PHARMACOLOGICAL DIGEST

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Pfizer not Moving Ahead with Viagra for Women

Pfizer Inc. reported that it was unable to prove that its impotence drug Viagra was effective in treating women, and it would not seek regulatory approval for it as a treatment for female sexual arousal disorder. Female sexual arousal disorder (FSAD) is an emerging area of research and is far more complex than male erectile dysfunction. It began studying Viagra for use in women in 1996 and has conducted several large-scale studies involving about 3,000 patients. While the drug was found to be safe in all studies, data on its effectiveness in treating sexual arousal problems in women did not support submitting the drug for review by the U.S. Food and Drug Administration. It would end the program soon. Diagnosing FSAD involves assessing physical, emotional and relationship factors, and these complex and interdependent factors make measuring a medicine's effect very difficult. Several drug makers have been trying to develop a so-called female Viagra in hopes of establishing an enormous untapped market. Analysts have said that any drugs for female sexual dysfunction that prove effective in treating problems with arousal, diminished desire or inability to achieve orgasm could garner sales of well over $1 billion a year.

[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4459157&section=news]

FDA Approves Bevacizumab for Colorectal Cancer

The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin), manufactured by Genentech, Inc., as a first-line treatment for metastatic colorectal cancer. Bevacizumab targets vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation within the tumor. Although angiogenesis inhibitors have been studied for the past three decades, this is the first such product shown to delay tumor growth and prolong survival. When given intravenously in combination with the Saltz regimen (IFL; irinotecan, 5-fluorouracil [5-FU], and leucovorin) used as standard chemotherapy for colon cancer, bevacizumab prolonged survival by about five months. In a randomized, double-blind trial enrolling more than 800 patients with metastatic colorectal cancer, patients receiving bevacizumab in combination with IFL also had a longer time to progression by about four months than patients receiving IFL alone. The overall response rate was 45% with bevacizumab and 35% for IFL alone. For tumors to grow they need a blood supply, and for blood vessels to grow, they need growth factors. VEGF appears to be one of the most important of these growth factors. Bevacizumab appears to work by binding to the VEGF receptor and blocking signals for blood vessel growth. Without these signals, tumor blood vessels are stunted in their growth, causing a similar effect in the tumor itself. VEGF is the first growth factor shown to be effective in this fashion. Bevacizumab

also has nice pharmacokinetic properties, which may allow it to be effective, where other drugs were limited by not being able to achieve adequate drug levels for sufficient periods of time. Compared with most chemotherapy, the safety profile of bevacizumab appears quite favorable. It caused a modest increase in blood pressure, and about 11% needed to use an oral antihypertensive medication but no hypertensive crises. There is a serious but rare event, which is the risk of gastrointestinal perforation. This can occur in 2% to 3% of patients with colorectal cancer who are receiving any chemotherapy. In the study, there were six events in 400 patients in the bevacizumab arm, or a rate of 1.5%; however, no perforation events were seen in the control arm. Of the six patients with perforation, three patients recovered and restarted treatment without any subsequent problems, two patients discontinued treatment permanently, and one patient died. Overall, there was still a major survival benefit, but this risk needs to be respected for patients with issues related to bowel integrity, particularly those [who] would not have fit the eligibility criteria in our phase III trial. The effect is rare and often seen in the context of an overall clinical response, but it can be serious, so it needs to be respected and followed with close clinical management.

[http://www.medscape.com]

Oral Contraceptives Lower Risk of Developing Rheumatoid Arthritis

The use of oral contraceptives, but not estrogen replacement therapy, lowers the risk of developing rheumatoid arthritis. Although observational and epidemiologic evidence suggests a role for sex hormones in the development and progression of rheumatoid arthritis (RA), studies investigating the influence of exogenous estrogen on the development of RA have yielded conflicting results. The researcher investigated whether exposure to either oral contraceptives or postmenopausal estrogen replacement therapy (ERT) influenced the development of rheumatoid arthritis in women using data from The Rochester Epidemiology Project. Ever-use of oral contraceptives was associated with a 43% reduction in the risk of RA, though there was no association between the current use of oral contraceptives and RA (albeit in a small number of women). The protection was more pronounced for RF-positive than for RF-negative rheumatoid arthritis. Based on population attributable-risk estimates, the investigators calculate, the number of women who develop RA could drop by about 38.6% if the entire female population of Rochester were exposed to oral contraceptives. The majority of the decrease in incidence (of RA) from an incidence of 72/100,000 to the estimated 48/100,000 (between 1985 and 1994) is still unaccounted for. Therefore, the protective effect of oral contraceptive exposure on the development of RA can only explain a small portion of the dramatic decrease in RA incidence over the past few decades. Further research, including both clinical studies and laboratory studies in the field of immunoendocrinology, may help to explain the complex relationship between estrogen, progestins, and RA.

[J Rheumatol 2004;31:207-213]

ACE Inhibitors No Better Than Other Antihypertensives at Preventing Heart Failure

Although ACE inhibitors can improve survival after a diagnosis of heart failure, findings from a new study suggest that these drugs are no better than other antihypertensive agents at preventing the cardiac condition. However, in certain subgroups, ACE inhibitors may offer an advantage over other antihypertensives. They performed a meta-analysis of six trials that looked at the occurrence of heart failure in hypertensive patients who were treated with an ACE inhibitor or another agent. Together, the studies included 20,430 patients treated with an ACE

inhibitor and 46,904 who received another drug. The follow-up periods ranged from 4.1 to 8.4 years. Overall, 922 new cases of congestive heart failure were diagnosed in the ACE inhibitor group and 2589 were diagnosed in the other drug group. In the context of the total study group, ACE inhibitors are comparable to other BP agents at preventing heart failure. A possible advantage for ACE inhibitors over other drugs emerged as patient age and the degree of blood pressure control increased, but the trend was nonsignificant. The hypothesis that ACE inhibitors are superior to other antihypertensive drugs for prevention of congestive heart failure in hypertension remains unproven.

[Am J Cardiol 2004;93:240-243]

Disulfiram and CBT Reduce Cocaine Dependence

Disulfiram and cognitive behavioral therapy (CBT) are effective for reducing cocaine dependence. Given clinical observations of high rates of alcohol dependence among cocaine-dependent outpatients, the initial rationale for disulfiram therapy was as a strategy to reduce alcohol use among cocaine users. In this double-masked (for medication condition), 2 x 2 factorial trial, 121 individuals with current cocaine dependence were enrolled from a community-based outpatient substance abuse treatment program and randomized to treatment with disulfiram, 250 mg/day, plus CBT; disulfiram plus interpersonal psychotherapy (IPT); placebo plus CBT; or placebo plus IPT. A riboflavin marker procedure helped monitor medication compliance. CBT and IPT were guided by a manual and given as individual sessions for 12 weeks. Random regression analyses of self-reported frequency of cocaine use and results of urine toxicology screens revealed that disulfiram was more effective than placebo in reducing cocaine use, and CBT was more effective than IPT ($P < .01$ for both). Disulfiram and CBT were most effective in subjects who were not dependent on alcohol at baseline and in those who fully abstained from drinking alcohol during treatment. Adverse effects associated with disulfiram were mild and similar to those associated with placebo. Study limitations include drop-out rate of 50%. Because alcohol use during treatment was strongly related to cocaine use, independent of the patient's medication condition, the authors recommend that the use of disulfiram in alcoholic cocaine abusers should be combined with efforts to enhance patient commitment to alcohol abstinence.

[Arch Gen Psychiatry 2004;61:264-272]

Fat-Blocker Improves Cholesterol Reduction

Adding a drug that inhibits cholesterol absorption from the gut to treatment with a statin drug, which inhibits cholesterol production in the liver, is more effective than statin treatment alone in lowering LDL cholesterol. Statins such as Zocor or Lipitor have become standard treatments for high cholesterol. The results of a trial called EASE, in which the cholesterol absorption blocker Zetia (generic name, ezetimibe) was added to a statin show that the combination reduced LDL cholesterol 26 percent compared with a 3 percent reduction with single therapy in a 6-week comparison of the two treatments. The EASE trial involved 3030 patients on stable doses of statins who had not achieved LDL target levels. Two-thirds of the participants were randomized to take statins plus Zetia or statins only for 6 weeks. The combination therapy was effective across all ages, genders and races. 71 percent of the total group on combination therapy achieved target LDL cholesterol levels. If a patient is not at goal with a statin, a good strategy is to add ezetimibe.

[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4551015&section=news]

New Gene Linked with Cancer Found

U.S. scientists had tracked down another gene involved in several different cancers, which seems to become active just before a tumor begins to spread. The gene, called PIK3CA, might be a good "marker" for diagnosing cancer, or a target for new cancer drugs. The researchers found PIK3CA mutations in 74 of 234 colon cancer patients, or 32 percent of them. Mutations in the gene were found in 27 percent of patients with brain tumors known as glioblastomas, 25 percent of stomach cancer patients and 8 percent of breast cancer patients. They found 92 mutations in all. The sheer number of mutations observed in this gene strongly suggests that they are functionally important. The mutations seem to come about late in tumor development, just as a benign tumor becomes invasive cancer. Many different cancer genes have been found, from the p53 gene found in dozens of cancers to the BRCA genes linked with breast and ovarian cancer. Experts note cancer is a complex disease, caused by the interaction of possibly hundreds of genes and the environment.

[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=4550419&section=news]

Antibacterial Soap Doesn't Prevent Viral Infection

Using antibacterial soaps and cleansers at home may not necessarily reduce risk of getting sick. In a new study, people who used antibacterial soaps and cleansers developed cough, runny nose, sore throat, fever, vomiting, diarrhea and other symptoms just as often as people who used products that did not contain antibacterial ingredients. Since most common infections, including colds and flu, are caused by viruses, the lack of an effect on symptoms is not surprising. According to one study, approximately 75 percent of liquid soaps and 29 percent of bar soaps in the U.S. contain antibacterial ingredients. But the benefits of antibacterial products in preventing infectious diseases in households are still unproven. They studied 238 Manhattan families who were given almost a year's supply of free soap and household cleaners. Half of the families were given antibacterial products, while the other half received products that did not contain antibacterial ingredients. For nearly a year, the families were closely followed to see how often they experienced a wide variety of symptoms. Runny nose, cough and sore throat were the most common symptoms, followed by fever, vomiting, diarrhea and skin symptoms. These symptoms occurred just as frequently in people who used antibacterial products at home as they did in people who did not. Throughout the study, use of antibacterial products did not have a significant effect on any of the symptoms. During the study, participants had fewer infections and lower bacterial counts on their hands than at the start of the study. In a previous analysis of the results found that families experienced a drop in bacterial counts whether they used antibacterial or normal soaps and cleansers. Despite the lack of an effect on symptoms antibacterial products may be appropriate for preventing bacterial symptoms, or in other specific situations, such as when a family member has a weakened immune system or has skin or gastrointestinal infections. The authors note that any potential benefits of antibacterial products need to be weighed against the possibility that bacteria may develop resistance to antibacterial products. Although there is no evidence that this has happened, laboratory tests suggest that it may be possible.

[Annals of Internal Medicine, March 2, 2004]

Sex Differences in Analgesic Response to Opioids

For acute pain management, women respond better to a kappa agonist than to a mu agonist. Two commonly used opioid analgesics for uncomplicated patients are morphine sulfate and butorphanol.

Preliminary studies suggest that there may be a sex difference in response to the site of action of these two medications. The objective of this trial was to evaluate whether there is a sex difference in the analgesic response to the prototypical mu-receptor agonist, morphine sulfate, compared with the prototypical kappa agonist, butorphanol, in the emergency department. Of 94 patients with acute moderate to severe traumatic pain of injury who were enrolled in this study, 49 (52%) were men and 45 (48%) were women. Subjects were randomized to receive morphine or butorphanol. Both groups were similar in demographics. At 60 minutes, women had significantly lower visual analog scale (VAS) scores with butorphanol than with morphine (P = .046). There was a nonsignificant trend suggesting that men responded better to morphine than women did (P = .06). At 30 minutes, diastolic blood pressures were lower in women than in men. Study limitations include use of patient self-report of pain. Females had better pain scores with butorphanol than morphine at 60 minutes. Kappa receptor agonists should be chosen preferentially for female patients with acute traumatic injury pain.

[South Med J. 2004;97:35-41]

IV Lidocaine Helpful for Mechanical Allodynia

Intravenous (IV) lidocaine is helpful for mechanical allodynia. It was previously shown, using quantitative sensory tests, that IV lidocaine induced selective and differential analgesic effects in patients with central neuropathic pain. Thus the treatment alleviated spontaneous pain and mechanical allodynia/hyperalgesia, but had no effect on thermal allodynia/hyperalgesia. This argued against a generalized effect on pain perception, but rather emphasized that lidocaine presented with specific antiallodynic and anti-hyperalgesic effects in such patients. In this double-blind, crossover design study, 22 patients with pain caused by postherpetic neuralgia or nerve trauma received lidocaine, 5 mg/kg IV, or placebo infusion over 30 minutes and were evaluated using quantitative sensory testing. On an open-label basis, 16 patients subsequently received mexiletine titrated from 400 to 1,000 mg per day (mean, 737 mg/day). Lidocaine significantly decreased ongoing pain for up to six hours, with a peak effect 60 to 120 minutes after injection. It also decreased mechanical dynamic allodynia and static or punctate mechanical allodynia/hyperalgesia, but not thermal allodynia and hyperalgesia, suggesting that the analgesic effects of the drug were modality-specific. Compared with patients without allodynia, those with concomitant mechanical allodynia had significantly greater effects from lidocaine and mexiletine on spontaneous pain intensity. The authors suggest that patients with mechanical allodynia may be good candidates for treatment with local anesthetic, like drugs and possibly with other sodium-channel blockers. The usual definition of a responder to a certain drug in the context of neuropathic pain, although it has the advantage of simplicity and permits a clinical comparison between different drugs, is probably too broad and may lack sensitivity. The response to a drug rather depends on a combination of symptoms that may relate to specific common mechanisms and favors the importance of a mechanism-based classification of neuropathic pains.

[Neurology 2004;62:218-225]

Ezetimibe: A Selective Cholesterol Absorption Inhibitor

Ezetimibe is the first agent of a novel class of selective cholesterol absorption inhibitors recently approved by the Food and Drug Administration for treatment in the United States. Ezetimibe inhibits the absorption of biliary and dietary cholesterol from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides, or bile acids. Ezetimibe localizes at the brush

border of the small intestine and decreases cholesterol uptake into the enterocytes. Preclinical studies demonstrated lipid-lowering properties of ezetimibe as monotherapy and showed a synergistic effect in combination with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). The efficacy and safety of ezetimibe 10 mg/day have been established in phase III clinical trials. In these trials, ezetimibe was investigated as monotherapy, as an add-on to ongoing statin therapy, and as combination therapy with statins in patients with primary hypercholesterolemia. In addition, ezetimibe has been evaluated in patients with homozygous and heterozygous familial hypercholesterolemia and in those with sitosterolemia. When given as monotherapy or in combination with statins or fenofibrate, ezetimibe reduces low-density lipoprotein cholesterol (LDL) by 15-20% while increasing high-density lipoprotein cholesterol by 2.5-5%. Unlike other intestinally acting lipid-lowering agents, ezetimibe does not adversely affect triglyceride levels and, due to its minimal systemic absorption, drug interactions are few. Ezetimibe's side-effect profile resembles that of placebo when given as monotherapy or in combination with statins. In clinical practice, ezetimibe has a role as monotherapy for patients who require modest LDL reductions or cannot tolerate other lipid-lowering agents. In combination therapy with a statin, ezetimibe is used in patients who cannot tolerate high statin doses or in those who need additional LDL reductions despite maximum statin doses.

[Pharmacotherapy 2003; 23:1463-1474]

High-Dose Melphalan With Stem-Cell Transplant Improves Outcomes in AL Amyloidosis

High-dose melphalan with autologous stem-cell transplant improves five-year survival, induces remission, or reverses disease in a substantial proportion of patients with AL amyloidosis. AL amyloidosis is a fatal disease resulting from tissue deposition of amyloid fibrils derived from monoclonal immunoglobulin light chains. Treatment with oral chemotherapy is minimally effective. This longitudinal analysis of clinical effectiveness followed 701 consecutive new patients with AL amyloidosis treated at a university-affiliated specialty referral clinic. Of 394 patients (56%) who were eligible for high-dose intravenous melphalan (100-200 mg/m^2) and autologous blood stem-cell transplantation, 82 did not proceed with treatment because of patient choice or disease progression. Median survival of the 312 patients who began treatment with high-dose melphalan and stem-cell transplantation was 4.6 years. Complete hematologic response, defined as no evidence of an underlying plasma cell dyscrasia one year after treatment, occurred in 40% of patients, and it was associated with longer survival and greater improvements in end-organ disease. Mortality rate within 100 days of treatment was 13% overall, but it was highest in patients with cardiomyopathy. Treatment of selected patients with AL amyloidosis by using high-dose melphalan and stem-cell transplantation resulted in hematologic remission, improved five-year survival, and reversal of amyloid-related disease in a substantial proportion. These data suggest that treatment with high-dose melphalan and stem-cell transplantation should be considered early in the course of the disease for eligible patients with AL amyloidosis. This treatment is a clinically significant improvement in treating AL amyloidosis and shows promise in reversing amyloid cardiomyopathy.

[Ann Intern Med 2004;140:85-93]

Melatonin May Lower Nocturnal Blood Pressure

Three weeks of melatonin therapy significantly reduces nocturnal blood pressure and improves sleep. A single dose had no effect on blood pressure or

heart rate. Patients with essential hypertension have disturbed autonomic cardiovascular regulation and circadian pacemaker function. Nighttime melatonin amplifies circadian rhythms directly via the central pacemaker as in dementia, shift work, and blindness. In this double-blind, crossover design trial, the investigators studied the effect of a single and repeated doses of oral melatonin, 2.5 mg, given one hour before sleep, on 24-hour ambulatory blood pressure and actigraphic estimates of sleep quality in 16 men with untreated essential hypertension. Although a single dose of melatonin had no effect on blood pressure, melatonin given nightly for three weeks reduced systolic blood pressure during sleep by 6 mm Hg and diastolic blood pressure by 4 mm Hg. Heart rate was not affected. With three weeks of melatonin treatment, the day-night amplitudes of systolic and diastolic blood pressure rhythms increased by 15% and 25%, respectively. Sleep quality was also better, but improvements in blood pressure and sleep were statistically unrelated. Study limitations include the small number of patients studied. This is the first double-blind crossover study to investigate the effect of repeated melatonin intake on 24-hour blood pressure rhythm in untreated hypertensive patients, while recommending future studies in larger patient groups to define subgroups of patients who would benefit most from melatonin intake. The present study suggests that support of circadian pacemaker function may provide a new strategy in the treatment of essential hypertension.

[Hypertension 2004;43:1-6]

Vitamins E, C may Reduce Risk of Alzheimer's Disease

Use of high-dose supplements of vitamins E and C is associated with a reduction in the prevalence and incidence of Alzheimer's disease (AD) in a select elderly population. Antioxidants may protect the aging brain against oxidative damage associated with pathological changes of AD. From 1995 to 1997, the investigators assessed the prevalence of dementia and AD and collected information about supplement use in 4,740 residents of Cache County, Utah, aged 65 years or older. There were 200 prevalent cases of AD between 1995 and 1997, and 104 incident cases of AD during follow-up from 1998 to 2000. Vitamin E users were defined as those who reported taking an individual supplement of vitamin E or a multivitamin containing more than 400 IU of vitamin E; vitamin C users were defined as those who took at least 500 mg of ascorbic acid. Multivitamin users were defined as those who reported taking multivitamins containing lower doses of vitamin E or C. The greatest reduction in both prevalence and incidence of AD was in subjects who used individual vitamin E and C supplements in combination, with or without an additional multivitamin. Use of vitamin E and C supplements in combination reduced AD prevalence by about 78% (adjusted odds ratio, 0.22; 95% confidence interval [CI], 0.05 - 0.60) and incidence by about 64% (adjusted hazard ratio, 0.36; 95% CI, 0.09 - 0.99). There was a trend toward lower AD risk in users of vitamin E and multivitamins containing vitamin C. However, there was no apparent protective effect with the use of vitamin C alone, vitamin E alone, with multivitamins alone, or with vitamin B-complex supplements. Study limitations include cross-sectional prevalence data; limited (three-year) follow-up for incidence data; and the pitfalls inherent in observational studies, such as possible confounding factors associated with vitamin use. The authors note that the current recommended daily allowance (RDA) for vitamin E is 22 IU (15 mg), and for vitamin C (ascorbic acid), 75 to 90 mg. Multivitamin preparations typically contain the RDA, while individual supplements typically contain doses up to 1,000 IU of vitamin E and 500 to 1,000 mg or more of vitamin C ascorbic acid). These findings suggest that vitamins E and C may offer protection against AD when taken together in the higher doses available from individual supplements.

Formal proof of such an effect can come only from randomized prevention trials. If proven efficacious in such trials, antioxidant vitamins (believed to offer other health benefits) would offer an attractive prevention strategy for AD.

[Arch Neurol 2004;61:82-88]

Prolonged Regular Aspirin Use may Increase Pancreatic Cancer Risk

Regular use of aspirin for 20 years or more is associated with an increased risk of pancreatic cancer. Because this differs from findings in other studies, the editorialist suggests that there are no easy answers, but that the conflict should be an impetus to additional research. Earlier studies have shown that use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce risk of some cancers and precancerous lesions, and in vitro and animal models have suggested that aspirin and NSAIDs may inhibit the development of pancreatic cancer. However, studies analyzing the association between analgesic use and pancreatic cancer in humans have been infrequent and have yielded inconsistent results. These findings do not support a protective effect of analgesic use on the risk of pancreatic cancer. Rather, aspirin appears to increase the risk of pancreatic cancer after extended periods of use. As part of the Nurses' Health Study, beginning in 1980, 88,378 women completed biennial questionnaires, including items about aspirin use. Of these women, 34% were current regular aspirin users, defined as consumption of two or more 325 mg aspirin tablets weekly, and 66% consumed fewer than two tablets weekly. During 18 years of follow-up, 161 new cases of pancreatic cancer occurred, with no statistically significant difference in risk of pancreatic cancer between regular aspirin users and nonusers. However, compared with women who regularly consumed fewer than two aspirin tablets per week, women with more than 20 years of regular aspirin use had a 58% increased risk of pancreatic cancer (relative risk [RR], 1.58; 95% confidence interval [CI], 1.03 - 2.43; P = .01 for trend). Compared with women who were nonusers during the same time period, the risk of pancreatic cancer in regular aspirin users increased with increasing aspirin dose (P = .02 for trend). Compared with nonusers, women who consumed 14 or more aspirin tablets weekly had an 86% increased risk of pancreatic cancer (RR = 1.86; 95% CI, 1.03 - 3.35; P = .02 for trend). Higher pancreatic cancer risk linked to aspirin use seemed to be confined to women with a higher body mass index, suggesting that obesity may have served as a marker for inflammation. Risks and benefits associated with the use of aspirin have to be weighed carefully in any recommendations made by health care providers. In an accompanying editorial notes that these findings raise questions about the actions of aspirin and other NSAIDs and the mechanisms underlying pancreatic cancer. There are no easy answers to the question of what aspirin and other NSAIDs do to pancreatic carcinogenesis. Fortunately, conflicting data from diverse threads of research are often a very effective push toward scientific progress.

[J Natl Cancer Inst 2004;96:4-5, 22-28]

Double Stem Cell Transplant Better Than Single Transplant in Myeloma Patients

Double transplantation of autologous stem cells improves overall survival among patients with myeloma, as compared to single transplant. Stem cell transplantation is currently recommended for young patients with multiple myeloma as part of initial therapy or upon progression of the disease. However, the median duration of response after this procedure did not exceed three years, and almost all patients ultimately relapse. In order to evaluate the effect of double-transplant therapy on prolonging duration of response, investigators enrolled 399 patients under 60 years of age with previously untreated

myeloma. All patients received 3 or 4 cycles of vincristin 0.4 mg/m^2, doxorubicin 9 mg/ m^2, and dexamethasone 40 mg (VAD), after which 199 patients were randomized to receive a single transplant following a preparative regimen of 140 mg/m^2 mephalan and total body irradiation (8 Gy delivered in 4 fractions over 4 days). The other group of 200 patients received the same dose of mephalan without irradiation prior to the first transplant, followed by the combination in preparation for the second. After hematologic reconstitution, both groups received alfa interferon 3 million units thrice weekly for maintenance. While similar rates of complete or very good partial responses were seen both double and single transplant groups (50% vs. 42%, P = .10), the seven-year event-free survival rate was significantly higher in the double-transplant group (20% vs. 10%, P = .03). Likewise, overall survival at seven years was significantly higher in the double-transplant group (42% vs. 21%, P = .01). In multivariate analysis, survival was found to be significantly related to four factors: base-line serum levels of beta$_2$-microglobulin (P < .01) and lactate dehydrogenase (P < .01), age (P < .05), and treatment group (P < .01). Among patients who did not show very good response rates after the first transplant, seven-year survival rate was dramatically higher for the double transplant group (42% vs. 11%, P < .001). The results indicated that double transplantation could benefit patients who do not have a very good partial response with in three months after undergoing a single transplantation. Hematopoietic reconstitution was similar between the two groups, as were rates of treatment-related death (6% vs. 4%, P = .4). However, nonfatal adverse events are not well described in this report, longer hospitalization and an increased risk of toxic effects such as mucositis would be expected in the double-transplant group. This report establishes double transplantation as one of the options for treating patients who have myeloma, particularly those younger than 60 years of age who have a suboptimal response to a single transplant. Though commending the investigators, progressive myeloma will develop in over 80% of patients within seven years after they have undergone double transplantation. In light of these results symptomatic patients younger than 70 years of age should be treated initially with dexamethasone alone or in combination with chemotherapy or thalidomide, in the expectation that autologous stem cell transplantation will be included in the treatment.

[New Engl J Med 2003;349:2495-2502, 2551-2553]

COX Inhibition Blunts Antihypertensive Effects of ACE Inhibitor Therapy

Both selective COX-2 inhibition and nonselective COX inhibition dampen the blood pressure lowering effects of angiotensin-converting enzyme (ACE) inhibitors. Nonselective COX inhibition also adversely effects renal function in ACE-treated patients. Using a crossover design, they examined the effects of the selective COX-2 inhibitor celecoxib (200 mg/d) and the nonselective COX inhibitor diclofenac (75 mg twice daily) on BP and renal function in 25 patients with osteoarthritis and hypertension being treated with an ACE inhibitor and a diuretic. All the patients were black or Hispanic, because these classes of drugs are recommended by recent guidelines as initial therapy for treatment of blood pressure in blacks. At 4-weeks, diclofenac worsened overall 24-hour systolic BP control (+4.1 mm Hg) significantly more than celecoxib (+0.6 mm Hg) in the presence of an ACE inhibitor and diuretic, the team reports. However, at peak drug levels, diclofenac and celecoxib had similar effects on systolic BP (+3.6 and +4.2 mm Hg, respectively). Thus, if celecoxib is needed twice daily, as is frequently the case, then a rise in BP of similar magnitude to diclofenac would be anticipated. Glomerular filtration rate (GFR) was also differentially affected by selective and nonselective COX inhibition.

In the presence of ACE inhibitors, kidney function was worsened more with nonselective than selective COX-2 inhibitors. Diclofenac significantly reduced GFR and this was associated with marked urinary sodium retention, which led to ankle edema, despite diuretic therapy. Celecoxib, on the other hand, preserved GFR and was not associated with urinary sodium retention or ankle swelling. Hypertension and arthritis commonly co-exist in the elderly, leading to frequent co-administration of COX inhibitors and ACE inhibitors. They believe their study provides new information regarding the BP and kidney effects of COX inhibition in ACE-inhibitor treated patients.

[Hypertension 2004;43:573-577]

Azithromycin Failures Reinforce Penicillin as Preferred Drug for Syphilis

A recent report of syphilis patients in San Francisco who did not respond to azithromycin reinforces current recommendations that penicillin is the preferred agent for this disease. Syphilis rates have been increasing throughout the US in recent years. A particular problem area has been San Francisco, which had one of the highest rates of primary and secondary syphilis in the country in 2002. In an effort to treat syphilis cases early, certain disease-control programs have begun administering azithromycin as a single oral regimen, a more convenient alternative to IM penicillin. Support for this approach is based on several small studies that have shown efficacy in patients without HIV infection. However, in April 2003, the San Francisco Department of Public Health became aware of a syphilis patient who failed treatment with azithromycin. Further investigation uncovered seven other apparent treatment failures that occurred between September 2002 and July 2003. All of the patients were male and self-reported as homosexual. Five patients were infected with HIV. Treatment with penicillin or doxycycline successfully cleared the syphilis infection in all cases. Although penicillin remains the treatment of choice for syphilis, a 2-gram dose of azithromycin may be considered for penicillin-allergic patients, but only with close follow-up because treatment efficacy is not well documented and has not been studied in persons with HIV infection.

[Mor Mortal Wkly Rep CDC Surveill Summ 2004;53:197-198]

Antiviral Combination Therapy Shows Promise Against SARS

Combination therapy with lopinavir/ritonavir and ribavirin may reduce the risk of ARDS and death in patients with severe acute respiratory syndrome (SARS). The findings are based on a study of 41 SARS patients who were treated with the three agents and followed for 3 weeks. The clinical outcomes of these patients were compared with those of 111 historical controls who were treated with ribavirin alone. At follow-up on day 21, the cumulative rate of ARDS or death in the lopinavir/ritonavir group was 2.4%, much lower than the 28.8% rate seen in the control group ($p < 0.001$). This difference held true for patients diagnosed early in the epidemic and for those diagnosed later. Initial treatment with lopinavir/ritonavir was associated with a reduction in steroid usage and nosocomial infections compared with ribavirin monotherapy or rescue treatment with lopinavir/ritonavir. Moreover, receiving combination therapy from the start was tied to a progressive drop in viral loads and an increase in peripheral lymphocyte counts. On multivariate analysis, advanced age, hepatitis B carrier status, and not receiving combination therapy were identified as predictors of death or ARDS, the authors note.

In light of these encouraging findings, a controlled trial of lopinavir/ritonavir therapy for SARS is warranted. We propose that the combination of lopinavir/ritonavir and

ribavirin should be tested against lopinavir/ritonavir alone and placebo.

[Thorax 2004;59:252-256]

Hepatic Injury With the Beta-Interferons for MS More Common Than Thought

A greater proportion of patients receiving a beta-interferon for multiple sclerosis develop elevated aminotransferase levels than were reported in clinical trials leading up to approval of these agents. That's according to a postmarketing study in which researchers took a look back at biochemical liver tests of 844 MS patients prescribed one of the three commercially available beta-interferons in British Columbia, Canada, between 1995 and 2001. Overall, 36.9% of patients developed new elevations of alanine aminotransferase (ALT). All of the beta-interferons subcutaneous IFN-beta-1a and IFN-beta-1b (IM), and intramuscular IFN-beta-1a caused elevated aminotransferase levels compared with pretreatment levels ($p<0.005$) and the incidence aminotransferase elevation was substantially higher than reported in clinical trials. For example, 11% of patients had mild or moderate ALT elevations in a pivotal trial of IFN-beta-1b compared with 38.9% in the current study and 37.5% in another postmarketing study published recently. Likewise, in a pre-approval IFN-beta-1a (SC) trial, 19.6% and 27% of patients treated with low and high doses, respectively, experienced ALT increases, compared with 33.6% and 38.0% in the current study. No evidence of liver enzyme elevations was reported in a pivotal trial of IFN-beta-1a (IM), whereas in the current study 23.0% developed de novo ALT elevations. The postmarketing experience prompted a Food and Drug Administration MedWatch warning in March 2003 of hepatic injury including elevated serum hepatic enzyme levels, some of which have been severe. The researchers was unable to identify predictors of IFN-beta-induced liver injury. They suggest regular monitoring of the liver tests, particularly during the first year of treatment, emphasizing, however, that a balance should be found because frequent testing can cause anxiety, pain, inconvenience, and is not without cost.

[Neurology 2004;62:628-631]