PHARMACOLOGICAL DIGEST

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High-dose estrogen prevents stroke damage in laboratory animals

Estrogen likely produces its beneficial effects by enhancing the blood flow to the brain after arterial occlusion and by somehow rescuing damaged neurons. The study of the time-line of estrogen's effects on brain injury in an experimental model of stroke in rats show that the volume of the experimentally induced ischemic lesions was significantly reduced by intravenous administration of a high dose of estrogen (100 mcg/kg) as late as 3 hours after middle cerebral artery occlusion (MCAO). The lesion volume of 20.9% to 21.8% in untreated rats was reduced to 6.3%, 10.3%, 11.8%, and 13.5% when estrogen was given 0.5 hour, 1 hour, 2 hours, and 3 hours, respectively, after occlusion. In a separate experiment, cerebral blood flow in ovariectomized rats was confirmed to be decreased at 5 minutes after MCAO. In rats that received estrogen, blood flow rebounded within 2 days, and the rate was significantly greater than that in rats that did not receive estrogen. This study raises the possibility that estrogen compounds could be a useful therapy in preserving brain tissue, even if administered after the ischemic insult. In the second report, the investigators show that mice bred to lack estrogen receptor-alpha showed the same amount of neurologic disability and ischemic tissue damage as normal mice after experimentally induced stroke. There was no difference in blood flow in the brain during and after stroke between the two groups of mice. The researchers interpret these results to mean that estrogen inhibits brain injury by mechanisms that do not depend on activation of [the estrogen receptor-alpha] subtype. They add that the findings argue against targeting estrogen receptor agonists with selective estrogen receptor-alpha activity in the brain. They are just beginning to do the same experiments in mice lacking the beta subtype. These experiments will be helpful in designing estrogens that act at the right receptor in brain.

[Stroke 2000; 31:738-744, 745-750]

Genetic info may lead to meningitis vaccine

Researchers have not only mapped the complete genetic code of a bacterium that causes some cases of meningitis, but also identified several proteins on its surface that might lead to a vaccine against the infection. There are five types of bacteria that can cause meningitis -- a potentially fatal inflammation of membranes that surround the brain and spinal cord -- and septicemia. There are vaccines that protect against two types of meningitis bacteria, but there is no vaccine against serotype B, the strain that most often causes illness in the United States and Europe. The reseacheres report on the successful identification of all genes found in this strain of meningitis bacteria. This process helped the researchers identify which genes appear to allow the bug to defeat the body's immune system. Using the genetic information and cloned proteins found on the surface of meningitis bacteria. After testing several hundred of these proteins in mice, the researchers identified seven proteins that hold promise as vaccines against meningitis. The hope is that vaccination with one or more of these proteins will trigger the immune system to produce antibodies, which will protect against infection with meningitis bacteria. Even though developing vaccines is a lengthy, difficult process, the research shows the enormous potential of using genetic information to battle infectious diseases.

[Science 2000; 287: 1767-1768, 1809-1820]

Pamidronate prevents skeletal complications in breast cancer patients

Pamidronate therapy reduces the risk of skeletal fractures in breast cancer patients with osteolytic bone metastases for at least 2 years, follow-up data from two trials show. In fact, the treatment reduces the number of skeletal complications in this population by 35%, and the number of patients who experience this

complication by 20%. The team combined data from two multicenter randomized studies of pamidronate versus placebo. The participants had stage IV breast cancer with osteolytic bone metastases and were receiving either hormonal therapy or cytotoxic therapy at study initiation. Patients in both cohorts were randomized to 90-mg infusions of pamidronate or placebo every 3 to 4 weeks. Approximately one third of the 367 women randomized to pamidronate and one quarter of the 384 patients receiving placebo completed the 2-year follow-up. Pamidronate significantly reduced the skeletal morbidity rate, from 3.7 to 2.4, the investigators report. The drug also significantly reduced the number of patients who had skeletal complications, from 64% to 51%, and nearly doubled the median time to the first skeletal complication, from 7 months to 12.7 months. The results in the current report confirm that skeletal complications and the proportion of patients with such complications...are lower for at least 2 years in a [broad] population of patients with advanced breast carcinoma receiving either hormonal or cytotoxic chemotherapy. Moreover, results from this and other trials suggest that it is likely that pamidronate would be effective in the treatment of osteolytic metastases associated with a broad range of tumors. While additional, larger studies are needed to confirm their results, they conclude that 90-mg pamidronate infusions can be recommended as an addition to standard hormonal or chemotherapy regimens for the treatment of bone metastases in patients with breast carcinoma.

[Cancer 2000; 88: 1082-1090]

HIV infection accelerates onset of smoking-induced emphysema

As survival rates of patients with HIV infection increase with improved therapies, the rate of emphysema related to smoking in these patients is also likely to increase. Specifically, they found that HIV infection accelerates the onset of smoking-induced emphysema. The reseacheres conducted a cross-sectional study with 114 consecutive HIV-seropositive subjects without AIDS-related pulmonary complications. These subjects were matched to 44 HIV-seronegative controls for smoking history and age. Along with pulmonary function measurements, the subjects underwent bronchoalveolar lavage and high-resolution computer tomography of the chest. Emphysema was identified in 17 of 114 HIV-seropositive participants compared with 1 of 44 HIV-seronegative controls. The incidence of emphysema in participants with a smoking history of 12 pack-years or greater was 37% (14 of 38 persons) in the HIV-seropositive group compared with 0% (0 of 14 persons) in the HIV-seronegative group. When lymphocyte subtypes of the subjects were evaluated, the researchers found that HIV-seropositive persons with emphysema [had] the highest percentage of lavage lymphocytes bearing the cytotoxic phenotype. Given the relatively young age of the patients in the study (the median age was 33 years), they believes that the percentage of HIV-seropositive smokers who developed emphysema is striking. They therefore suggest that smoking-related respiratory symptoms and impairment may assume increasing importance as part of the natural history of HIV, particularly in light of the prevalence of cigarette smoking in this population. The study findings also support a role for cytotoxic lymphocytes in the pathogenesis of emphysema.

[Ann Intern Med 2000: 132: 369-372]

Janssen to pull propulsid from US market

Janssen Pharmaceutica will stop marketing the prescription heartburn drug Propulsid (cisapride) in the United States as of July 14, 2000. A Food and Drug Administration (FDA) statement notes that the drug has been associated with 341 reports of heart rhythm abnormalities including 80 reports of deaths. Most of these adverse events occurred in patients who were taking other medications or suffering from underlying conditions known to increase risk of cardiac arrhythmia associated with cisapride. The move to withdraw the drug is voluntary and the effective date is intended to provide time for patients and physicians to make treatment decisions. Patients who are currently prescribed Propulsid are urged to promptly contact their healthcare providers to discuss alternatives. The drug is used to treat severe nighttime heartburn in adult patients with gastroesophageal reflux disease (GERD) that does not adequately respond to other therapies. Its labeling has been revised several times since it was approved in 1993, to point out its risks. Despite these risk management efforts, the firm decided in consultation with the Food and Drug Administration that

continued general US prescription access to the drug poses unacceptable risks. The FDA advises physicians who are treating patients with severely debilitating conditions for whom they believe the benefits of cisapride outweigh its risks to contact Janssen. The Titusville, New Jersey company will continue to make the drug available to patients who meet specific clinical eligibility criteria for a limited-access protocol. In light of the decision to withdraw the drug, the FDA has canceled a public advisory meeting scheduled for April 12, in which ways to reduce adverse effects associated with Propulsid were to be discussed.

[http://www.reutershealth.com/cgi-bin/ssi/framethis?catalog=eline&file=200003 2419.html]

Gene variation may increase drug potency

About 8% of the Caucasian population in the US has a gene variation that could increase the risk of serious complications associated with certain medications, including the clot-preventing drug warfarin. Only 2% of African Americans have the same gene version, but they are more likely to possess another altered gene that may also cause problems. It has been found that 8% of white Americans have a certain version of the gene for a liver enzyme -- known as cytochrome P450 2C9 -- that metabolizes certain drugs. The altered gene causes some people to process particular drugs more slowly. They need a lower dose. They have a higher level of the drug with the same dose (as other people). In cases of people taking warfarin, an anticoagulant often given to people to prevent stroke, the gene variation could increase the risk of excessive bleeding. The gene, known as CYP29C*3, may also affect the drugs tolbutamide (used by diabetics to lower blood sugar), and phenytoin (an anti-seizure medication). People with the gene variation who take tolbutamide could end up with excessively low blood sugar, and people with the altered gene taking phenytoin could end up with toxic levels of the drug in their blood. The same gene could cause problems with the metabolism of other drugs, but these appear to be the main ones. While searching for gene variations known to be common in certain populations, another altered gene was found in about 3% of African Americans, but not present in Caucasians. This new variation needs to be studied further, but may cause problems with the same drugs as CYP29C*3. The test for CYP29C*3 is not widely available because it is expensive. As yet, there is no option for patients in a regular practice to get this test. People concerned about having an extra sensitivity for these drugs should ask their doctor about participating in clinical trials, she suggested. People taking warfarin who experience excessive bleeding should definitely be tested for the gene variant, she added.

[http://www.reutershealth.com/cgi-bin/ssi/framethis?catalog=eline&file=200003 2419.html]

C-reactive protein levels improve prediction of cardiovascular risk in women

C-reactive protein (CRP) measurement adds to the predictive value of other risk factors for cardiovascular disease in women. The finding is reported in the March 23rd issue of the New England Journal of Medicine by Dr. Paul Ridker and colleagues from Harvard Medical School in Boston, Massachusetts. They used a commercial assay to measure hs-CRP (high-sensitivity CRP) and 11 other serum markers in 122 women (cases) who subsequently experienced a fatal or nonfatal myocardial infarction, stroke, or coronary revascularization procedure and in 244 women (controls) matched for age and smoking status. Cases had significantly higher baseline levels of four markers of inflammation--hs-CRP, serum amyloid A, sICAM-1, and interleukin-6 - and higher baseline measures of total and LDL cholesterol, apolipoprotein B-100, homocysteine, and total cholesterol:HDL cholesterol ratio than did controls, the authors report. Cases also had significantly lower HDL cholesterol levels than did controls. Of the 12 measures, the level of hs-CRP was the most powerful predictor of risk in the univariate analysis (relative risk for women in the highest quartile as compared with the lowest quartile, 4.4). Apolipoprotein B-100 and total cholesterol:HDL cholesterol ratio were less powerful risk predictors (relative risk of 3.4 for each). In logistic-regression analyses, only hs-CRP level and total cholesterol:HDL cholesterol ratio independently predicted subsequent cardiovascular events after adjustment for other significant risk factors such as obesity, hypertension, diabetes, and parental history of premature coronary artery disease. [E]ven among women with 'safe' levels of LDL cholesterol, the adjusted relative risk

of cardiovascular events increased approximately 39% with each increasing quartile for hs-CRP. Half of strokes and myocardial infarctions occur in people without any lipidemia. This study, along with at least seven others like it, show that cardiovascular risk can be predict in individuals with and without elevated lipid levels. Physicians need to recognize a fundamental issue, that atherosclerosis is an inflammatory disease. Whereas high cholesterol might foster the development of atherosclerosis, plaque instability and adverse cardiovascular outcomes result from inflammation. By identifying these people at risk--through measuring CRP levels, for example—we can determine which individuals might benefit most from statin therapy, which can reduce the inflammation beyond the anti-inflammatory effects provided by aspirin.

[N Engl J Med 2000; 342: 836-843]

Vitamin C, E may protect the aging brain

Taking vitamin C and vitamin E supplements may help protect memory and mental decline as you age, researchers report. A new study has found that elderly men who took vitamin E and C supplements at least once a week over a number of years were protected from dementia and actually showed improvements in cognitive function – a catch-all term including memory, creativity and mental acuity. Although a protective effect was seen for two different types of dementia in men who took both vitamins, the supplements did not appear to prevent dementia due to Alzheimer's disease. In the study, the researcheres looked at supplement use among 3,385 Japanese-American men in 1988, and for a subset of the men, data was collected from 1982 as well. The amount of each vitamin the men took was unknown. The men, who ranged in age from 71 to 93 years, were tested 4 years later in 1993. At that time, most men were not experiencing any memory problems, although 47 of the men had Alzheimer's dementia, 35 had vascular dementia (a dementia associated with artery-clogging and stroke), 50 had mixed/other types of dementia, and 254 performed poorly on the cognitive tests without diagnosed dementia. Men who took either vitamin C or E alone in 1988 scored better on the 1993 memory tests than men who took no supplements, the investigators report. Men who took both vitamins exhibited only a small improvement over those taking no supplements. However, that men who took both vitamin E and C supplements together for many years showed a substantially greater improvement, suggesting that long-term use is required to improve cognitive function in late life. The researchers believe that vitamin C and E may protect from brain damage because they are antioxidants and can mop up brain-damaging free radical particles.

[Neurology 2000; 54: 1265-1272]

New drug reduces pain of prostate cancer

Prostate cancer patients who are in severe pain because cancer has spread to their bones may be able reduce their need for morphine-based painkillers with a new anti-cancer drug called suramin, which is not yet on the market. In a study, suramin, also slowed the progression of the cancer. In the clinical trial, 460 patients received either suramin plus hydrocortisone or an inactive placebo plus hydrocortisone. All the patients had prostate cancer that had spread to their bones, and required a very strong painkiller, such as morphine, to control their pain. The patients who were taking suramin experienced greater reduction in pain and morphine intake than patients on placebo, the researchers report. Forty-three percent of the suramin group achieved a reduction in pain that lasted about 240 days compared with only a 28% of the placebo group who had a reduction in pain that lasted for 69 days. The cancer also spread more slowly in the suramin group and more patients in this group had a decrease in prostate specific antigen level, which is a marker that indicates the progression of prostate cancer. Overall survival was similar in the two groups, the researchers report. Small noted that the survival advantage of suramin might have been reduced in this study because patients on placebo were allowed to cross over and begin taking suramin late in the trial.

[Journal of Clinical Oncology 2000; 18: 1440-1450]

Rezulin to be withdrawn from the market

The US Food and Drug Administration (FDA) has asked the manufacturer of Rezulin (troglitazone) a drug used to treat type 2 diabetes mellitus to remove the product from the market. The drug's manufacturer, Parke-Davis/Warner-Lambert, has agreed to the

FDA's request. The FDA took this action after its review of recent safety data on Rezulin and 2 similar drugs, rosiglitazone (Avandia) and pioglitazone (Actos), showed that Rezulin is more toxic to the liver than the other 2 drugs. Data to date show that Avandia and Actos, both approved in the past year, offer the same benefits as Rezulin without the same risk. When considered as a whole, the premarketing clinical data and postmarketing safety data from Rezulin as compared to similar, alternative diabetes drugs indicate that continued use of Rezulin now poses an unacceptable risk to patients. Severe liver toxicity has been known to occur with Rezulin since 1997. In consultation with the FDA, Parke-Davis has strengthened the drugs labeling several times and has recommended close monitoring of liver function in patients taking Rezulin. In March 1999, the FDA's Endocrine and Metabolic Drugs Advisory Committee reviewed the status of Rezulin and its risk of liver toxicity and recommended continued availability of this drug in a select group of patients ? patients not well-controlled on other diabetes drugs. Since then, the FDA has continued to actively monitor adverse events associated with Rezulin, as well as those associated with Avandia and Actos. After up to 9 months of marketing experience with these 2 newer drugs, it has become clear that these newer drugs have less risk of severe liver toxicity than Rezulin. Patients using Rezulin are urged to contact their physicians for information about alternative treatments. Patients should not discontinue taking Rezulin or other treatments for diabetes without discussing alternative therapies with their physicians.

[http://pharmacotherapy.medscape.com/MedscapeWire/2000/0300/medwire0322.rezulin.html]

Use of NSAIDs increases the risk of hospitalization for CHF in elderly

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) by elderly patients doubles the risk of being hospitalized for congestive heart failure (CHF), and for those with a history of heart disease it increases the risk by more than 10 times. Dr. David Henry and Dr. John Page, both of The University of Newcastle in Australia, interviewed 365 patients with a mean age of 76.6 who were admitted to hospitals with a primary diagnosis of congestive heart failure. Controls were 658 age- and sex-matched patients without CHF admitted to the same hospitals. Apart from the use of low-dose aspirin, NSAID use during the week before admission to the hospital was associated with a 2.1 odds ratio for hospital admission with CHF, compared with patients who had not used NSAIDs. Patients with a history of heart disease who used NSAIDs had an odds ratio of 10.5 for first admission with heart failure compared with 1.6 for those without such a history. The odds ratio for a first admission to a hospital with CHF rose with increasing dose of NSAIDs taken the previous week, the researchers report. Furthermore, the risk of hospitalization for CHF was greater for NSAIDs with a long half-life. Guidelines should discourage the use of NSAIDs in individuals with a damaged but compensated left ventricle. These drugs should be used with caution in such individuals, in the lowest possible dose, and drugs with a long plasma half-life should be avoided. The investigators say that it is possible that drugs that are selective inhibitors of the inducible cyclo-oxygenase 2 will have a lower rate of adverse effects on the kidney and cardiovascular system, but this remains to be established in well-designed pharmaco-epidemiological studies.

[Arch Intern Med 2000; 160: 777-784]

Low folate levels linked to Alzheimer's disease

Women who have low levels of folate, the by-product of folic acid found in the blood, appear to be at greater risk of Alzheimer's disease. In the study of 30 nuns who participated in a long-term study of Alzheimer's disease, half had brain changes consistent with the memory-robbing illness at autopsy. The women, aged 78 to 101 when they died, had lived at the same convent for most of their lives. Those women with Alzheimer's disease were more likely to have low blood levels of folate than women without the illness. None of the other nutritional markers analyzed in the blood samples was related to brain degeneration or Alzheimer's disease, according to the report in the April issue of the American Journal of Clinical Nutrition. The authors note that the study could not determine whether low levels of folate actually cause Alzheimer's. And the findings do not provide any evidence that taking folic acid supplements can prevent the

disease or slow it down. It is possible that the women had low blood levels of folate due to problems absorbing or metabolizing the nutrient. The women all ate in the same kitchen and, presumably, had similar intakes of folic acid. The researchers call for further research in this area, noting that there are several possible explanations for the relationship between the nutrient and this disease. Folic acid, a nutrient found in green leafy vegetables, liver, kidney, whole grains and nuts, is important in the development of the central nervous system and in the maintenance of blood vessels. Lack of this nutrient can cause birth defects in the developing fetus.

[American Journal of Clinical Nutrition 2000; 71: 993-998]

Vaccine recharges chickenpox immunity

The vaccine that protects against chickenpox appears to reactivate itself and boost the immune system when the body's immunity to the virus diminishes, new study findings suggest. While this boost can cause mild illness, or even a few red spots, it may mean that the vaccine provides more protection to people as they age -- rather than less, as has been feared, researchers report. Chickenpox is caused by the varicella zoster virus, which also causes shingles --a painful outbreak of blisters on the body trunk. Since the Food and Drug Administration (FDA) approved a chickenpox vaccine in 1995, more than 10 million Americans have been vaccinated against the virus. It was feared that the protection offered by the vaccine might wane with age, leaving adults vulnerable to infection. While chickenpox tends to be mild in children, it can be potentially life threatening in adults who have never had the disease. In a new study, the reseacheres of the FDA's Center for Biologics Evaluation and Research in Bethesda, Maryland, followed nearly 5,000 children who had received the chickenpox vaccine. In children who initially had a strong immune response to the vaccine, immunity tended to decline during the 4 years of the study. But in children whose initial response to the vaccine was weaker, immunity increased over time. The investigators discovered that about 500 children experienced substantial increases, or boosts, in their chickenpox immunity. The vaccine, which contains a live, but weakened, form of the chickenpox virus, appears to cause a latent (or dormant) infection. Most of the time, the virus is quiet, but as immunity declines, the latent virus wakes up. Most likely, the boost won't make a child sick, but will strengthen the immune system. Still, the authors note that children who have been vaccinated against the chickenpox should continue to be monitored to keep track of the long-term effects of the vaccine. While the vaccine appears to boost itself in many cases, some people may need to be revaccinated if their immunity drops too low. It may seem like bad news that the latent chickenpox virus wakes up from time to time, but it really shows that the vaccine can provide life-long protection against the illness. For people who do get sick during these boosts, antiviral medication should help. The vaccine was studied extensively before being approved, but how long its protection lasts is unknown.

[Nature Medicine 2000; 6: 381-382, 451-454]