Medical Association. All Rights Reserved.*

The Endocrine Society's Clinical Guidelines — Coming Soon!

The Endocrine Society is pleased to announce the development of rigorous evidence-based, independently supported clinical practice guidelines. They are distinguished by a level of scrutiny and examination that are unmatched in the field of endocrinology and metabolism.

Content is written by leaders in the major areas of endocrinology, using evidence-based methodologies, incorporating clinical evidence grading, expert opinion and stringent peer-review. The five-step development process is as follows:

1. The Endocrine Society's Clinical Guidelines Subcommittee (CGS) selects guideline topics.
2. An expert task force writes the guideline and incorporates evidence-based reviews.
3. The guidelines are reviewed by the CGS, the Clinical Affairs Committee and Council.

> "They are distinguished by a level of scrutiny and examination that are unmatched in the field of endocrinology and metabolism."

4. Guidelines are posted on the web for member review and comment.
5. Guidelines are submitted to ***The Journal of Clinical Endocrinology & Metabolism (JCE&M)*** for peer-review and publishing.

The extensive process that goes into creating the clinical guidelines not only provides validation and assurance, but also raises the standard for the development of guidelines for clinical practice everywhere.

Guidelines on the following topics are under preparation:

- Evaluating and treating growth hormone deficiency in adults.
- Testosterone therapy in men with androgen deficiency.
- Thyroid disease in pregnant and postpartum women.
- Metabolic Syndrome.
- Pediatric obesity.
- Role of androgens in women.

Look for news on the publishing of The Endocrine Society's clinical guidelines in the coming months. ■

ENDOCRINE Society update

Jobs

➤ Got a job to fill? Searching for the right endocrinologist?

Advertise in *Endocrine News*!

The *Classifieds* section offers universities, research laboratories and private practice offices a place to list their openings.

Your information will reach more than 33,000 readers and be posted online for job seekers to find.

And don't forget to search our complimentary online CV Database at *www.endo-society.org/placement services*.

With these resources, you can't miss! For more information contact Christine Whorton at *placement@endo-society.org* or call 1-800-361-3906.

2004 Outstanding Reviewers *Molecular Endocrinology*

➤ The editors of ***Molecular Endocrinology*** have selected the following people as the outstanding reviewers for the journal in 2004. The dedication and expertise of these reviewers are greatly appreciated. Congratulations to:

- Michael J. Garabedian, Ph.D.
- Gary D. Hammer, M.D., Ph.D.
- Robert A. Nissenson, Ph.D.
- Peter J. Tontonoz, M.D., Ph.D.

News Flash

➤ Over the past few months the Society's promotional activities have led to major news coverage of endocrine research and patient care. Here are several examples of news coverage:

- The May 9 issue of *Newsweek* featured a Letter to the Editor on obesity, written by Society member Henry Anhalt, D.O. Dr. Anhalt recommended addressing the disease "on all fronts" and not just blaming one factor for the epidemic.
- On May 4, *Medical News Today* reported a study highlighted in ***The Journal of Clinical Endocrinology & Metabolism (JCE&M)*** on Post-Traumatic Stress markers passed on from mothers who witnessed the 9/11 attacks to their unborn babies.
- The May 1 issue of *Diabetes Forecast* informed readers about a study explained in ***JCE&M*** that concluded that people with Asian Indian ancestry are at a higher risk for type 2 diabetes.
- A March 22 report from *Reuters Health* cited ***JCE&M*** for its study of the effects of light drinking. Consuming small amounts of alcohol appears to improve factors associated with the risk of diabetes and cardiovascular disease.

The Society is also actively seeking media spokespersons and is willing to provide media training for members who are interested. *For more information, contact Tadu Yimam, Coordinator, Public Relations, at media@endo-society.org.*

2005 Clinical Investigators Workshop for Trainees – Applications Available

➤ The Endocrine Society is pleased to announce that applications are available for the 2005 Clinical Investigators Workshop for Trainees. Building on the success of the 2004 workshop, this year's program will continue to focus on introducing a small, select group of clinical fellows to hypothesis-driven clinical and translational research. Led by leaders in endocrine clinical research, the workshop is specially designed to foster one-on-one interaction between participants and senior clinical scientists while also providing a knowledge base for the fellows to develop their clinical research careers. The 2005 faculty includes the following leaders in the field: David Altshuler, M.D., Ph.D.; Robert M. Carey, M.A.C.P., M.D.; Robert G. Dluhy, M.D.; Steven Grinspoon, M.D.; Janet Hall, M.D.; Mark Hartman, M.D.; James F. Hyde, Ph.D.; Ursula Kaiser, M.D.; Joan Lakoski, Ph.D.; David Nathan, M.D.; Ora H. Pescovitz, M.D., and Ellen W. Seely, M.D.

The 2005 workshop will be held in Boston at the Hyatt Regency Downtown. The program begins Friday afternoon, November 11, 2005, with sessions about career paths and goals. Saturday's program will be devoted to research resources and pathways and will include critiques of research proposals presented by the fellows. The program will conclude midday on Sunday, November 13, 2005 with sessions on making a successful transition from a fellowship.

To preserve the interpersonal nature of instruction, the 2005 workshop will be limited to 40 trainees. **Trainees wishing to participate must be nominated by their program directors. Nominees must have an M.D. or M.D./Ph.D. and must be currently enrolled in an endocrinology training program anywhere in the world.** Program directors are encouraged to nominate individuals in their fellowship program who meet the specified criteria and whose education would be most enhanced by attending the workshop. Nominations must be received in The Endocrine Society office no later than July 25. The Student Affairs Committee will evaluate each applica-

tion and select 40 fellows to attend the workshop. The Society will email the selection results to all nominees and program directors by September 1. Selected fellows will receive complimentary lodging and meals. Fellows are responsible for their travel and a nominal registration fee. For the full program and an application, please visit the Society's Web site at *http://www.endo-society.org/awards/awardsgrants*.

The Endocrine Society would like to thank the following supporters for their contributions to the 2005 workshop: Bristol-Myers Squibb; Genentech, Inc.; Novo Nordisk Pharmaceuticals; Takeda Pharmaceuticals North America, Inc.; and Theratechnologies, Inc.

Questions may be directed to Colleen Gorman at 301-951-2611 or awards@endo-society.org.

New Horizon for The Hormone Foundation

➤ In accordance with the *Hormone Foundation Committee Creation Plan*, approved by The Endocrine Society's Council on January 8, 2005, The Hormone Foundation has changed its governance structure from a Board of Directors to a committee of the Society. The newly formed Hormone Foundation Committee (HFC) reports directly to Council.

The HFC chair is Lisa Fish, M.D., a former two-term member of the Foundation Board. HFC membership includes a broad range of experts from all over the country. The committee benefits from a mix of members with Foundation experience and members new to The Hormone Foundation, providing both institutional perspectives and new ways of addressing the mission of the Foundation.

The HFC's charge will be to identify emerging areas for public education, respond to those opportunities and assist the Foundation staff with the development of proposal concepts. The HFC will also identify and supervise directors for projects in their area of expertise, and work to insure high-quality content in the Foundation's programs and services. In 2005, the committee will be reviewing the direction of the Society's public education outreach through Foundation programs, making appropriate adjustments when necessary.

Lisa H. Fish, M.D., Chair
Park Nicollet Clinic, Endocrine Dept.
Robert M. Carey, M.A.C.P., M.D.
University of Virginia Health System
Michael W. Draper, M.D, Ph.D.
Lilly Research Labs
Marjorie E. Ewertz, R.N., B.S.N.
Johns Hopkins University
Robert B. Jaffe, M.D., M.S.
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Vanderbilt University School of Medicine
Mary F. Lopez, Ph.D.
Children's Hospital, Boston
Alvin M. Matsumoto, M.D.
VA Puget Sound Health Care System
Alan D. Rogol, M.D., Ph.D.
University of Virginia
Richard J. Santen, M.D.
University of Virginia Health System
Connie Trump
Abbott Laboratories
Hershel Raff, Ph.D. Council Liaison
Medical College of Wisconsin

Web site Tips

Can I still view the abstracts from ENDO 2005?

Yes. Under the Education & Events navigation item on the left-hand side, select Annual Meeting. On that page you will see all the information that is available from The Endocrine Society's Annual Meeting, ENDO 2005, including: Abstracts2View Online, CME Certificates, and tapes and audio CDs of sessions.

calendar

JULY 30 – AUGUST 4, 2005: FASEB SUMMER RESEARCH CONFERENCES* - NUTRIENT CONTROL OF GENE EXPRESSION & SIGNALING, TUCSON, ARIZ. For more information, contact Peggi McGovern at *pmcgovern@faseb.org*.

JULY 30 – AUGUST 4, 2005: FASEB SUMMER RESEARCH CONFERENCES* - RECEPTOR & SIGNAL TRANSDUCTION, SNOWMASS, COLO. For more information, contact Julie Levin at *jlevin@faseb.org*.

AUGUST 6 – 11, 2005: FASEB SUMMER RESEARCH CONFERENCES* - GLUCOSE TRANSPORTER BIOLOGY, SNOWMASS, COLO. For more information, contact Julie Levin at *jlevin@faseb.org*.

AUGUST 29 – SEPTEMBER 1, 2005: HYPOTHALAMIC INTEGRATION OF ENERGY METABOLISM, 24TH INTERNATIONAL SUMMER SCHOOL OF BRAIN RESEARCH, AMSTERDAM, NETHERLANDS. For more information, contact T. Eikelboom at *summerschool@nih.knaw.nl*.

OCTOBER 6, 2005: THYROID SONOGRAPHY HANDS-ON WORKSHOP, TORONTO, CANADA. Visit *http://endo-society.org/educationevents/ceu* or e-mail *fmoxley@endo-society.org*.

OCTOBER 7 – 10, 2005: CLINICAL ENDOCRINOLOGY UPDATE (CEU), TORONTO, CANADA. Visit *http://endo-society.org/educationevents/ceu* or e-mail *fmoxley@endo-society.org*.

OCTOBER 10 – 11, 2005: BOARD REVIEW SESSION, TORONTO, CANANDA. Visit *http://endo-society.org/educationevents/ceu* or e-mail *fmoxley@endo-society.org*.

Find much more on the Worldwide Endocrine Events Calendar at *http://www.endo-society.org*.

* Co-sponsored by The Endocrine Society

In Memoriam

Cesar Bergada, M.D.
Buenos Aires, Argentina
1929 – 2005
Melvin J. Bryson, M.S., Ph.D.
Salt Lake City, Utah
1916 – 2005
Dr. John D. Crawford, M.D.
Massachusetts General Hospital
1920 – 2005
Paul I. Jagger, M.D.
La Jolla, California
1931 – 2005
Phillip Rayford, M.S., Ph.D.
University of Arkansas
(d. 2005)
Peter Stokes, M.D.
NY Hospital/Cornell Medical Center
1926-2005 ■

If you are interested in submitting classified advertising to Endocrine News *please contact Christine Whorton at placement@endo-society.org or 1-800-361-3906.*

ENDOCRINOLOGIST FOR COASTAL NORTH CAROLINA

BC/BE endocrinologist wanted to join three well-established endocrinologists practicing 100% endocrinology in a busy 18 physician multispecialty practice. Bone densitometer, in-house laboratory, and thyroid ultrasound equipment on site. Low managed-care penetration. Located in beautiful coastal resort area of North Carolina. Competitive salary/benefits package leading to partnership. Contact Barbara Maisenhelder, CEO, Hanover Medical Specialists, 1515 Doctors Circle, Wilmington, NC 28401; telephone (910) 815-0889; fax (910) 763-0291.

PEDIATRIC ENDOCRINOLOGIST

All Children's Hospital–University of South Florida–St. Petersburg, Florida. Pediatric Endocrinology Opportunity. All Children's Hospital in collaboration with University of South Florida's Department of Pediatrics, seek a board certified/board eligible Pediatric Endocrinologist. An interest in metabolic disease is desirable, but not required. In this position, you will join USF's well established endocrinology department and participate in a shared call arrangement of one in six. Practice offers the opportunity for teaching and research with programs in growth, obesity and diabetes care. Academic rank is based upon credentials and experience. Work out of All Children's Hospital, named as one of the top 20 Children's hospitals in the U.S. by Child Magazine and Tampa Bay's #1 hospital dedicated to healing children.

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20th Anniversary of First Nuclear Receptor Cloning

By Cathy Kristiansen

Unlocking How Hormones Work

It was 20 years ago that scientists first began cloning nuclear hormone receptors, confirming for the world the existence of these cellular proteins that altered the expression of key target genes and triggered functional changes in cells, tissues and organs. Today, we know nuclear receptors make up a large class of transcription regulators in animals, regulating homeostasis, reproduction, development and metabolism. The path to these cloning discoveries, dating back decades, was peopled by scores of scientists from various biochemical and molecular fields, many of whom continue related work today.

Once scientists discovered the way to cloning nuclear receptors, they opened the door for the discovery of human nuclear receptor superfamily members, totaling about 50. These include receptors for the steroid hormones, nuclear hormones such as vitamin D, retinoic acids and thyroid hormones, and nuclear orphan receptors—amounting to about half of the total—which have no identified natural ligand.

Nuclear receptors are exciting drug targets, given that they control functions associated with major diseases, such as cancer, diabetes, depression, osteoporosis and autoimmune diseases. Furthermore, the small molecules that they bind can be readily modified by drug design. Among the many discoveries that have helped lead to therapies are those involving:

- Glucocorticoid receptor mutants, showing their connection to genetic disease predisposition.
- Estrogen receptors, providing a way to measure which breast cancers are not estrogen-dependent and should be tackled with chemotherapy, rather than endocrine ablation or antiestrogen treatment.
- Tamoxifen as the primary prototype selective estrogen receptor modulator (SERM) for breast cancer therapy. Other SERMs and new modulators for androgens, glucocorticoids and progesterone are under development.
- Receptor cooperation with oncogenes in transforming normal cells in culture. Work with the estrogen receptor in mice has helped lead to a proliferation of trials in selective ER agonists to treat autoimmune diseases (rheumatoid arthritis and inflammatory bowel disease), benign prostatic hyperplasia, prostate cancer, infertility and depression.
- The over-expression of certain coactivators and how this led to breast cancers in older mice, a finding recently matched in humans.

Pharmaceutical companies have already developed several drugs targeting orphan receptors. These include:

- Tamoxifen for estrogen-dependent breast cancer.
- Panretin and a synthetic analogue, Targretin, for cancer (approved by the Food and Drug Administration).
- Anti-diabetic thiazoladinedione compounds that work by activating PPARγ (FDA approved).
- Retonoic acid treatment for acute promyelocytic leukemia.
- LXR and FXR, which are promising new-drug targets for cholesterol and triglyceride control, but are not yet in clinical trials.
- Tests using the cloned human receptor to screen for drugs with activity that causes many drug-to-drug interactions.

The biology of nuclear receptors is very complex and scientists are working busily to expand our understanding of their receptor specificity, ligand selectivity, the role of cytoplasmic and nuclear accessory proteins, chromatin, and their transcriptional machinery. There is no question that in the next two decades, this blossoming molecular endocrinology field will bring many more discoveries and drugs to combat human disease.

In celebrating the two decades of nuclear receptor cloning breakthroughs, The Endocrine Society's peer-reviewed publication, ***Molecular Endocrinology***, in its June issue ran perspectives from five distinguished scientists chronicling their role in the discovery of the nuclear receptor superfamily. To read the articles, by Bert W. O'Malley, M.D., Jan-Åke Gustafsson, M.D. Ph.D., Pierre Chambon, M.D., Ronald M. Evans, Ph.D., and Elwood V. Jensen, Ph.D., visit http://mend.endojournals.org. ■

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