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The Prevalence of Interstitial Cystitis in Gynecologic Patients with Pelvic Pain, as Detected by Intravesical Potassium Sensitivity

ABSTRACT & COMMENTARY

THE POTASSIUM SENSITIVITY TEST (PST) WAS ADMINISTERED TO 244 patients with pelvic pain and 47 control patients by enrolling gynecologists at 4 separate facilities. Previous work by these physicians had shown that the test appears to identify the presence of interstitial cystitis (IC) by detecting abnormal permeability of the bladder epithelium. The patients were enrolled consecutively at each site, with no exclusion criteria applied. Pelvic pain patients as well as age-matched control patients, completed a survey addressing both pelvic pain and urinary issues. The PST consisted of: 1) instillation of 40 cc of water into the bladder for 5 minutes; 2) grading of pain/urgency on 0-5 scale; 3) drainage of water; 4)instillation of 40 cc KCl solution (40 mEq KCl in 100 cc water); and 5) grading of pain/urgency. Of note, the patients were blinded to the solution contents, and they were also asked afterward which solution caused more symptoms.

The PST was positive in 81% of patients with pelvic pain with similar rates across centers. None of the control patients had a positive test. Eighty-four percent of the patients with pain had urologic symptoms, but only 1.6% had originally been assigned a diagnosis of IC. Parsons and colleagues conclude that IC appears to be a common, unrecognized cause of pelvic pain in gynecologic practice. They wonder whether IC shouldn't be given greater, or even primary, consideration in our differential diagnosis (Parsons CL, et al. *Am J Obstet Gynecol*. 2002;187:1395-1400).

COMMENT BY FRANK W. LING, MD

Whoa! Time out! Isn't the primary author of this study, who is also the primary author of other articles on the PST, a urologist? Where does he get off telling gynecologists how to diagnose the cause of pelvic pain? Aren't ob/gyn physicians the specialists that patients and other physicians turn to for answers in these tough cases? Aren't gynecologic surgeons the ones who "when in doubt, cut it out?"

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INSIDE

I'm confident that the reader clearly sees my tongue firmly planted in my cheek. Yes, we are the surgeons, but we are also the physicians who see the whole patient, who review all organ systems, looking for clues to the often-difficult cases. Since our relationship with our patients often encompasses far more than the surgical experience, this article is even more timely. One albeit simplistic approach to patients with pelvic pain is to remember "GUMP." This helps keep the gynecologist focused on nongynecologic causes of pelvic pain, sometimes avoiding unnecessary surgery or, at least, identifying concurrent conditions that may also be causing pain.

G: gastrointestinal causes. Primarily this leads to a diagnosis of irritable bowel. Patients who have pain associated with intermittent constipation, diarrhea, bloating, etc should be evaluated and treated before a commitment is made to gynecologic surgery.

U: urologic causes. In contemporary parlance, I suppose this should read urogynecologic causes. The point is that IC should certainly be considered, particularly when patients present with urologic symptoms. Even though urogynecology as a subspecialty is gaining broader recognition and acceptance, urologists are often the primary resources for many gynecologists. Regardless of what resources are available, the astute clinician can greatly enhance his/her ability to diagnose IC knowing that patients with IC void frequently (in this study, patients could not be included in the control group if they voided more than 8 times in a 24 period), have urge, often void small amounts, have dyspareunia, and even can feel better after voiding. Bladder tenderness on vaginal examination that recreates the chief complaint increases the index of suspicion.

M: musculoskeletal causes. Both abdominal wall and pelvic floor muscles can potentially cause pain that is mistakenly assumed to originate from pelvic organs. A history of trauma (eg, a fall or motor vehicle accident) or positional impact on pain is helpful in making this diagnosis. A physical therapist may be of some benefit if the pain can be recreated with light palpation of the abdominal wall or direct pressure of the pelvic floor.

P: psychiatric causes. Most commonly, considerations of depression, somatization disorder, and history of sexual abuse should be explored. Because depression has been found to be an inherent part of the chronic pain process, trying to figure out "which came first, the chicken or the egg," is often fruitless. Pain and depression both need attention when both are present. As the experienced clinician has discovered, often the hard way, the patient with somatization (multiple somatic complaints without identifiable organic cause) cannot be cured, merely managed over time. To address sexual abuse, whether child or adult, the question must be posed at some time. Patients need to sense the safety of a provider who is sensitive and willing to listen and help. The question "Have you ever been touched against your will, either as a child or as an adult?" is a nonthreatening way to convey to the patient your willingness to help address this concern.

The bottom line: Causes of pelvic pain in any particular patient are potentially multiple. An organized approach to what otherwise may seem a complex problem can often lead to findings that might have been missed. Perhaps this article can serve as an aid to help some more of our patients get care for pelvic pain that looks outside the pelvis. ■

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Effects of Oral Androstenedione Administration on Serum Testosterone and Estradiol Levels in Postmenopausal Women

ABSTRACT & COMMENTARY

Synopsis: *Acute oral administration of 50 mg and 100 mg of androstenedione to postmenopausal women increases serum testosterone and estrone but not estradiol.*

Source: Leder BZ, et al. *J Clin Endocrinol Metab.* 2002;87:5449-5454.

The use of androgenic preparations to support libido and energy in postmenopausal women has been advocated, but few studies on the use of androgenic preparations are available to guide physician practices. Testosterone has poor oral bioavailability, so other preparations have been suggested. Androstenedione is available without a prescription, but its safety and efficacy have not been established. To delineate more about the fate of orally ingested androstenedione, 30 postmenopausal women were randomly assigned to receive 0, 50, or 100 mg of androstenedione as a single oral dose. Hourly measurements were made for androstenedione, estrone, estradiol, and testosterone for 12 hours. There was, not surprisingly, considerable individual variability in the levels achieved. Testosterone levels exceeded the upper limit of normal in 4 of 10 women given the 50-mg dose and in 6 of 10 women given the 100-mg dose. Peak serum androstenedione levels exceeded the upper limit of normal for young reproductive-age women (200 ng/dL) in all subjects given the 100-mg dose and in 8 of 10 given the 50-mg dose. Estrone, but not estradiol, levels were increased, but did not exceed physiological concentrations. All hormone levels had returned to baseline by 12 hours.

COMMENT BY SARAH L. BERGA, MD

On a molar basis, the androgen secreted in greatest abundance by the ovaries is androstenedione and not testosterone. However, testosterone binds much more avidly than androstenedione to the androgen receptor. Thus, on a molar basis, testosterone is a more potent androgen. Because adipose tissue, sebaceous glands, and other tissues can convert androstenedione to testosterone, androstenedione is nonetheless an important androgen from a physiological perspective, and too much or too little may have clinical consequences. In women, approximately 50% of the circulating level of androstenedione derives from the adrenal glands, with the other half being secreted by the ovaries. In contrast to testosterone, androstenedione has a long half-life and is not so avidly bound by SHBG. Therefore, it is easier to estimate circulating androstenedione concentrations from a single blood sample than testosterone concentrations. Given these considerations, androstenedione use has been promoted to restore androgen levels, libido, muscle mass, bone density, and well-being in older men and women undergoing "adrenopause." "Andro" use also has been promoted for enhancing athletic performance. Since a large fraction of the circulating testosterone in women is derived from androstenedione, its use has been advocated also for women who undergo natural or surgical menopause to restore libido and boost well-being. There are few data on what would constitute an appropriate dose for women. The present study was designed to address that gap. The data would suggest that a more appropriate dose might be 25 mg, but to maintain testosterone levels around the clock would require twice-daily dosing. Of note, there was a large degree of intersubject variability, so it might be necessary to use both smaller and larger doses to achieve physiological levels in some individuals. Because the use of oral androgens induces hepatic enzymes and binding proteins, one would need to determine levels of androstenedione and its metabolites after several weeks of use to determine steady state, circulating concentrations. No safety data were collected in the present study, and there are no data about how the use of androstenedione would impact coagulation, insulin action, and other important physiological parameters.

It would be interesting to know how topical administration compares to the oral route of delivery in terms of peak levels and the distribution of metabolites (estrone, estradiol, testosterone, and cortisol). Presumably, there would be different levels of metabolites with oral vs topical delivery because when it is given orally, the liver actively metabolizes and alters the androstenedione before it is released into the systemic circulation. Absorption might not be as rapid when applied topically and this would likely be a benefit. Compounding pharmacies make and often promote topical preparations, so this information would be relevant to those of us still struggling with the aftermath of the WHI. Many women have the mistaken belief that over-the-counter, nonprescription products such as androstenedione are safe and well studied. Thus, they may abandon conventional

medications in favor of "natural" products. As one can see, there are far too little data to endorse this practice.

Leder and colleagues discuss how androstenedione use might compare to DHEA (dihydroepiandrosterone) use. Androstenedione is derived from DHEA, but DHEA can also be sulfated. DHEA-S circulates in microgram rather than nanogram concentrations. Oral DHEA increases both testosterone and estradiol in women. These levels may be more sustained because the reservoir of DHEAS is available for desulfation and aromatization. There are few studies, however, on the long-term safety of DHEA, although at least 1 long-term study is ongoing. Again, a physiological pattern might result if this pre-androgen is administered topically rather than orally, and it is unlikely to require twice-daily dosing to maintain levels in the "desired" range. Again, the use of androstenedione or DHEA makes more sense if the patient in question has a true hormonal deficiency as a result of adrenalectomy, Addison's disease, or surgical menopause. The use of androgens to retard the aging process has not been substantiated, although, because of the 1994 Dietary Supplement Health and Education Act, patients are free to conduct their own experiments on themselves without the benefit of medical advice or oversight. ■

VBAC Revisited Again

ABSTRACT & COMMENTARY

Synopsis: *Postpartum fever after cesarean delivery is associated with an increased risk of uterine rupture during a subsequent trial of labor.*

Source: Shipp TD, et al. *Obstet Gynecol*. 2003;101: 136-139.

Vaginal birth after cesarean (VBAC) continues to be a hot topic, and in the most recent issue of *Obstetrics & Gynecology*, Shipp and colleagues attempted to determine which intrapartum or postpartum events correlated with uterine rupture in a subsequent pregnancy.

Shipp et al searched their database to find patients with uterine rupture (for a 12-year period) who had previously delivered in the same institution. Each of the 21 cases found were then matched carefully with 4 control VBAC cases that delivered initially by cesarean section over the same time period (without uterine rupture).

The only variable that emerged as being significantly related to uterine rupture was postpartum fever (> 38° C). Specifically, 8/21 (38%) of the uterine rupture group had a postpartum fever in their prior cesarean, compared with 13/84 (15%) in the control group ($P = 0.03$).

■ COMMENT JOHN C. HOBBINS, MD

As mentioned in previous *OB/GYN Clinical Alerts*, the rate of cesarean section has risen to about 25% in the United States because of medico-legal, convenience, and other reasons, and there is every indication that this trend will head further skyward. Although some have taken a "who cares?" attitude to the point of making a case for cesareans on demand, there are plenty of data to indicate they are more costly and far from innocuous. Data aside, birth represents one of life's most natural processes. However, 1 in 4 of these is now accomplished by a major surgical operation. What's wrong with this picture?

This article suggests that patients with postpartum fever have a higher rate of later rupture during VBAC than those without this complication. The obvious take-home message is that postpartum fever is an indirect indicator of an infection that may adversely affect the quality of the scar, ultimately being tested during labor in the next pregnancy. Since the overwhelming majority of patients with postpartum fever will not have later uterine rupture, Shipp et al's finding should in no way be a contraindication to VBAC. On the other hand, the absence of intra-uterine infection could drop the risk of VBAC in those wishing to undertake this option.

Parenthetically, although the numbers of patients in the study were small, Shipp et al found no relationship between rupture and 1) single or double layer closure of the uterine incision; 2) the use of antibiotics (75% of both ruptures and controls got them); and 3) white blood cell count (WBC).

From this and other studies, it seems that the most critical variable in uterine rupture is the strength of the scar, and, to date, the literature has provided few clues as to how to assess this. Until something else comes along, perhaps the best way to indirectly evaluate the potential for uterine rupture is through ultrasound assessment of wall thickness in the vicinity of the uterine scar. In a previous issue, this topic was tangentially covered. In 2 papers from Japan involving small numbers of patients, there appeared to be a relationship between wall thickness and uterine rupture. However, I overlooked a paper published in 1996 in the *Lancet* by a group of French investigators that provided much stronger evidence of the efficacy of using wall thickness to roughly determine risk of rupture for a given patient.[1]

The group evaluated 642 patients about to undergo VBAC at term with transabdominal ultrasound assess-

ment of uterine wall thickness just under the bladder reflexion. The uterine rupture rate was 2.5%, and the rate of dehiscence was 1.5%. If the smallest thickness was 1.6-2.5 mm, the defect rate was 16%. If that diameter was greater than 4 mm, there were no uterine defects and if one used a cutoff of 3.5 mm, the negative predictive value was 99.3%.

The major argument against VBAC is its potential for increased neonatal and maternal morbidity. This is directly related to uterine rupture so if we had a very good idea of which patients were at very low risk of this through historical information (fever postpartum), scar strength (uterine wall thickness), and other variables such as cervical ripeness (another story), it should be possible to identify the majority of patients who could sail through labor as if they did not have a scar.

I promise this will be the last time for a while that this topic will be covered. ■

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Anti-HER2 Antibody, Trastuzumab in Patients with Recurrent or Refractory Ovarian or Primary Peritoneal Carcinoma with Overexpression of HER2

ABSTRACT & COMMENTARY

Synopsis: *The clinical value of single-agent trastuzumab in recurrent ovarian cancer is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 overexpression.*

Source: Bookman MA, et al. *J Clin Oncol.* 2003;21: 283-290.

In a phase II clinical trial of the Gynecologic Oncology Group (GOG), Bookman and colleagues evaluated the feasibility, toxicity, and efficacy of single-agent monoclonal antibody therapy targeting the human epidermal growth factor receptor 2 (HER2)/neu receptor in ovarian and primary peritoneal cancer. Eligible patients had measurable persistent or recurrent epithelial ovarian or primary peritoneal carcinoma with 2+ or 3+ HER2 overexpression documented by immunohistochemistry. Intravenous trastuzumab was administered initially at a dose of 4 mg/kg, then weekly at 2 mg/kg. Patients without progressive disease or excessive toxicity could continue treatment indefinitely. Those with stable or responding disease at 8 weeks were offered treatment at a higher weekly dose (4 mg/kg) at time of progression. Patient sera were analyzed for the presence of the soluble extracellular domain of HER2, host antibodies against trastuzumab, and trastuzumab pharmacokinetics. A total of 837 tumor samples were screened for HER2 expression, and 95 patients (11.4%) exhibited the requisite 2+/3+ expression level. Forty-five patients, all of whom received prior chemotherapy, were entered, and 41 were deemed eligible and assessable. There were only mild expected toxicities and no treatment-related deaths. Although an elevated level of the soluble extracellular domain of HER2 was detected in eight of 24 patients, serum HER2 was not associated with clinical outcome. There was no evidence of host antitrastuzumab antibody formation. Serum concentrations of trastuzumab gradually increased with continued therapy. An overall response rate of 7.3% included 1 complete and 2 partial responses. Median treatment duration was 8 weeks (range, 2-104 weeks), and median progression-free interval was 2.0 months. Bookman and colleagues concluded that the clinical value of single-agent trastuzumab in recurrent ovarian cancer is limited by the low frequency of HER2 overexpression and low rate of objective response among patients with HER2 overexpression.

COMMENT BY DAVID M. GERSHENSON, MD

Over the past few years, with the completion of the Human Genome Project and the explosion of knowledge in the field of cancer biology, targeted therapeutics is foremost in the minds of both patients and oncologists. While chemotherapy is very much a "shotgun" approach, the hope for targeted therapy is that one will be able to eventually individualize therapy based on the molecular profile of each patient's tumor. Although we are not currently near that goal, several potential targets involved in tumorigenesis have been identified. These include growth factors, oncogenes, tumor suppressor genes, and angiogenic/vascular factors. The HER-2/neu oncogene is one of the prime candidates. Abnormal expression of HER-2/neu has been reported in a number of cancers, including ovarian cancer. Initial studies suggested that approximately 30% of ovarian cancers overexpress the HER-2/neu oncogene. However, this study and several others, including our own experience, peg the overexpression rate at about 10% based on immunostaining. Therefore, HER-

2/neu may not be such an attractive target for the majority of ovarian cancer patients. Furthermore, as a single agent, the monoclonal antibody to HER-2/neu had limited activity in patients with HER-2/neu overexpressing, refractory ovarian or peritoneal cancers, with a response rate of only 7.3%. This response rate is lower than the 12-15% response rate reported with trastuzumab in the treatment of metastatic breast cancer. Additionally, combinations of the monoclonal antibody plus chemotherapy have been reported to achieve response rates exceeding those for the single agents. Therefore, we may see additional studies with this agent in combination with chemotherapy for ovarian cancer patients. As Bookman et al point out, however, the low frequency of HER-2/neu overexpression may make such trials impractical. ■

Special Feature

Measuring Testosterone

By Leon Speroff, MD

THERE ARE 2 IMPORTANT POTENTIAL USES FOR THE measurement of testosterone levels: 1) to monitor the dosage of testosterone supplementation; and 2) to diagnose hyperandrogenism, whatever the cause. Unfortunately, the measurement of testosterone is particularly difficult in women because of the low circulating levels. The situation is further complicated by how testosterone circulates in the blood and by having more than 1 assay available to measure testosterone.

In the circulation, testosterone is bound to sex hormone-binding globulin (SHBG) and to albumin. Free testosterone is that which is unbound and available for target tissue activity. In healthy women, approximately 50-60% of testosterone is bound to SHBG and 30-40% to albumin, leaving only 0.5% to 3.0% as unbound and active. Estrogen and thyroid hormone increase SHBG levels, and androgens, glucocorticoids, growth hormone, and insulin decrease levels. Bioavailable testosterone refers to the free and unbound testosterone and that which is bound to albumin (because testosterone binding to albumin is weak and thus some, but not all, of albumin-bound testosterone is available for tissue activity).[1]

The total testosterone assay measures by direct radioimmunoassay with commercial kits free testosterone, albumin-bound testosterone, and the testosterone that is bound to SHBG. The other available assays include the following:

Free testosterone, measured by equilibrium dialysis and ultracentrifugation-α is a laborious, time-consuming method that requires strict temperature controls and is expensive. However, this is the gold standard against which other methods estimating the amount of active testosterone must be compared. Free testosterone is also measured by direct immunoassay with commercial kits. The normal range is from 0.3-0.8 to 3-6 pg/mL in most laboratories.

Bioavailable testosterone, measured by ammonium sulfate precipitation of SHBG, followed by radioimmunoassay with commercial kits is also time-consuming and expensive.

Free androgen index, also called the free testosterone index, is calculated by dividing the total testosterone by the SHBG concentration and multiplying by 100 (T/SHBG × 100).

The direct immunoassay of free testosterone is very attractive because of its ease, rapidity, and relative cost. This method, however, is subject to considerable inaccuracy and variability. The results with this assay measure only 20-60% of the levels measured by the more difficult and expensive method that uses dialysis.[2] In addition, this assay is affected by the changes in the levels of SHBG. The free testosterone index and measurement of the bioavailable testosterone correlate well with the gold standard dialysis method. However, these methods are also affected by the circulating amounts of SHBG and testosterone.[3] With a lot of SHBG and lower levels of testosterone, there are abundant binding sites on the SHBG giving falsely elevated values for these methods, and vice-versa.

The clinical problem is the fact that there are discrepancies among the values for these various methods reported in the literature. For appropriate clinical use, each method requires the establishment and validation of normal ranges and changes with pathologic conditions. This has not been done. The salivary concentration of sex steroids represents only a very small fraction of the amount in the ciruclation.[4] Salivary measurements also have not been validated; specifically, there is a lack of studies establishing the correla-

Table

Circulating Hormone Levels[6,10,11]

	Premenopause	Postmenopause
Estradiol	40-400 pg/mL	10-20 pg/mL
Estrone	30-200 pg/mL	30-70 pg/mL
Testosterone	20-80 ng/dL	15-70 ng/dL
Androstenedione	60-300 ng/dL	30-150 ng/dL

tion between salivary levels and serum levels, and between salivary levels and clinical presentations and/or responses.

Testosterone production decreases by approximately 25% after menopause, but the postmenopausal ovary in most women secretes more testosterone than the premenopausal ovary. With the disappearance of follicles and estrogen, the elevated gonadotropins drive the remaining stromal tissue in the ovary to a level of increased testosterone secretion. The total amount of testosterone produced after menopause, however, is decreased because the amount of the primary source, peripheral conversion of androstenedione, is reduced. The early postmenopausal circulating level of androstenedione decreases approximately 62% from young adult life.[5] The menopausal decline in the circulating levels of testosterone is not great, from no change in many women to as much as 15% in others.[5-8] Nevertheless, compared with young women, the overall androgen exposure of postmenopausal women to androgens is less.[9] After age 60, testosterone levels are about half those measured in young women. The key question is whether the free and active amount of testosterone decreases or increases.

The conclusions in the preceding paragraph are derived from studies that have been hampered by small sample sizes and by their cross-sectional nature. A prospective longitudinal study in Australia followed 172 women for 7 years as they passed through menopause.[8] The circulating levels of total testosterone did not change. SHBG levels decreased about 43%, and the free androgen index increased (by 80%!) because of the decrease in SHBG. But does this have clinical meaning, and in view of the variabilities with these methods, is this observation accurate? Why wouldn't this substantial increase in a measure indicating an increase in free testosterone produce behavioral changes? By preventing the decrease in SHBG, postmenopausal estrogen therapy would prevent this increase in free testosterone. Is this important clinically? These are questions currently without answers.

One study concluded that the free androgen index displayed a good correlation with hyperinsulinemia.[12] However, the range of values was very great with considerable overlap comparing normoinsulinemic women with hyperinsulinemic women. The free testosterone level has been reported to decrease after 2 years of treatment of postmenopausal women with oral estrogen in contrast to no change with transdermal treatment.[13] But again there was impressive overlap; in fact, the decrease within the group on oral therapy did not reach statistical significance. Some have argued for measuring free testosterone as a screening method for polycystic ovary syndrome. The variability found both within individuals and among the assays is a strong argument against this practice.

Testosterone supplementation might favorably affect muscle strength, sexuality, and psychological state. There is little doubt that the administration of pharmacologic amounts of testosterone can produce these favorable effects, but it remains unknown whether maintaining testosterone levels within the normal physiologic range (10-20 to 60-90 ng/dL, depending on the laboratory) can have a beneficial impact on health. Furthermore, the long-term consequences of pharmacologic amounts of testosterone are totally unknown.

I am reluctant to support the pharmacologic use of testosterone given the difficulties in monitoring dosage and the lack of knowledge regarding the long-term effects on health. 17α-Methyltestosterone is administered orally in combination with estrogen. The available doses are definitely pharmacologic. The problem is that this androgen is not demethylated in the body and cannot be measured by testosterone assays; therefore, it is impossible to monitor dosage. If a clinician and a patient choose to use supplemental androgens, my advice is to select a treatment that can be monitored with measurements of total testosterone in serum. The choices include the testosterone transdermal patch (not yet on the market), a testosterone skin gel (on the market for use in men), and testosterone compounded for individual use by a pharmacist. ■

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CME Questions

7. **Which of the following is *not* a metabolite of androstenedione?**
   a. DHEA
   b. estrone
   c. estradiol
   d. testosterone
   e. cortisol

8. **HER-2/neu is overexpressed in approximately 10% of ovarian cancers and is a:**
   a. tumor suppressor gene.
   b. oncogene.
   c. mitochondrial fragment.
   d. hormone receptor.
   e. transcription factor.

Answers: 7:a; 8:b

PHARMACOLOGY WATCH

Smallpox Vaccination Guidelines Published by CDC

The CDC published "Smallpox Vaccination and Adverse Reactions—Guidance for Clinicians" in the Jan. 24th edition of *Morbidity and Mortality Weekly Report.* The guidance is a thorough review of the smallpox vaccine with a well-illustrated compendium of complications. Some of the highlights include:

Inoculation is administered using a multiple-puncture technique with the bifurcated needle. The inoculation site progresses from papule to vesicle, eventually becoming a pustule within 10 days. The pustule scabs over within 2-3 weeks usually leaving a pitted scar. Development of a pustular lesion is considered a major reaction and a successful vaccine take. Lesser reactions are considered equivocal and are nontakes. Large vaccination reactions may occur in 10% of first-time vaccinees. Systemic reactions are common in all vaccinees and include fatigue, headache, myalgias, chills, nausea, and fever. The vaccine is made from live vaccinia virus (it does not contain variola virus) and transmission is possible from the vaccination site up to 3 weeks after vaccination. The shedding period may be less for revaccination. The inoculation site is generally considered infectious from the time just after vaccination until the scab separates from the skin. Vaccinia is transmitted by close contact and can lead to the same adverse events in an infected contact as in the vaccinee. The inoculation sites should remain covered and vaccinees should wash their hands immediately after touching vaccination sites or changing dressings. The smallpox vaccination is generally considered safe, but is contraindicated in patients who have, or are in close contact with, those who have atopic dermatitis (eczema) regardless of the severity, skin diseases that disrupt the epidermis, pregnant women or women who plan on becoming pregnant within 1 month after vaccination, and immunocompromised patients. Others who should not receive the vaccine include those who have an allergy to a component of the vaccine, are breast-feeding, are using ocular steroids, have moderate-to-severe intercurrent illness, or are younger than 18 years of age.

The CDC has an excellent web site for health-care providers who wish to learn more about the smallpox vaccine: www.bt.cdc.gov/training/smallpox-vaccine/reactions/default.htm

Nurses: Delay Vaccination Program

Meanwhile, not everyone is happy with the national smallpox vaccination program. Recently the American Nurses Association (ANA) requested that the Bush administration delay the smallpox vaccination program until certain safety issues can be addressed. Specifically, the ANA is seeking information regarding potential transmission of vaccinia virus to family members of vaccinated nurses, coverage of medical costs related to vaccination, safety of the vaccination materials, adequate educational materials and staffing issues, and job security issues related to the vaccination program. Others such as Thomas Mack, MD, MPH, argue in the Jan. 30 edition of the *New England Journal of Medicine* that

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smallpox is overrated as a bioterrorist weapon. His view is that the current vaccination policy would provide little protection and the cost from vaccine complications would outweigh any benefit (*N Engl J Med*. 2003;348:460-463). However, a special article in the same issue developed scenarios of smallpox attacks and reviewed possible outcomes of control policies. Their analysis favors a program of prior vaccination of health care workers but favors vaccination of the public only in the likelihood of a national attack, or multiple attacks is very high (*N Engl J Med*. 2003;348:416-425).

Viagra Effective for Depression Treatment

Sildenafil (Viagra) is an effective treatment for antidepressant-associated sexual dysfunction in men. The drug was tested in a multicenter randomized double-blind placebo-controlled trial. Ninety men with major depression in remission on SSRI antidepressants were randomly assigned to take sildenafil (50 to 100 mg) or placebo for 6 weeks. Men who were most affected by antidepressant-associated sexual dysfunction were significantly more likely to improve with sildenafil (24/44, 54.5% response rate) vs placebo (2/45, 4.4% response rate) ($P < .001$). Erectile function, arousal, ejaculation, orgasm, and overall satisfaction measures improved significantly with sildenafil compared with placebo (*JAMA*. 2003;289:56-64). This study is important because sexual dysfunction is a common cause of noncompliance with serotonin reuptake inhibitors, and use of sildenafil may improve compliance with antidepressant treatment.

Finisteride/Doxazosin no Better than Placebo for Urinary Obstruction

Finisteride (Proscar) is no better than placebo when used in combination with doxazosin for the treatment of urinary obstruction due to benign prostatic hypertrophy, according to the recently published Prospective European Doxazosin and Combination Therapy (PREDICT) trial. These findings come in contradiction to the Medical Therapy of Prostatic Symptoms (MTOPS) trial published in May 2002, which showed a benefit of the combination of finasteride and doxazosin. In the current study, more than 1000 men were randomized to doxazocin, finisteride 5 mg per day, the combination of both, or placebo. The groups receiving doxazocin alone or in combination with finisteride had significant improvements in total maximal urinary flow rates and International Prostate Symptoms Score compared to the finisteride alone group and placebo group ($P < .05$). There was no significant difference between treatment with finisteride and placebo. Doxazosin was initiated at 1 mg per day and titrated to a maximum of 8 mg per day. All treatments were well tolerated (*Urology*. 2003;61:119-126).

Sildenafil, however, may be effective of relieving obstructive urinary symptoms in men who use the drug on a regular basis. British researchers looked at 112 men with erectile dysfunction at 1 and 3 months after taking sildenafil as needed before sexual intercourse. Only 20 of the 112 men complained of lowered urinary tract symptoms, but of those men, improved urinary scores at 3 months strongly correlated with improvement in sexual function. The authors suggest that an increase in nitric oxide associated with the resumption of normal sexual activity may be responsible for the improvement in urinary symptoms (*Br J Urol Int*. 2002;90: 836-839).

Serevent Receives 'Dear Doctor' Letter

GlaxoSmithKline has issued a "Dear Doctor" letter regarding its asthma bronchodilator salmeterol (Serevent). The warning is based on interim results from a large study of salmeterol that was initiated in 1996. The Salmeterol Multi-center Asthma Research Trial (SMART) was a postmarketing study designed to investigate reports of several asthma deaths associated with use of salmeterol. Analysis of the interim results showed a trend "toward a greater increase in asthma deaths and serious asthma episodes" with the largest increase in African-American patients. Data on almost 26,000 patients were available for analysis. While there was no significant difference for the primary end point of combined respiratory related deaths and respiratory related life-threatening experiences including incubation and mechanical ventilation between salmeterol and placebo, a higher, but not statistically significant number of asthma related life-threatening experiences including deaths occurred in the salmeterol group. The number of adverse events reached statistical significance in African-Americans who represented 17% of the study. No other ethnic group drew any conclusions. The use of inhaled corticosteroids reached only 47% in the entire population of the SMART study. Because of these findings, GlaxoSmithKline has decided to discontinue the study and continue reviewing data from the interim analysis. The FDA is involved in this process and will likely require label changes for Serevent that will reinforce guidance on appropriate and safe prescribing. ■

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By Louis Kuritzky, MD

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The Metabolic Syndrome and Total and Cardiovascular Disease Mortality in Middle-Aged Men

Source: Lakka HM, et al. *JAMA*. 2002;288:2709-2716.

THE METABOLIC SYNDROME (MBS) HAS 2 currently popular definitions. According to the National Cholesterol Education Program, MBS exists when a patient has at least 3 of the following characteristics: fasting glucose (FPG) > 110 mg/dL, abdominal obesity, triglycerides > 150, HDL < 40 mg/dL, and elevated blood pressure (> 130/85). The World Health Organization (WHO) definition stratifies things just a bit differently, defining MBS as either hyperinsulinemia (upper quartile of the adult, nondiabetic population) or FPG, and any 2 or more of abdominal obesity, dyslipidemia (triglycerides > 150 mg/dL or HDL < 35), and BP > 140/90. Despite these modest differences, the criteria basically define the same group of individuals. Lakka and associates prospectively studied for a mean of 11.6 years a random, age-stratified sample of men in Finland (n = 2682) aged 42 and older, to examine cardiovascular and overall mortality in relation to MBS.

MBS patients had reduced (79%) Kaplan-Meier estimates of overall survival when compared with patients without MBS. Similarly, CHD mortality was 2.4-3.4 times higher in persons with MBS. The prevalence of MBS at baseline was 9-14%. The public health impact of MBS is substantial. Whether specific treatment of MBS will reduce mortality has not been determined. ■

Amlodipine Fosinopril Combination on Microalbuminuria in Hypertensive Type 2 Diabetic Patients

Source: Fogari R, et al. *Am J Hypertens*. 2002;15:1042-1049.

NUMEROUS STUDIES HAVE CONfirmed the role of ACE inhibitors in modulation of microalbuminuria. The data on effects of calcium channel blockers (CCB) have been conflicting, especially as concerns dihydropyridine CCB (eg, amlodipine, felodipine, nifedipine). Fogari and associates addressed the effects of fosinopril (FOS) and amlodipine (AML), alone or in combination (COM), in an open-labeled, randomized, prospective, parallel group study for 4 years (n = 309).

By 3 months' time, the FOS group had demonstrated a decline in urinary albumin excretion (UAE), which decreased slightly further in the first year, and then stabilized. The AML group also demonstrated a decline in UAE, but not until 18 months into the study, after which point the UAE stabilized. COM therapy produced an impact at 3 months, which increased at 12 months and again at 36 months, and was statistically significantly greater than either monotherapy.

The mechanism by which COM therapy is superior to either monotherapy is uncertain, but the greater reduction in BP achieved (approximately 12/5 greater reduction by the former) is thought to have figured prominently. ■

Relation Between Alcohol Consumption and C-Reactive Protein Levels in the Adult United States Population

Source: Stewart SH, et al. *J Am Board Fam Pract*. 2002;15:437-442.

EPIDEMIOLOGIC DATA CONSISTENTLY indicate that moderate intake of alcohol (ETOH) is associated with reductions in cardiovascular mortality. Though the mechanism by which this effect is achieved is uncertain, increases in HDL by alcohol may explain as much as 50% of the protective effect.

C-reactive protein (CRP) is increasingly recognized as an independent risk factor for cardiovascular endpoints, suggesting an important role of inflammation in promoting atherosclerotic events. To evaluate the relationship between CRP and ETOH, Mainous and associates analyzed data from the National Health and Nutrition Evaluation Survey (NHANES III), which included complete information on 11,572 US adults.

Almost half of the NHANES population were alcohol abstainers; CRP levels in abstainers were significantly greater than in those who drink alcohol, regardless of level of alcohol ingestion. The mechanism by which ETOH might reduce CRP (or inflammation) remains unknown. A small trial of ETOH in healthy volunteers has shown a reduction in CRP and is stimulus for follow-up evaluation in larger studies. ■

Prostate Cancer Screening

Source: Ransohoff DF, et al. *Am J Med*. 2002;113:663-667.

In contrast to screening for breast and colon cancer, both of which have been demonstrated to reduce mortality, prostate cancer screening (PCS) has not yet been proven to favorably affect overall mortality, although some trials have found that PCS screening reduces prostate cancer-related mortality. Hence PCS has not met the same standard as other commonly used screening tools. Because of the discordance between the relative lack of supportive data to provide justification for PCS and the very high frequency of PCS testing, Ransohoff and colleagues sought to evaluate what factors promote PCS. That PCS can result in harm (eg, postsurgical impotence, incontinence) is clear; whether PCS can provide benefit (ie, reduction in mortality) remains to be demonstrated.

Ransohoff et al describe the PCS model as "lacking negative feedback:" a patient who undergoes PCS and has no cancer-suggestive findings feels reassured by these findings and is happy to have participated; a patient who has an elevated PSA often undergoes medical or surgical intervention. Even in the face of postintervention sequelae, the screened patient may feel that, ultimately, the intervention has spared his life, and he too may be grateful for the PCS.

Currently, whether PCS is mortality-effective is uncertain. Nonetheless, public satisfaction and enthusiasm for PCS remains high. It is conceivable that, in the long run, harm from PCS-stimulated intervention may outweigh benefit. Until the relative risks and benefits of PCS are more clearly defined, clinicians are well advised to review the decision path of PCS with patients before the process is embarked upon, in order that fully informed consent, dispassionately, may be attained. ■

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Can We Trust Home BP Measurement?

Source: Bachmann LM, et al. *J Clin Hypertens*. 2002;4:405-407,412.

The window of observation of blood pressure as obtained in the typical office setting has important limitations, with both exaggerations (ie, "white-coat" hypertension), and underestimates (ie, "masked hypertension") of hypertension burden being well documented. Abnormal circadian BP patterns, such as failure to experience the normal nocturnal decline in blood pressure, predict higher cardiovascular risk yet are not discerned by simple office measurement. Twenty-four-hour Ambulatory Blood Pressure Monitoring (ABPM) can resolve all 3 of these issues but is not without significant expense, and despite the endorsement of ABPM by the JNC VI report and the WHO guidelines, this technique remains only rarely used. Whether home blood pressure measurement, perhaps an intermediate step between office measurement and ABPM, is reliable is the subject of this report.

Bachmann and colleagues included 48 hypertensive patients from a single practice, who had been referred for 24-Hour ABPM. Subjects were randomly assigned to either a group which was asked to keep a personal log of the BP measurements recorded by the ABPM, and advised that their log would be checked for accuracy against that registered by the ABPM device, or a group who were also advised to periodically record BP measurements as registered by the ABPM device, but who were unaware that the ABPM automatically records and stores BP measurements. Discrepant results occurred when patient-recorded records either had an incorrect time, an incorrect BP value, or a BP was entered as recorded when the ABPM device had not performed such a measurement. Although patients unaware of the ABPM recording capacity were found to have more "fictional" registrations than the "informed" group (10/728 vs 29/616), ultimately these discrepant recordings did not confound the overall mean accuracy of averaged home blood pressure readings. ■

Systolic and Diastolic Dysfunction

Source: Redfield MM, et al. *JAMA*. 2003;289:194-202.

Congestive heart failure (CHF) is typically classified as systolic (ie, reduced ejection fraction), diastolic (normal ejection fraction, with impaired ventricular filling), or both. Indeed, though CHF may have been generally conceptualized solely as "inadequate pumping," some degree of diastolic dysfunction accompanies almost all patients suffering systolic dysfunction. Additionally, isolated diastolic dysfunction, which may present with identical clinical symptoms as systolic dysfunction, has recently been recognized to be approximately as common as systolic dysfunction in patients with manifest CHF. Redfield and associates evaluated with doppler echocardiography adults older than 45 years of age participating in the Rochester (Minnesota) Epidemiology Project (n = 2042), none of whom entered the study with a diagnosis of CHF.

In this asymptomatic (for CHF) group, validated CHF prevalence was 2.2%, approximately equally divided between systolic and diastolic dysfunction. Diastolic dysfunction, whether mild, moderate, or severe, was found by multivariate analysis to be predictive of all-cause mortality. This trial indicates that diastolic dysfunction, previously regarded as more "benign" than systolic dysfunction, portends significant adverse health outcomes. ■