THOMSON
AMERICAN HEALTH CONSULTANTS

Primary Care Reports™

The Practical, Peer-Reviewed Journal for Primary Care and Family Physicians

Volume 12, Number 9 **September 2006**

Undoubtedly the most famous person with testicular cancer is cyclist Lance Armstrong. When he was first diagnosed in October 1996, he had hemoptysis with evidence of metastatic disease to his abdomen and chest. His oncologist told him that the cure rate for testicular cancer in the advanced stage was between 60% and 85%. He was assured that there was no reason that he could not make a full and complete recovery. At a press conference shortly after his diagnosis, he stated, "… I want you all to know that I intend to beat this disease, and further, I intend to ride again as a professional cyclist…. Had I been more aware of the symptoms, I believe I would have seen a doctor before my condition had advanced to this stage. I want this to be a positive experience and I want to take this opportunity to help others who might someday suffer from the same circumstance I face today." The rest, as they say, is history. As winner of seven Tour de France races, he represents the epitome of a cancer survivor and is a true inspiration to all cancer patients.

—The Editor

Testicular Cancer

Author: **Marc B. Garnick, MD**, Clinical Professor of Medicine, Harvard Medical School, Physician, Beth Israel Deaconess Medical Center, Boston, MA.

Peer Reviewer: **Gregory Gordon, DO**, Medical Oncologist, Dayton, OH.

Introduction

Testicular cancer is one of the most common cancers that affects men in their third and fourth decade of life; however, in absolute numbers, it is relatively uncommon. Once incurable if the cancer was metastatic, testicular cancer now represents one of the most curable of all solid neoplasms, even in the setting of widespread metastatic disease. The multidisciplinary management that incorporates surgery, chemotherapy (sometimes with stem cell transplantation), radiation therapy, and post-chemotherapy surgery (so-called tumor reductive surgery) has become a model for modern-day testicular cancer management.

Because of this cancer's rarity, the optimal treatments generally are undertaken by specialists experienced in utilizing intensive chemotherapy regimens and centers that perform a specialized type of surgery known as retroperitoneal lymph node dissection. However, the primary care physician is a critical member of the patient's health care team, since the PCP is often the first provider to consider and establish the

Statement of Financial Disclosure

To reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief), and Dr. Garnick (author), and Dr. Gordon (peer reviewer) report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

diagnosis of testicular cancer. Having a high index of suspicion about the possibility of testicular cancer often will lead to a timely diagnosis, appropriate referral, and early treatment intervention.

This review will focus on the important clinical and protean presentations of men that lead to the diagnosis testicular cancer and provide an understanding about: the differences between the two major types of testicular cancer—seminomas and non-seminomas; the use of tumor-specific markers as an aid in both the diagnosis and management decisions; the role of active surveillance in the management of good-risk patients; the acute and chronic toxicities of testicular cancer chemotherapy; and the role of the physician in following up patients who have achieved long-term cure following cancer-specific treatment for testicular cancer.

Basic Epidemiology, Risk Factors, and Diagnosis of Testicular Cancer

It is estimated that in calendar year 2006, there will be approximately 8250 new cases of germ cell testicular cancer diagnosed in the United States. Approximately 370 deaths are expected to occur in this year as well.[1] While this represents a slight increase over the past several decades, testis cancer still is relatively rare, although it is one of the most common cancers in men under the age of 35 years old.[2] Given its rarity, few primary care physicians in any given year will ever see a documented case of testicular cancer and even specialist oncologists (medical and urologic)also are unlikely to see more than an isolated case of testicular cancer. On the other hand, because the manifestations of localized, regionally advanced, and metastatic testicular cancer are shared by many common disorders, it is important for the physician to appreciate and consider the possible diagnosis of a testis cancer. Thus, it is completely appropriate for the clinician to consider and rule out many more cases of testis cancer than are actually diagnosed.

The disease is distinctly more common in whites than blacks. Children with a history of cryptorchidism have a greater incidence. In general, these undescended testicles are treated with an orchiopexy at a young age, generally at 1 year. Abdominal testes need to be corrected or removed. There is about a 6- to 10-fold increase in testicular cancer in family members who have a history of testicular cancer. Those with a long history of an atrophic testis also may have an increased incidence. Patients who are HIV positive may develop seminomas at a higher rate than the general population.[1] There is speculation about whether a prior history of mumps orchitis, maternal exposure to diethylstilbesterol, Vietnam veterans exposed to agent orange, or those with the finding of microlithalisis are more likely to develop testis cancer. There are certainly a spectrum of genituourinary abnormalities associated with these disorders, and careful evaluation of the testis in these circumstances is appropriate. In situ or intratubular carcinoma may be found in association with an evaluation of infertility when a testicular biopsy is obtained and many of these may go on to develop an invasive cancer.[3] Finally, there is a 2-3% lifetime risk of developing a contralateral metachronous testis cancer in patients who have developed one testis cancer.[4]

Association of Genetic Abnormalities and Extragonadal Germ Cell Cancers. In approximately 80% of germ cell cancers of the testis, there is a distinctive chromosome abnormality on the short arm of chromosome 12, called [i(12p)]. A similar abnormality has been described in patients with carcinoma in situ and extragonadal germ cell tumors. Excessive 12 p genomic material has been observed in a large number of germ cell cancers. Other cytogenetic abnormalities and oncogene expression, including c-kit proto-oncogene, have been described.[5-8] The rare variant of germ cell tumors of the testis, the extragonadal germ cell tumor syndrome (EGGCTS), is characterized by mid line germ cell cancers of the anterior mediastinum or retroperitoneum, or rarely the pineal gland of the central nervous system, without any obvious primary cancer in the testis. These lesions generally are very advanced at the time of initial presentation and are associated with a markedly less favorable prognosis. Within this rare disease is the even more rare association of idiopathic thrombocytopenia, acute megakaryocytic leukemia of the M7 variety, and Kleinfelter's syndrome. The two associated platelet abnormalities seem to be an intrinsic characteristic of the disease rather than a secondary consequence induced by chemotherapy.[9]

Suspected Diagnosis and Diagnostic Workup[10,11]

The spectrum of presentations of primary testicular cancer are varied. Most often, the patient will complain of a painless swelling or hardening of the testis, either found by himself during testicular self-examination or by a partner. In the author's

Primary Care Reports™, ISSN 1040-2497, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
SPECIALTY EDITOR: Shelly Morrow Mark.
MARKETING PRODUCT MANAGER: Nan Webb.
GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports™***, P.O. Box 740059, Atlanta, GA 30374.

Periodicals postage paid at Atlanta, GA.
Back issues: $26. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.

E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: shelly.mark@thomson.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $349
(Student/Resident rate: $170).

Multiple Copies
1-9 additional copies: $314 each; 10 or more copies: $279 each.

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 36 AMA PRA Category 1 Credit(s)™. It is in effect for 24 months from the date of publication. Physicians should only claim credit commensurate with the extent of their participation in the activity.*

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This CME activity was planned and produced in accordance with the ACCME Essentials.

Primary Care Reports has been reviewed and is acceptable for up to 27 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/06. Term of approval is for one year from this date. Each issue is approved for 2.25 Prescribed credits. Credit may be claimed for 1 year from the date of this issue.

This program is intended for primary care and family practice physicians.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments

Please call **Shelly Morrow Mark,** Specialty Editor, at (352) 351-2587 or e-mail: shelly.mark@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

experience, the most common physical finding is a diffusely indurated testis on one side compared to the other. Less commonly, there is a specific discernable lump or nodule. The clinician should be able to distinguish the epididymis from the testis itself as well as have an appreciation for the general physical appearance and presentation of hydroceles, varicoceles, spermatoceles, epididymal cysts, as well as the more painful presention of torsion of the testis, epididymitis, and orchitis. It is not unusual for a patient to be diagnosed with epididymitis and be given a prescription for an antibiotic, only to have the symptoms resolve. Yet later, the diagnosis of a testicular neoplasm is made when the symptoms recur and a more detailed evaluation is done. This is explained by the concomitant presence of both epididymitis and cancer in the same testis, with the infectious component resolving with antibiotic treatment, masking and delaying the diagnosis of the underlying cancer. It is not uncommon for a patient to emergently present with a rapidly expanding scrotal mass accompanied with testicular and scrotal pain. The presentation may reflect an acute hemorrhage into a testis neoplasm causing rapid expansion of the scrotal contents and is more commonly seen with a non-seminoma lesion (see below) that contains choriocarcinoma elements. The important differential diagnosis (in addition to cancer) under these circumstances is acute torsion of the testis or acute orchitis or epididymitis (assuming that there is no obvious trauma to explain the findings). An ultrasound of the scrotal contents or a radionuclide scan of the testis may be helpful in distinguishing these entities.

In a small percentage of patients, the first manifestation of testicular cancer may reflect signs or symptoms from metastases. Enlargement of a supraclavicular lymph node or new onset back pain in a previously asymptomatic young male that persists despite routine interventions may represent retroperitoneal adenopathy. Dyspnea and/or hemoptysis are recognized, though uncommon, initial manifestations of testicular cancer. A detailed exanimation of the testicles should be undertaken in these individuals. Persistence of symptoms, especially back pain, should focus the workup on an evaluation of the retroperitoneum, generally best accomplished with an abdominal pelvic CT scan. In these circumstances, clinical judgment must be exercised that balances the substantially more common musculo-skeletal etiologies of back pain from that due to retroperitoneal adenopathy. Unfortunately, many of the substantial delays in diagnosis of a testicular cancer occur in the setting of an incomplete evaluation of the etiology of back pain and no documentation of a testicular examination in otherwise healthy young men. The presence of pulmonary symptoms generally is evaluated more promptly, especially if a patient complains of hemoptysis. Gynecomastia, either bilateral or unilateral, or rarely galactorrhea should alert the physician to the possibility of a human chorionic gonadotropin (hCG) containing tumor and the associated endocrine manifestations.

Extragonadal Germ Cell Tumor Syndrome (EGGCT)[12,13]

Approximately 10% of men who present with germ cell cancer will have no demonstrable evidence of a testicular primary lesion. Typical presentations include the presence of an abdominal mass, hydronephrosis secondary to retroperitoneal adenopathy, pulmonary manifestations secondary to mediastinal adenopathy (especially anterior mediastinal adenopathy), and rarely a central nervous system presentation of bleeding, or stroke secondary to a pineal neoplasm. These patients often are marker-positive, strongly suggesting the presence of a germ cell tumor. These cancers are thought to develop from primordial germ cells migrating along the embryonic midline structures during fetal development which maintain their aberrant anatomic position and never migrate into the scrotum. Biopsy will reveal either seminoma, non-seminoma, or mixed tumors, similar in appearance to their testicular counterparts. These cancers have a worse prognosis from testicular primaries due to either an intrinsically different genetic makeup or due to later clinical presentations since attention is not focused on a testicular abnormality. The author's view is that these cancers are intrinsically more resistant to chemotherapy and other therapies and are genetically different compared to the testis primary cancers, leading to the worse prognosis.

Establishing the Diagnosis. If a testicular cancer is suspected and in the differential diagnosis upon completion of a history and physical examination, there are three critical steps that the primary care physician can consider: referral to a urologic surgeon; obtaining a testicular ultrasound; and obtaining a blood test for determination of the tumor markers alpha-fetoprotein (AFP), hCG, and lactic dehydrogenase (LDH). The communication of the results from steps two and three will be extremely helpful for the urologist in decision making regarding the necessity for performing a radical inguinal orchiectomy. Under most circumstances, the urologist referral may take one to two days; by that time, important information will be available if indeed the lesion suspected is a marker-secreting tumor, and a testicular ultrasound will have already been obtained.

Surgical Approach to Establish the Diagnosis[11]

The generally accepted approach to a primary testicular cancer is the performance of a radical inguinal orchiectomy with high ligation of the spermatic cord. The role of a trans-scrotal testicular biopsy is not recommended and actually contraindicated, since the drainage of the testicular lymphatics may be altered by disruption and possible contamination of the scrotal lymphatic drainage sites. The testis primary lymphatic drainage is to the retroperitoneal lymph chains located between lumbar levels 1 and 3; the drainage of the scrotum is to the inguinal area—an anatomic area rarely affected by testicular cancer in the absence of a so-called scrotal violation.

Once the scrotal contents that include the testis, paratesticular tissues, and spermatic cord are delivered from the operating field, the surgeon may bivalve the testis and gain an appreciation of the gross appearance of lesion resected. In general, pure seminomas (see below) have a waxy, fleshy, and lobulated appearance, with little in the way of necrosis and hemorrhage. In contrast, nonseminomatous lesions often may have gross evidence of hemor-

rhagic areas and necrosis. Oftentimes, the entire testis is replaced by neoplasm, especially if the testis on physical examination was indurated in its physical texture.

Pathology and Relationship of Spread[14]

Nearly 95% of tumors of the testis in adults are germ cell cancers. The remaining 5% include Leydig cell or Sertoli cell tumors or tumors of other primitive structures and will not be discussed further in this review.

The germinal cell tumors can be either seminomas, non-seminomas or a mixture of the two types. In most series, pure seminomas make up between 50-60% of the primary cancers, while either non-seminomas or a mixture of seminoma make up the remainder. Non-seminomas can include embryonal carcinoma, yolk sac tumors, choriocarcinoma, or teratoma. Teratomas may be either mature or immature; the term teratocarcinoma generally refers to the combination of embryonal carcinoma and teratoma. The management of non-seminomas often takes into consideration the cell type that comprises the testicular primary lesion.

Reasons for Distinguishing Seminoma from Non-seminoma[15,16]

There are several important reasons for distinguishing seminomas from non-seminomas. Seminomas tend to occur in a slightly older population than that of non-seminoma patients. Seminomas also tend to spread via the lymphatic system, first to the retroperitoneal lymph nodes and then to the mediastinal lymph nodes. In contrast, non-seminomas metastasize both via the lymphatic system as well as hematogenously. Thus, the presence of multiple pulmonary nodules is more likely to be associated with either choriocarcinoma component or embryonal carcinomas, as opposed to seminoma.

The biggest difference between seminoma and non-seminoma is the relative responsiveness to radiation therapy. Seminomas are exquisitely sensitive to relatively low doses of radiation therapy, which serves as the mainstay for treatment of seminomas. In contrast, non-seminomas are relatively more radioresistant and rarely are treated with radiation therapy except under certain circumstances.

Another distinction between the two pathologic cell types relates to the role of surgery for metastatic disease following chemotherapy. Tumor reductive surgery is a mainstay for removing residual masses, usually located in the retroperitoneum, following chemotherapy for non-seminomatous disease. The management of residual retroperitoneal masses after chemotherapy for bulky seminomas is a more difficult clinical challenge, since the masses that remain after chemotherapy often are fibrotic and adherent to surrounding great blood vessels and the kidney, making surgical resection technically difficult and often associated with major operative or post-operative complications. Thus, these masses often are watched and therapeutic decisions such as surgery are made based upon the size of the residual mass and an assessment of any change in size or appearance in the months following completion of chemotherapy.

Biological Markers[17]

There are three biological markers or tumor associated markers that are associated with germ-cell tumors of the testis—alpha fetoprotein, human chorionic gonadotropin and lactic dehydrogenase. The first two are germ cell specific, while the LDH represents a non-specific marker of extent of tumor. AFP is an oncofetal protein produced by primitive germ cells, especially non-seminomas that contain yolk sac elements. The marker hCG often is associated with non-seminomas that contain choriocarcinoma elements or embryonal carcinoma elements. On occasion, patients with pure seminomas may have elevations of hCG that reflect the presence of synctiotrophoblastic giant cells, capable of producing hCG. The use of a fourth marker, placental alkaline phosphatase, occasionally may be elevated in patients with seminoma.

The clinician must appreciate that seminomas, in the pure form, are unable to produce AFP, and the elevation of AFP in the blood of a patient thought to have a pure seminoma dictates that the patient has occult non-seminomatous elements. Thus, in the setting of a testicular primary lesion that is pathologically interpreted as being a pure seminoma, an elevation in the AFP indicates that occult non-seminomatous tissue is present. This can be an overlooked focus in the testicular primary lesion itself (uncommon) or the presence of non-seminomatous elements in metastatic lesions. The unfortunate consequence of treating a patient thought to have a pure seminoma and elevated AFP with radiation therapy is treatment failure, since the dose of radiation is unlikely to sterilize the non-seminoma components, making relapse highly likely. Thus a detailed and meticulous evaluation of the testicular tissue is needed under these circumstances.

The clinical use of biological markers, especially AFP and hCG, has many roles. During the initial presentation of a testicular mass, the elevation of these markers essentially secures the diagnosis of germ cell testicular cancer even before the final pathology is obtained. The decline to normal of these markers is helpful in determining the likelihood of remission. For example, the biologic half life of AFP is approximately 6 days, and for hCG it is 24-36 hours. Thus following removal of a testicle that contains cancer, the elimination from the blood of these markers according to the half-lives is a necessary component in determining whether residual cancer exists. If the markers do not decline rapidly according to the half life determinations, and the patient remains "marker positive" after removal of the primary testicular lesion, the patient generally is treated as having metastatic disease. Markers also may signal the earliest presence of relapse in patients who have been in remission and often predate the radiographic evidence of cancer by weeks to months. The presence of an elevated AFP, as stated previously, mandates that the patient is treated as a non-seminoma. Finally, the absolute value of the elevated marker is prognostic and serves as a criterion for risk assessment and outcome.

Staging Evaluations and Staging of Testicular Cancer[18]

The general evaluation for a patient with the pathologically

Table 1. Staging of the Primary Tumor

STAGING OF PRIMARY TUMOR

T1: Tumor confined to the testis/epididymis and no evidence of lymphovascular invasion within the cancer (negative LVI)
T2: T1 + LVI
T3: Spermatic Cord involvement with tumor ± LVI
T4: Scrotum extension of the tumor ± LVI

STAGE

I: No evidence of retroperitoneal lymph node involvement below the diaphragm (-RPLN)
II: + RPLN
- IIA: < 2 cm lymphadenopathy
- IIB: 2-5 cm
- IIC: > 5 cm

III: Metastatic disease above the diaphragm and or visceral involvement
- M1: Pulmonary metastases
- M2: Non-pulmonary visceral metastases

Markers also are used to establish prognosis according to Table 2.

Key:
LVI = lymphovascular invasion ; RPLN = retroperitoneal lymph node dissection

Table 2. Marker Classification (LDH, HCG, AFP)

S0
- Markers are at the upper limit of normal (ULN)

S1 (GOOD)
- LDH < 1.5 X ULN and hCG < 5000 and AFP < 1000

S2 (INTERMEDIATE)
- LDH 1.5 – 10 X ULN or hCG = 5000 or AFP = 1000

S3 (POOR)
- LDH > 10 X ULN or hCG > 5000 or AFP > 1000

Key:
LDH = lactic dehydrogenase; ULN = upper limit of normal; hCG = human chorionic gonadotropin; AFP = alpha-fetoprotein

established diagnosis of germ cell cancer of the testis is a thorough physical examination, determination of the biological markers, routine hematology, chemistries evaluating function of the liver and kidneys, metabolic chemistries, abdominal and pelvic computerized tomography, chest computerized tomography (CT). In general, routine evaluation of the central nervous system (MRI or CT scan) or obtaining a radionuclide bone scan generally is not needed unless the patient fits into a poor prognosis classification (see below). The patient can be staged according to the following conventions. (*See Tables 1 and 2.*)

Treatment Options According to Stage of Disease

Non-seminoma.[19] For stage I non-seminoma, the standard of care is to perform a retroperitoneal lymph node dissection (RPLND). This invasive surgical procedure is both diagnostic, and in certain circumstances, therapeutic, in that removal of lymph nodes that contain cancer may be considered definitive treatment. While open surgical procedures have been the standard, advances in laparoscopic techniques recently have been introduced. The optimal candidates are those whose tumors show evidence of lymphovascular invasion (LVI), or in whom the tumor that has spread to the tunica albuginea or spermatic cord. These patients would experience a 50% relapse rate based upon the primary tumor if they did not undergo an RPLND. The advantages of performing an RPLND are the identification of micrometastases early, fewer cycles of chemotherapy would be needed if RPLND is positive, and chemotherapy can be avoided for those who don't need it.

If RPLND is negative, the primary care physician in association with the oncologist or urologist can help play an important role by performing a physical examination, chest x-ray, and checking marker levels monthly for the first year, then every two months for the second year. Under these circumstances, CT scans generally are not routinely required.

Active Surveillance.[20] The concept of active surveillance for Stage I non-seminoma has gained in popularity, especially given the excellent effectiveness of cisplatin containing chemotherapy for more advanced stages of disease. The optimal candidates are those with a T1 tumor that shows no evidence of LVI and does not contain embryonal carcinoma. Here, the goal is to cure 98-99% of patients and spare 75-80% the necessity for a RPLND. This treatment option requires a very compliant patient and a system within the physician's office to assure that the follow-up is done on time. That follow-up includes in the first year of diagnosis, a monthly physical examination, chest x-ray, marker levels; and abdominal pelvic CT scan every two months. During year two, the physical exam, chest x-ray, and markers can be done every 2 months, with the abdominal pelvic CT scan done every 4 months.

The relapse rate (usually first seen in the retroperitoneum) is generally 20-25% and occurs within the first 7-8 months following completion of treatment.

Stage IIB and IIC Non-seminoma.[21] While in the past patients with stage IIB with retroperitoneal disease of $\leq$ 5 cm were treated with RPLND, today both IIB and II C patients are treated with chemotherapy followed by post-chemotherapy tumor reductive surgery. Surgical removal of residual masses was advocated since such masses could contain residual teratoma in 40% and viable cancer in 15%, with the remainder representing fibrosis and necrosis. Both of the first two histologic findings require surgical removal; unfortunately there is no reliable method to determine the histology in the marker-negative patient after chemotherapy. If there are no radiographic lesions in the retroperitoneum and the patient's biological markers are negative, no post-chemtherapy RPLND would be required.

Table 3. Risk Stratifications for Patients with Metastatic Disease

NONSEMINOMA

Good Risk
- 1° testicular or 1° retroperitoneal extragonadal tumor and "good" markers
- No non-pulmonary visceral metastases

Intermediate Risk
- 1° testicular or 1° retroperitoneal and "intermediate" markers" *AND*
- No non-pulmonary visceral mets

Poor Risk
- 1° mediastinal EGGCCT *OR*
- 1° testicular or 1° retroperitoneal with either visceral metastases or "poor" markers

SEMINOMA

Good
- 1° testicular or 1° retroperitoneal or 1° mediastinal EGGCCT *AND*
- Any markers *AND*
- No non-pulmonaray visceral metastases

Intermediate
- 1° testicular or 1° retroperitoneal or 1° mediastinal EGGCCT *AND*
- Any markers *AND*
- Non-pulmonary visceral metastases

Please note: There is no poor risk classification for seminomas
Adapted with permission from: American Society of Clinical Oncology. *Oncology Medical Knowledge Self Assessment Program*. Third Edition, Chapter 9, 2003.

Follow-Up for Cancer.[22] Following curative surgery, radiation therapy or chemotherapy, patients are often followed-up closely during the first two years. While many patients continue to follow-up with their urologist or medical oncologist, it is also common for the presumed cured patient to be followed by their primary care physician or intenist. Although there are no formal established guidelines, general recommendations would include physical examination, chest x-ray, and markers every 6 months for year three; for years 4-5, physical examination and markers every 6 months, and chest x-ray every year; and then physical examination and markers yearly thereafter. While the likelihood of a testicular cancer relapse is very small, it is never completely eliminated. There is also a risk of developing a metachronous, second testicular primary cancer. For patients with seminoma, the rate of late relapse is greater after 5 years compared to non-seminomas, and these patients are followed life-long.

There is also a 2-3% lifetime risk of patients developing second testicular cancers, which represents another reason for life-long follow-up. Whether routine testicular cancer screening for second cancers is justified is debatable; there are circumstances in which there are a variety of nonspecific and non-neoplastic testicular ultrasound abnormalities when, if found, may require a work-up and potentially unnecessary diagnostic procedures.

Seminoma. For stage I and stage II A and II B seminoma,[23,24] radiation is the standard of therapy for the majority of patients. Generally, a dose of 25 Gy is given. In cases of stage IIA and IIB, a boost of 30-35 Gy is administered to areas of bulk disease. No mediastinal radiation is required. However, in stage I seminoma, nearly 80% of patients would not necessarily need radiation, since the retroperitoneal lymph nodes would not contain any metastatic cancer. Thus, the possibility of active surveillance is also appropriate in compliant patients, with a follow-up schema similar to that outlined for patients with non-seminoma. Recently, several publications have advocated the use of single agent carboplatin as an alternative to either radiation or active surveillance and overall results from European studies suggest similar long-term outcomes.[25,26] Patients with a horseshoe kidney are relatively contraindicated to receive radiation and their care could include surveillance or chemotherapy.

Advanced Seminoma. With retroperitoneal adenopathy measuring greater than 5 cm, chemotherapy generally is recommended. in doses and schedules similar to non-seminoma (see below). While in the past post-chemotherapy radiation was used, today it no longer is recommended. Residual retroperitoneal masses, as mentioned above, generally are not surgically removed, but rather observed for changes in the size of the mass, and consideration for biopsy if there are any changes.

During the past decade, based upon data generated by the International Germ Cell Cancer Consensus Working Group,[27] there has been a risk stratification (predominantly addressing those patients with metastatic disease) based upon the likelihood of cure that integrates parameters of stage of disease, site of origin (primary testis versus extragonadal) and marker status. Table 3 illustrates this stratification.

Chemotherapy Treatment Regimens

Testicular germ-cell tumors are remarkable in that they are uniquely sensitive to chemotherapeutic agents. The most frequently used regimen is the BEP (bleomycin, etoposide, and cisplatin). Bleomycin is a cytotoxic agent as it generates activated free radicals, which cause breaks in single- and double-stranded DNA leading to cell death. Its main side effects include skin reactions, pulmonary toxicity, and rarely myelosuppression. Etoposide is a topoisomerase II inhibitor that is derived from a plant alkaloid. Its main side effects include myelosuppression, gastrointestinal upset, anorexia, alopecia, and an increased risk of secondary malignancies including acute myelogenous leukemia. Cisplatin is a platinum analog, which covalently binds to DNA resulting in formation of DNA adducts, resulting in inhibition of DNA synthesis and function. Its main side effects include nephrotoxicity, gastrointestinal upset, myelosuppression, neurotoxicity, ototoxicity, hypersensitivity reactions, and transient elevation in liver function tests, hair loss, SIADH (syndrome of inappropriate antidiuretic hormone), vascular events, and metallic taste leading to loss of appetite.

Treatment According to Risk Stratification[18,19,27]

Remarkably, the overall cure rate for advanced metastatic

germ cell cancer is reported to be 70-80% from world wide studies. The treatment resulting in these spectacular results includes cisplatin based chemotherapy and, in the case of non-seminomas, tumor reductive surgery following chemotherapy. The objective of treatment in any patient with metastatic disease, regardless of the extent of disease, is *cure*. Lance Armstrong, with widely metastatic pulmonary and brain metastases, is the most visible example of this. For good-risk patients, the clinical objective is to minimize the toxicity associated with therapy and maximize the cure rate. For the poor risk stratification, the therapeutic goals are to increase the probability for cure, even though the treatment may be associated with greater toxicity.

Non-Seminoma Good Risk Stratification. The standard treatment for this group of patients, who constitute nearly 80% of those who present with metastatic disease, is either the combination of cisplatin plus etoposide for four cycles or a combination of cisplatin plus etoposide with or without Bleomycin for three cycles. The dose and schedule are beyond the scope of this review. However, for the primary care physician whose role is increasingly important in the long-term follow-up for chemotherapy complications, it is important to appreciate the potential significant toxicities associated with Bleomycin (see below).

Seminoma and Non Seminoma Intermediate Risk Stratification. These patients generally are treated with four cycles of cisplatin plus etoposide plus Bleomycin. In those patients with non-seminomatous disease, retroperitioneal lymphadenectomy is generally indicated post chemotherapy given the high percentage of residual masses that are present following chemotherapy.

Non-seminoma with Poor Risk Stratification. This group represents approximately 20% of patients in whom a less than 50% likelihood of cure is anticipated. The standard of care is four cycles of cisplatin plus etoposide plus Bleomycin, in doses and schedules used in the lower risk stratifications. However, these patients should be considered for investigational randomized studies evaluating the efficacy of stem cell transplant with higher doses of chemotherapy as well as the addition of other chemotherapeutic agents, such as cyclophosphamide. Again, the role of surgery is a critical component of the overall management in these patients. Surgical removal of masses in the retroperitoneum, thoracic cavity or other viscera, including the brain, are all warranted in the patient who has been rendered marker negative but still demonstrating residual masses. As stated above, the residual mass may consist of either teratoma, cancer, or fibrosis/necrosis. In the former two, the resection of the masses is considered therapeutic if the lesions are completely resectable.

Chemotherapy Programs for Relapsed Germ Cell Cancers.[28-30] The use of chemotherapy programs that include ifosphamide, paclitaxel, and gemcitabine and programs that incorporate high dose chemotherapy with stem cell transplantation support (sometimes requiring two separate transplants) are all viable options and require the detailed evaluation of specialists in institutions that commonly care for these very complicated patients.

Special Considerations in Patients with Germ Cell Tumors

There is a spectrum of important clinical situations that require the skill of both specialist and non-specialist alike in diagnosing, managing and following patients with germ cell cancers. Four of these are of particular importance, since appropriate recognition and intervention often may mean the difference between fatal and non-fatal outcomes. These include:

- Understanding the risks of bleomycin;[32,33]
- Recognizing the platelet disorders associated with anterior mediastinal extragonadal germ cell cancers;[34,35]
- Appreciating the importance of surgical removal of post-chemotherapy residual masses that contain teratoma;[36]
- Managing and recognizing both the acute and chronic complications of chemotherapy. These include second cancers following etoposide chemotherapy and radiation, and toxicities of the hematologic, renal, pulmonary, gonadal, neurologic, and cardiovascular systems.[18,37]

Understanding the Risks of Bleomycin. No chemotherapeutic agent in urologic cancer requires more care and vigilance than bleomycin. Nearly 50% of treatment-related deaths are due to bleomycin pulmonary toxicity. This complication is devastating, especially if it occurs in a patient who is otherwise cancer free. The development of a non-productive cough, rales, or shortness of breath and/or a chest radiograph that shows a reticulonodular or nodular pattern is often the presenting feature of developing bleomycin pulmonary toxicity. The diffusion capacity, which should be monitored carefully during treatment, may show a decline. Under these circumstances, the bleomycin should be discontinued and closely monitored with serial diffusion capacities and chest x-rays. The fatal complications occur when a patient with developing or unrecognized bleomycin pulmonary toxicity is scheduled for his tumor reductive surgery. Whether the operative combination of excess fluid administration or high inspired oxygen concentrations administered during the operation is contributory is debated; nevertheless, such operations are to be avoided until the pulmonary toxicity is resolved and, when the operation takes place, excess fluids and high inspired oxygen are best avoided. Additional considerations for increasing the incidence of bleomycin toxicity or worsening its outcome include patients who have undergone thoracic irradiation or who have compromised renal function.

Recognizing the Platelet Disorders Associated with Anterior Mediastinal Extragonadal Germ Cell Cancers. Although rare, EGGCTs of the anterior mediastinum, especially embryonal cancers, are disproportionatly associated with platelet disorders not associated with chemotherapy administration. These include idiopathic thrombocytopenia, which makes the administration of full-dose chemotherapy difficult because of the bleeding tendencies associated with the low platelets. A second, more ominous association is that of acute megakaryocytic leukemia. When the two diseases co-exist, the outcome is nearly universally fatal.

Appreciating the Importance of Surgical Removal of Post-Chemotherapy Residual Masses that Contain Teratoma. The development of teratomas in residual masses, both of the

retroperitoneum and thoracic cavity, following chemotherapy requires surgical removal in the marker-negative patient. This is especially important, since the teratomatous component of these lesions, if left in situ, may undergo malignant degeneration in the form of embryonal rhabdomyosarcomas, primitive neuroectodermal tumors, or other neural crest tumors. The teratomas may contain elements of endoderm, ectoderm, and mesoderm, which probably accounts for the cellular components that eventually undergo malignant degeneration. There may be special circumstances where surgical removal of teratoma is warranted even if the patient is marker-positive following chemotherapy; these cases must be individualized. These lesions tend to be unresponsive to chemotherapy, providing yet another reason for their removal.

Managing and Recognizing both the Acute and Chronic Complications of Chemotherapy. Although usually not managed by the primary care physician, the acute complications of germ cell chemotherapy include anticipated myelosuppression, which is best managed by growth factor support and an erythropoietin-sensitive anemia, often ameliorated with the use of recombinant erythropoietin preparations. Renal toxicities, usually due to cisplatin containing programs, are manifested by decrements in creatinine clearance and salt wasting nephropathies, hypomagnesemia, and hypophosphatemia. Meticulous attention to fluid and electrolyte status during cisplatin infusions is mandatory. With long-term follow-up of cured testis cancer patients, there can be a persistent decrement in glomerular filtration rates. Rarely, the hemolytic uremic syndrome can occur. Gonadal toxicities and oligospermia or azospermia and associated infertility as well as retrograde ejaculation resulting from RPLND are expected, especially since many men may have pre-existing oligospermia prior to the diagnosis of germ cell cancer. Sperm banking often is recommended prior to instituting systemic or surgical therapies. Neuropathies manifesting as paresthesias may be secondary to cisplatin containg programs

Cardiovascular toxicities are being recognized with increasing frequency and are likely to be diagnosed and managed by the primary care physician, especially as patients are cured and no longer being seen by their urology or oncology specialist. The incidence of these complications is greater in those who have received both chemotherapy and radiation therapy. These include hypertension, hypercholesterolemia, hypertriglyceridemia, myocardial disease including ischemia and infarction, Raynaud's phenomena, and associated syndrome X or metabolic syndrome. Recent guidelines from the American Society of Clinical Oncology recommend screening the cured testis cancer patient for hypertension every two years, and every five years for lipid abnormalities.

Second Cancers. The physician must be aware that second cancers can occur not only in the contralateral testis, representing a lifetime risk, but also from treatment. These latter treatment-related cancers include the development of leukemia and other types of myelodysplastic syndromes following treatment with etoposide and gastrointestinal cancers in the irradiated field of seminoma patients who have received abdominal radiation. The primary care physician assumes a critical role in these circumstances, since the patient often no longer is followed by his oncologist, urologist, or radiation oncologist or has moved to a new geographic area from the institutions where curative therapies were administered.

Summary

The multidisciplinary approach for diagnosing, treating and following patients with germ cell cancers has transformed this once uniformly fatal disease into one that is highly curable, even in the face of wide spread metastases. The primary care physician plays a critical role in initially suspecting a diagnosis of testicular cancer and then making the appropriate referral. The rarer presentations of EGGCT also must be considered in young male patients with persistent back pain or pulmonary complaints.

The use of biological markers can be very suggestive and may expedite the facility of establishing a diagnosis of germ cell cancers before histologic confirmation or urologic referral. Following curative therapy, the primary care physician often is the responsible physician to monitor patients for both relapse and long term complications from chemotherapy or radiation treatment. These include the development of hypertension, hyperlipidemia, and myocardial disorders, among others. Long-term decrements in renal function and Raynaud's phenomenon also must be considered in the cured testis cancer patient as he ages and become susceptible to a multitude of other medical disorders.

References

1. American Cancer Society. Testicular Cancer. American Cancer Society web site http://www.cancer.org/downloads/PRO/TesticularCancer.pdf. Accessed 8-9-2006.
2. Buetow SA. Epidemiology of testicular cancer. *Epidemiol Rev* 1995;17:433-449.
3. Skakkebaek NE. Carcinoma in situ of the testis: Frequency and relationship to invasive germ cell tumors in infertile men. *Histopathology* 1978;2:157-170.
4. Steele GS, Richie JP, Stewart AK, et al. The National Cancer Data Base report on patterns of care for testicular carcinoma, 1985-1996. *Cancer* 1999;86:2171-2183.
5. Rodriguez E, Mathew S, Reuter V, et al. Cytogenetic analysis of 124 prospectively ascertained male germ cell tumors. *Cancer Res* 1992;52:2285-2291.
6. Rapley EA, Crockford GP, Teare D, et al. Localization to Xq27 of a susceptibility gene for testicular germ cell tumors. *Nat Genet* 2000;24:197-200.
7. Bokemeyer C, Kuczyk MA, Dunn T. Expression of stem cell factor and its receptor c-kit proto-oncogene in germ cell tumors. *J Pathol* 1996;122:301-306.
8. Strohmeyer T, Reese D, Press M, et al. Expression of the c-kit proto-oncogene and its ligand stem cell factor (SCF) in normal and malignant human testicular tissue. *J Urol* 1995;153:511-515.
9. Garnick MB, Ferry JA. Case Records of the Massachusetts General Hospital. A 23-year-old man with mediastinal

embryonal carcinoma and hematologic abnormalities. *N Engl J Med* 1997:337:1904-1912.
10. Garnick MB. Testicular cancer and other trophoblastic diseases. In: Isselbacher KJ, Braunwald E, Wilson JD, et al, eds. *Harrison's Principles of Internal Medicine*. 13th edition. New York: McGraw-Hill Book Company;1994:1858-1862.
11. Richie JP, Steele GS. Neoplasms of the testis. In: Walsh PC, ed. *Campbell's Urology*, 8th edition Philadelphia: Saunders;2002: 2876-2920.
12. Garnick MB, Canellos GP, Richie JP. Treatment and surgical staging of testicular and primary extragonadal germ cell cancer. *JAMA* 1983;250:1733-1741.
13. Bokemeyer C, Nichols CR, Droz JP et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: Results from an international analysis. *J Clin Oncol* 2002;20:1864-1873.
14. Garnick MB, Scully RE, Weber ET, et al. Cancer of the testis. In: Osteen RT, ed. *Cancer: A Manual for Practitioners*, 7th edition. Boston: American Cancer Society, Massachusetts Division, Inc.; 1986:268-277.
15. Horwith A, Bajorin D. Testicular cancer—presentation, assessment and prognosis. In: Steven A, Leibel SA, Scher HI, et al, eds. *Principles and Practice of Genitourinary Oncology*. Philadelphia: Lippincott Williams & Wilkins;1997:671-682.
16. Bosl GJ, Motzer. Testicular germ cell cancer. *N Engl J Med* 1997;337:242-253.
17. Lange PH, Raghavan D. Clinical applications of tumor markers in testiculara cancer. In: Donohue JP, ed. *Testis Tumors.* Baltimore: Williams and Wilkins; 1983:111-130.
18. American Society of Clinical Oncology. O*ncology Medical Knowledge Self-Assessment Program*, 3rd edition. 2003; Chapter 9.
19. Raghavan D. Testicular cancer: Maintaining the high cure rate. *Oncology* 2003;17:218-228.
20. Sturgeon JF, Jewett MA, Alison RE, et al. Surveillance after orchiectomy for patients with clinical stage I nonseminomatous testis tumors. *J Clin Oncol* 1992;10:564-568.
21. Williams SD, Stablein DM, Einhorn LH, et al. Immediate adjuvant chemotherapy versus observation with treatment at relapse I pathological Stage II testicular cancer. *N Engl J Med* 1987;317:1433-1438.
22. Raghavan D. Follow up of the patient with testicualr cancer. In: Johnson FS, Virgo K, eds. *Cancer Patient Follow up*. St. Louis: Mosby-Year Book; 1995.
23. Allhoff EP, Liedke S, deRiese W, et al. Stage I seminoma of the testis: Adjuvant radiotherapy or surveillance? *Br J Urol* 1991;68:190-194.
24. Ramakrishnan S, Champion AE, Dorreen MS, et al. Stage I seminoma of the testis: Is post-orchidectomy surveillance a safe alternative to routine postoperative radiotherapy? *Clin Oncol* 1992;4:284-286.
25. Oliver RT, Edmonds PM, Ong JY, et al. Pilot studies of 2 and 1 course carboplatin as adjuvant for stage I seminoma:

Should it be tested in a randomized trial against radiotherapy? *Int J Radiat Oncol Biol Phys* 1994;29:3-8.
26. Oliver RTD, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: A randomized trial. *Lancet* 2005;366:293-300.
27. International Germ Cell Cancer Collaborative Group: International germ cell consensus classification: A prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997;15:594-603.
28. Motzer RJ, Masumdaar M, Bosl GJ, et al. High dose carboplatin, etoposide and cyclophosphamide for patients with refractory germ cell tumors: Treatment results and prognostic factors for survival and toxicity. *J Clin Oncol* 1996;14:1098-1105.
29. Margolin K, Doroshow JH, Ahn C, et al. Treatment of germ cell cancer with two cycles of high-dose ifosphamide, carboplatin, and etoposide with autologous stem-cell support. *J Clin Oncol* 1996;14:2631-2637.
30. Motzer RJ, Sheinfeld J, Mazumdar M, et al. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. *J Clin Oncol* 2000;18:2413-2418.
31. Einhorn LH, Stendere MJ, Williams SD. Phase II trial of gemcitabine in refractory germ cell tumors. *J Clin Oncol* 1999;17:509-511.
32. Bauer KA, Skarin AT, Balikian JP, et al. Pulmonary complications associated with combination chemotherapy programs containing bleomycin. *Am J Med* 1983;74:557-563.
33. Balikian JP, Jochelson MS, Bauer KA, et al. Pulmonary complications of chemotherapy regimens containing bleomycin. *Am J Roentg* 1982;139:455-461.
34. Garnick MB, Griffin JD. Idiopathic thrombocytopenia in association with extragonadal germ cell cancer. *Ann Intern Med* 1983;98:926-27.
35. Nichols CR, Hoffman R, Einhorn LH, et al. Hematologic malignancies associated with primary mediastinal germ-cell tumors. *Ann Intern Med* 1985;102:603-609.
36. Carver BS, Bianco, FJ, Shavegan B, et al. Predicting teratoma in the retroperitoneum in men undergoing post-chemotherapy retroperitoneal lymph node dissection. *J Urol* 2006:176:1090-1103.
37. Travis LB, Curtis RE, Storm H, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst* 1997;89:1429-1439.

Physician CME Questions

14. Which of the following is *not* an important factor in determining the outcome of patients with metastatic testicular cancer?
    A. The pathology of the primary lesion
    B. The levels of hCG and AFP
    C. Duration and severity of symptoms before diagnosis
    D. History of an undescended testicle
    E. The anatomic site of the metastases

15. The earliest signs of bleomycin pulmonary toxicity may include changes on chest x-ray, development of rales on physical exam, and a lowering of the diffusion capacity (DLCO).
    A. True
    B. False

16. The primary care physician who suspects a diagnosis of testicular cancer should do all of the following *except*:
    A. refer the patient to a urologic surgeon.

In Future Issues:

Insomnia

Primary Care Reports

CME Objectives

To help physicians:

• summarize the most recent significant primary care medicine-related studies;

• discuss up-to-date information on all aspects of primary care, including new drugs, techniques, equipment, trials, studies, books, teaching aids, and other information pertinent to primary care;

• evaluate the credibility of published data and recommendations; and

• describe the pros and cons of new testing procedures.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a certificate of completion.* When your evaluation is received, a certificate will be mailed to you.

B. obtain a testicular ultrasound.
C. obtain a blood test for determination of the tumor markers alpha-fetoprotein, human chorionic gonadotropin, and lactic dehydrogenase.
D. transillumination with transcrotal biopsy of the suspected lesion.

17. The most commonly used chemotherapy agents for testicular cancer include all of following *except*:
A. bleomycin.
B. cisplatin.
C. actinomycin D.
D. etoposide.

18. Patients who have undergone curative therapy for testicular cancer with chemotherapy or radiation therapy have a higher incidence of all of the following *except*:
A. cardiovascular disease.
B. Raynaud's phenomenon.
C. neuropathy.
D. second cancers.
E. inflammatory bowel disease.

19. The biologic half-life of hCG is approximately 5-6 days, and that of alpha fetoprotein is approximately 24 hours.
A. True
B. False

CME Answer Key

14. D
15. A
16. D
17. C
18. E
19. B

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

The Truth About Multivitamins

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin B_6 was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin B_{12} has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■