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A monthly update of developments in female reproductive medicine

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Coagulation Testing in Hypertensive Disorders of Pregnancy

ABSTRACT & COMMENTARY

To determine which routinely ordered laboratory tests could best predict abnormalities in prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen, Barron and colleagues performed a retrospective pilot study of 73 women being evaluated for hypertensive disorders in pregnancy. They found that the platelet count and lactate dehydrogenase (LDH) best predicted coagulation abnormalities. These findings were then applied to a retrospective review of 732 women being evaluated for hypertensive disorders in pregnancy. About 30% of the larger group had coagulation tests obtained. An abnormal platelet count was defined as less than 150 × 109/L, an abnormal PT as a result exceeding the upper limit of normal or greater than 18 seconds, and an abnormal aPTT as exceeding the upper limit of normal or more than 40 seconds. Fibrinogen was considered abnormal if it was below 250 mg/dL. The overall likelihood of a coagulation abnormality was low in this population, no patient had a PT greater than 18 seconds, two had an aPTT greater than 40 seconds, and three had a fibrinogen below 200 mg/dL. All patients with a normal platelet count and a normal LDH had a normal PT and aPTT, and 99% had normal fibrinogen levels.

An abnormal platelet count or an elevated LDH had a sensitivity of 70% for the detection of an abnormal PT or aPTT and 79% for a fibrinogen below 250 mg/dL. There was no relationship between the results of the PT, aPTT, or fibrinogen in eight patients requiring transfusion of coagulation factors. Only the platelet count was correlated with this outcome.

Barron et al conclude that a PT, aPTT, or fibrinogen need not be ordered in patients suspected of having preeclampsia when there is no evidence of bleeding, or a condition that might produce a coagulopathy such as placental abruption, and the platelet count and LDH level are normal. (Barron WM, et al. *Obstet Gynecol* 1999;94:364-370).

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COMMENT BY STEVEN G. GABBE, MD

On many obstetric units, when a patient with suspected pregnancy-induced hypertension or preeclampsia is admitted, a battery of laboratory tests is ordered including a complete blood count, platelet count, urinalysis, creatinine, uric acid, hepatic transaminases, LDH, and albumin. In some institutions, coagulation tests are obtained as well including a PT, aPTT, and fibrinogen. The coagulation tests are not only expensive but are usually requested as a "rush," further stressing the laboratory. This retrospective study by Barron et al demonstrates that, when the platelet count and LDH are normal, the coagulation tests will rarely be abnormal.

Although not evaluated in this study, Barron et al point out that other coagulation studies such as fibrin-fibrinogen degradation products, D-dimer, and antithrombin III should not be ordered routinely. An unpublished research project I completed with Bruce Farringer, MD and Patricia Temple, MD. revealed similar findings. Unless the patient with preeclampsia had thrombocytopenia or right upper quadrant pain, coagulation abnormalities or abnormalities in liver function tests were unusual. This information should be helpful in reducing unnecessary lab studies in patients with hypertensive disorders in pregnancy. ❖

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Estrogen Replacement Therapy for Ovarian Cancer Survivors

ABSTRACT & COMMENTARY

Synopsis: *Postoperative estrogen replacement therapy did not have a negative influence on the disease-free survival and overall survival of ovarian cancer survivors.*

Source: Guidozzi F, Daponte A. *Cancer* 1999;86: 1013-1018.

Guidozzi and daponte have reported a prospective, randomized trial in which 130 patients younger than 59 years with invasive epithelial ovarian cancer were randomized to receive continuous, oral conjugated equine estrogen via estrogen replacment therapy (ERT) or no supplementation (non-ERT). All patients were followed prospectively for a minimum of 48 months. The purpose of the study was to determine whether postoperative ERT had a negative influence on the disease-free survival and overall survival. Three patients in the ERT group and two in the non-ERT group were lost to follow-up, so 59 and 66 were finally analyzed in their respective groups. Nine patients originally randomized to ERT refused or stopped their supplementation, whereas five in the non-ERT group commenced taking estrogens. A total of 32 recurrences occurred in the ERT group and 41 in the non-ERT group. The median disease-free survival was 34 vs. 27 months, respectively, whereas overall survival was 44 vs. 34 months, respectively, for the two groups. The differences in disease-free survival and overall survival between the two groups were not statistically significant. Guidozzi et al concluded that postoperative ERT did not have a negative influence on the disease-free survival and overall survival of ovarian cancer survivors.

COMMENT BY DAVID M. GERSHENSON, MD

More than 70% of epithelial ovarian cancers have already spread beyond the ovaries at diagnosis, and the recurrence rate for women with advanced stage disease is high, with a five-year survival rate of no better than 20%. Fear of recurrence is a common phenomenon among women with ovarian cancer, and they are natu-

rally anxious about anything that may increase their risk of recurrence. Women who are postmenopausal or who undergo bilateral oophorectomy in the premenopausal age group have the same incidence of menopausal symptoms as women without ovarian cancer. The use of ERT in this patient population has been controversial. Although I know of no scientific evidence that ERT increases a woman's risk of recurrence from ovarian cancer, the link between ERT and endometrial/breast cancers has been extrapolated to other "women's cancers." Many physicians do not believe that a woman with a diagnosis of any gynecologic malignancy, including ovarian cancer, should ever receive ERT. In fact, epidemiological studies have not found a significantly increased risk of ovarian cancer in women who have taken ERT. Reports have shown either no increased risk or nonsignificantly elevated risks.

In the present study, Guidozzi et al found no differences in disease-free survival or overall survival between ERT and non-ERT patients. However, there were only 59 and 66 evaluable patients in the two arms of the study, and I am concerned about the possibility of an underpowered study leading to a type II error. Guidozzi et al do not discuss statistical concerns in their paper. Nevertheless, until information to the contrary is forthcoming, I continue to believe that the decision about ERT for women with ovarian cancer is personal. My own bias is that the potential benefits outweigh any deleterious effects. ❖

The Effects of Famine on Prenatal Development

ABSTRACT & COMMENTARY

Synopsis: *Maternal nutritional deprivation (starvation) appears to be associated with antisocial personality disorder in resultant offspring.*

Source: Neugebauer R, et al. *JAMA* 1999;282:455-462.

Between october 1944 and may 1945, the german army severely restricted the flow of food supplies to the western area of The Netherlands. Because other studies have recently shown that restricting the nutritional intake of pregnant women may result in offspring with more psychiatric disorders than are seen in the general population, Neugebauer and colleagues use the famine conditions occurring in this geographic area to attempt to determine whether caloric restriction causes an increase in antisocial personality disorder (ASPD).

Upon reaching 18 years of age, Dutch men born in the 1944-1946 time frame were required to undergo psychiatric examination as part of their military induction process. Neugebauer et al used the results of these examinations as well as the known availability of food in the various regions in The Netherlands to compare the occurrence of ASPD between men who were exposed to famine conditions while in utero as opposed to those who were not so exposed.

Those males who were exposed to famine conditions (less than 1000 calories food ration per day) during the first and/or second trimester had more than a two-fold increased risk of ASPD compared to males who were not so exposed. Neugebauer et al carefully selected their methodology such that the most likely explanation for the increase in psychiatric illness was the lack of maternal nutrition.

COMMENT BY KENNETH L. NOLLER, MD

The reason I have chosen this article for review is to provide me with the opportunity to discuss an area of growing interest in the field of disease etiology—namely, that the intrauterine milieu may be responsible for diseases that occur many years later in life.

It has been known for a long time that insults such as infections can cause fetal maldevelopment and lifelong disease. Examples would include such things as maternal toxiplasmosis and German measles infections. Maternal nutritional deficiencies such as folate deficiency have now been shown to cause an increase in congenital anomalies. However, it is not nearly as well recognized that some diseases of adults might be the result of intrauterine exposures. The obvious and best example is the association between vaginal clear-cell cancer and maternal ingestion of DES.

Many other diseases are now being linked to maternal conditions. Although not yet proven, it is likely that women who have higher naturally occurring levels of estrogen predispose their female offspring to higher rates of breast cancer. Decreased nutritional intake during pregnancy has been linked to a variety of psychiatric illnesses including schizophrenia and, now with the publication of this paper, ASPD.

Some years ago, we reported the association of eating disorders occurring in adults with exposure before birth to DES. Thus, it appears that a disease need not be evident at the time of birth to be linked to the intrauterine milieu. This area of research is just beginning to blossom. I strongly suspect that we will see many more associations between maternal health and diseases in offspring that occur decades later. ❖

Diet and Ischemic Stroke

ABSTRACT & COMMENTARY

Synopsis: *Patients should focus on consuming fruit and vegetables and not try to replace them with dietary supplements.*

Source: Joshipura KJ, et al. *JAMA* 1999;282: 1233-1239.

The nurses' health study continues to provide helpful data on women's health trends. In this prospective cohort study, Joshipura and colleagues from Harvard followed the dietary intake of 75,596 healthy nurses aged 34-59 from 1980 to 1994. (They also followed a similar male cohort from the Health Professionals' Follow-Up Study). Both cohorts responded to surveys every two years to indicate their dietary and other health habits (with extensive food frequency questionnaires), as well as their incidence of cardiovascular disease and other health outcomes. For respondents who reported strokes, Joshipura et al reviewed medical records and imaging studies to verify the diagnoses.

Of the large cohort in the Nurses' Health Study, 366 women eventually suffered new ischemic strokes. It turned out that the women in the highest quintile for intake of fruit and vegetables (with a median of 5.8 servings daily) had a relative risk of ischemic stroke of 0.74 (95% CI 0.52-1.05) compared with women in the lowest quintile. Each daily serving of fruits or vegetables appeared to lower women's ischemic stroke risk by 7%, with the greatest effect seen with green leafy vegetables, cruciferous vegetables, and citrus fruit (including juices). Only legumes and potatoes appeared to confer no benefit. These statistically significant findings persisted after investigators controlled for smoking and other cardiovascular risk factors, for fat intake, and for use of multivitamins and other nutritional supplements. The men's cohort produced similar results.

COMMENT BY ELIZABETH MORRISON, MD, MSEd

Stroke affects half a million people every year, many of them women. Fortunately, those of us who provide primary care have opportunities to counsel women about lifestyle modifications that can make a difference. I enjoy finding articles like this one by Joshipura et al because they give me interesting new perspectives to share with patients when discussing dietary recommendations for health maintenance.

For prevention of coronary artery disease, the American Heart Association already recommends that all Americans consume a balanced diet emphasizing antioxidant-rich vegetables, fruits, and whole grains rather than specific antioxidant supplements.[1] We can now tell female patients that such a diet appears to prevent ischemic stroke as well. Current recommendations that patients consume at least five daily servings of fruit and vegetables appear to be right on the mark.

Joshipura et al discussed current evidence, they suggested mechanisms through which fruit and vegetables (particularly of the green, leafy, cruciferous, or citrus varieties) would prevent ischemic stroke—dietary flavonoids, folate and its effect on serum homocysteine, fiber, and potassium. They concluded that the data support no single mechanism. The important point from this study and others is that patients should focus on consuming fruit and vegetables and not try to replace them with dietary supplements.

Since this study is not a randomized, controlled trial, it is naturally subject to confounding factors. For example, women who consume more fruit and vegetables might also exhibit other health-promoting behaviors that limit ischemic stroke. Yet, when Joshipura et al painstakingly controlled for a multitude of possible confounders, the apparent benefit of fruit and vegetable intake persisted. Joshipura et al also note that their cohorts are fairly homogenous in terms of occupation and socioeconomic status, minimizing the risk that socioeconomic factors confounded the results. However, it would be interesting in future studies to see how dietary factors interact with ischemic stroke risk among populations of lower socioeconomic status. ❖

Reference

1. Tribble DL, et al. *Circulation* 1999;99:591-595.

Laparoscopy in Patients with Advanced Ovarian Cancer

ABSTRACT & COMMENTARY

Synopsis: *Laparoscopy with careful closure of the peritoneum, rectus sheath, and skin, followed by chemotherapy or cytoreductive surgery with excision of the trocar trajectories within one week, is safe in patients with advanced ovarian cancer.*

Source: van Dam PA, et al. *Am J Obstet Gynecol* 1999; 181:536-541.

Van dam and colleagues have reported their experience with 83 women with primary, advanced

ovarian cancer and 21 women with recurrent ovarian cancer undergoing laparoscopy for tissue diagnosis and for assessment of operability. The purpose of the study was to determine risk factors for trocar implantation metastasis after diagnostic laparoscopy in this patient population. A recurrence developed at the trocar site in seven of 12 (58%) patients undergoing a laparoscopy in which only the skin was closed at the end of the procedure, and in two of 92 (2%) patients undergoing a laparoscopy with closure of all layers. The stage, histologic type, histologic grade, maximal tumor diameter, estimated weight of metastatic tumor, residual tumor diameter, surgical characteristics, and type of chemotherapy were well balanced between both groups. Patients with implantation metastasis had significantly more ascites and a longer interval between the start of platinum-based chemotherapy or cytoreductive surgery compared with patients without abdominal wall recurrence. A palpable abdominal wall metastasis developed in none of the patients undergoing a laparoscopy within one week after the laparoscopy. Patients with abdominal wall implantation metastasis had a survival rate similar to that of the other patients. van Dam et al concluded that laparoscopy with careful closure of the peritoneum, rectus sheath, and skin followed by chemotherapy or cytoreductive surgery with excision of the trocar trajectories within one week is safe in patients with advanced ovarian cancer.

COMMENT BY DAVID M. GERSHENSON, MD

For the past decade, we have witnessed a resurgence in the use of operative laparoscopy in gynecologic surgery in general, and also within the subspecialty of gynecologic oncology. Most worrisome is the fact that there are an escalating number of case reports and small series detailing tumor implantation in abdominal wall trocar sites after laparoscopy in patients with ovarian, endometrial, and cervical cancers. Many gynecologic oncologists are obviously concerned about this phenomenon and question the safety of laparoscopy in patients with clinical findings diagnostic of, or suspicious for a gynecologic malignancy. Although they do occur, tumor implantation sites in laparotomy incisions of patients with gynecologic cancers are rare. Several theories exist regarding the pathophysiology of this entity—oxygen content, gas turbulence, contamination by ascites, etc. We currently do not completely understand this phenomenon. Of course, gynecologic oncologists have known for years that patients who undergo paracentesis for massive ascites may subsequently develop tumor implantation in the paracentesis site. This flies in the face of previous reports. Importantly, van Dam et al found a lower incidence of trocar site implantation if all layers of the abdominal wall were closed separately. However, even with a sample size of 104 patients, the numbers are small. Furthermore, all of the patients in this study had either advanced stage disease or recurrent disease. The most disturbing variation on this theme is trocar site implantation in a patient with stage I disease, converting a potentially curable situation to one that may not be curable. I agree with van Dam et al that, if chemotherapy is administered soon after laparoscopy, any microscopic implantation is probably not a serious threat. The other related issue regarding laparoscopy in patients with known or suspected malignancy is its abuse and unnecessary use prior to definitive treatment. But that is a subject for a future discussion. Clearly, more study is needed in this area before we can fully embrace laparoscopy in a patient with a gynecologic malignancy. ❖

Special Feature

Phyto Fantasies

By Sarah L. Berga, MD

The phrase "greening of america" was originally used to describe our national embrace of ecological principles in the 1970s. The "greening of America" now best describes the collective worship by a large segment of our population of phytopharmaceuticals and phytonutraceuticals. While the concept that plants contain many interesting substances that may have medicinal and nutritional value cannot be disputed, the wholesale and uncritical endorsement of all plants and plant-derived substances as beneficial is clearly unwarranted. The following quote provides an interesting perspective. "Anthropobotany. Plants are downright dangerous. Try to think of any food that makes eating irresistible which is not derived from plants! And if plant inventions like chocolate, coffee, wine, and spices would not do enough damage to the neat and trim appearance of human bodies, the plants provide us with addictive substances like nicotine, cocaine, or morphine! So let us not be too sentimental about some other slightly beneficial plant products like digitalis, aspirin, and five million other pharmaceuticals. Look at the inner city problems all over the United States and tell me that these problems were not caused by plants!" (Buehler GA, in the *Dynamic Genome*. McClintock B. *Ideas in the Century of Genetics*.) The point of this review is to help the practicing physician address the many "phyto fantasies" that our patients may have and provide some balance and perspective.

Unfortunately, the uncritical predisposition to view plant-based products and herbal therapies as good and "synthetic" products as "bad" has created consumer vulnerabilities that market forces have been happy to exploit. Consider the following vignette. You are asked if you would like a cup of tea. Yes, you reply. Would you like regular or herbal tea? You pause, confused. You think, isn't all tea "herbal?" You decide not to be snide. Chamomile, you reply, avoiding an inaccuracy by being specific. The unspoken idea is that traditional teas containing traditional tea leaves are not as "herbal" as teas with more trendy leaves. In this example, the word "herbal" has been given a connotation independent of its literal meaning. I remember when green-colored "herbal" shampoos were first introduced. What a marketing bonanza has followed. "Herbal" products cost more and sell well. We have herbal cosmetics, soaps, shaving cream, lotions, and toothpaste, to name a few!

The latest craze in this marketing bonanza, phytoestrogens, influences the practice of the ob/gyn. Do your patients ask you whether they should take phytoestrogens? Do you ask them if they are taking any products with phytoestrogens? I have added this question to my routine office checklist and the answers can be surprising. Optimally, patients will bring you the bottles so you can see for yourself what the products contain. That too can be surprising. I think many of us are reticent to get too deeply involved in a conversation about phytoestrogens because so little scientific information is known (or we are not certain what is known). Patients also suspect that we may not know enough about this topic. If we display negative attitudes about their habits or beliefs, they may feel highly suspicious or annoyed. So what should we say? I have a few suggestions.

First of all, I think it is fair to acknowledge that phytopharmaceuticals, including phytoestrogens, may have benefits. The concept has merit, but we need to be careful about the implementation of the concept. Any substance "strong enough" to be beneficial is likely to be "strong enough" to do harm when taken in excess or inappropriately. For instance, I recently saw a woman with a phytoestrogen-induced menstrual cycle disturbance. The individual in question had just begun what sounded like a large quantity of new dietary supplements containing soy. The menstrual disturbance and symptoms, including hot flashes, remitted when she discontinued the supplements. The main idea here is not that phytoestrogens are "toxic," but that dose matters. Unfortunately, it may be difficult to find products whose labels are accurate.

One of the merits of whole plants is that they likely contain many beneficial substances. Furthermore, it may be that the full range of benefits are derived from the constellation of "active ingredients" contained within that plant. There may even be synergism between the constituents. So the idea of going to the lab to isolate the active substances may not always be a good one. In nutrition, this idea has led to the recommendation that we eat a balanced diet full of variety rather than depend on a handful of vitamins and supplements to buttress poor food choices. This has recently been referred to as the "food first" paradigm, because there may be some substances such as vitamin D or folate that we need to get in part from "pills." On the other hand, the scientific urge to understand the benefits of certain foods has generally meant trying to isolate the one or two constituents that may be most potent. Rightly so, we want a way to standardize the product and the dose. In medicine, we have yet to derive a resolution of these two fundamentals. Thus, we may feel the urge to equivocate or avoid the topic altogether. This is not an area of medicine that is well funded, but there is at least a growing recognition that we will have to delve into this arena.

To counsel patients and help them with their "phyto fantasies," it is helpful to know what phytoestrogens are. There are two main families. The isoflavone family includes biochanin A, genistein, formononetin, daidzein, daidzin, equol, coumestrol, and prunetin. The lignan family includes matairesinol, secoisolariciresinol, enterolactone, and enterodiol. The estrogenic action of these compounds are in the range of 1/100th to 1/1000th

that of estradiol. They also have antioxidant and antiproliferative properties that are still being elucidated. Most importantly, phytoestrogens are not just found in soy! They have been isolated from more than 300 plants, including some we eat routinely in the United States, such as apples, carrots, oats, plums, sunflower seeds, olive oil, potatoes, and coffee. To my mind, the biggest "phyto fantasy" is that one must learn to love tofu to get phytoestrogens. The better recommendation, endorsed by most nutritionists, is that we eat five servings each of fruits and vegetables daily.

There is another element that needs to be addressed with patients. We need to understand the motivation that drives the behavior. Is it distrust of traditional medicine? Is it anxiety and a need to gain control? The director of cancer prevention at the National Cancer Institute (at NIH), Peter Greenwald, recently stated that the "best evidence indicates that at least a third of all cancers have dietary components." Patients may think that phytopharmaceuticals and phytoestrogens in particular are a way to avoid the negatives of "synthetic" drugs such as mainstream estrogen while simultaneously boosting their exposure to mother nature's healing substances. Patients rarely understand the notion that there can be too much of a good thing when it comes to substances labeled "food supplements."

Since the primary use of most phytoestrogens involves the treatment of menopausal symptoms or consequences, and in consideration of the goal of primer nocere, physicians should acquaint themselves with herbal therapies thought to be harmful. These agents and their potential side effects are shown in Table 1.

Table 1

Toxic Herbs

- Belladonna-3 toxic alkaloids, including atropine
- Blue cohosh-vasoconstriction, labor, hypertension
- Comfrey-liver failure
- Ephedra-cardiac arrhythmias
- Lobella-arrhythmias, coma, death
- Poke root-extremely toxic, respiratory failure
- Sassafras-carcinogen
- Scullcap-liver damage

Table 2 lists herbal products approved by the German Commission E for the use of menopausal symptoms. While the evidence behind these recommendations may be far from what we would consider scientifically valid, at least this agency has led the way in attempting to bring some scientific and medical order to consumer chaos. In the United States, our Congress declined in 1994 the opportunity to regulate food supplements, so these agents now fall under the review of the USDA rather than the FDA. Because of this lack of regulation, purity and labeling remain a huge problem in the United States. ❖

Table 2

Herbal Therapies Approved by the German Commission E for Treatment of Various Menopausal Symptoms

- Balm—anxiety
- Black cohosh—anxiety
- Chasteberry—emotional balance
- Ginko—memory
- Ginseng—depression, fatigue
- Passion flower—menopausal constellation
- St. John's wort—depression
- Valerian—sleep

References

1. Seidl MM, et al. *Can Fam Physician* 1998;44: 1299-1308.
2. Tyler, Varro E. *The Honest Herbal*: *A Sensible Guide to the Use of Herbs and Related Remedies*, 3rd ed. 1993.
3. www.nlm.nih.gov (Web site for National Library of Medicine, which provides a user-friendly way for you to search the extant medical literature)
4. www.nal.usda.gov/fnic/IBIDS (Governmental site that attempts to provide a complete compendium about food supplements)

CME Questions

22. Which of the following statements is true?

a. ERT increases the risk of recurrence in ovarian cancer patients two-fold.
b. ERT increases the risk of recurrence in ovarian cancer patients five-fold.
c. ERT decreases the risk of recurrence in ovarian cancer patients by 50%.
d. The influence of ERT on risk of recurrence in ovarian cancer patients is unknown.
e ERT has no negative or positive influence on recurrence in ovarian cancer patients.

23. Based on the data of Barron et al, which of the following laboratory tests is *not* needed when the patient with pregnancy-induced hypertension is found to have a normal platelet count and a normal LDH value?

a. fibrinogen
b. creatinine
c. complete blood count
d. urinalysis
e. albumin

24. In the Nurses' Health Study, daily intake of 5-6 servings of fruits and vegetables appeared to reduce women's risk of ischemic stroke by approximately:

a. 5%.
b. 15%.
c. 25%.
d. 35%.
e. 45%.

25. Maternal dietary deficiency has been shown to be associated with all of the following disorders in adult offspring *except*:

a. antisocial personality disorder.
b. spina bifida.
c. schizophrenia.
d. regional enteritis.

26. Which statement is *false*?

a. The two main families of phytoestrogens are the lignans and the isoflavones.
b. The "food first" paradigm suggests that nutritional benefits derive from the complex constellation of constituents in naturally-occurring foods and that it is difficult to replicate the nutritional benefits of whole foods with food supplements and vitamin pills.
c. Most of the common fruits and vegetables consumed in the United States do not contain phytoestrogens from the isoflavone family.
d. Soy products, including tofu, are a good source of phytoestrogens from the isoflavone family.
e. Phytoestrogens have antiproliferative and antioxidant properties.

27. The incidence of trocar site implantation after laparoscopy in patients with ovarian cancer is:

a. 1%.
b. 5%.
c. 10%.
d. 20%.
e. unknown.

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15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			2481	2428
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	2118	2078
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			2118	2078
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			21	21
f. Total Free Distribution *(Sum of 15d and 15e)*			21	21
g. Total Distribution *(Sum of 15c and 15f)*			2139	2099
h. Copies Not Distributed			342	329
i. Total *(Sum of 15g, and h.*			2481	2428
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/24/99

Donald R. Johnston

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

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