PHARMACOLOGICAL DIGEST

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Painless way of seeing into body wins Nobel Prize

Two scientists, Paul Lauterbur of the United States and Peter Mansfield of Britain, who developed a non-invasive method of imaging internal human organs (magnetic resonance imaging: MRI) that has revolutionized medical diagnosis won the 2003 Nobel prize for medicine. Lauterbur's and Mansfield's discoveries led to the development of modern MRI, a painless method yielding three-dimensional images of organs inside the human body. The now-routine technique makes it possible to see the extent of a tumor, localize an inflammation in the nervous system, or even see a beating heart. MRI has helped replace invasive examinations and reduced risk and discomfort for millions of people going through medical tests ahead of surgery. The laureates' innovations are based on the discovery of the magnetic resonance phenomenon, or how atomic nuclei rotate in a magnetic field, 30 years earlier. Felix Bloch and Edward Mills Purcell won the Nobel physics prize on this finding in 1952. Until Lauterbur's and Mansfield's studies in the early 1970s, which lead to practical applications a decade later, magnetic resonance was used mainly for studying the chemical structure of substances. Lauterbur found a way to create two-dimensional pictures by introducing radients in the magnetic field and build pictures of structures that could not be visualized with other methods. Mansfield, a professor of physics at the University of Nottingham in England, showed the signals could be analyzed mathematically, which made it possible to develop an imaging technique. More than 60 million MRI examinations are carried out each year and there are some 22,000 MRI cameras globally.

[http://www.reuters.com/newsArticle.jhtml?type=topNews&storyID=3562605]

Flu vaccine safe for asthma patients

A shot of the flu vaccine doesn't seem to cause serious side effects in patients with asthma or with another lung condition called chronic obstructive pulmonary disease (COPD). Use of the influenza vaccine in patients with chronic lung diseases is suboptimal, in part, because of concerns that it may induce flare-ups. Although a few studies have provided reassuring safety data, various issues have limited their ability to reach definitive conclusions. The new findings are based on a study of 12,000 older patients with asthma or COPD who did or did not receive the flu vaccine in the UK between 1991 and 1994. Vaccinated patients often had a lung diagnosis recorded or received an asthma drug on the day of vaccination. However, there was no evidence of an increased risk of lung problems within two weeks of vaccination. The researchers conclude that routine influenza vaccination in the general UK population of older individuals with asthma or COPD did not increase the short term rate of lung problems or the need for related drugs.

[Thorax 2003;58:835-9]

Selenium may raise skin cancer risk

In patients with a history of skin cancer other than melanoma, the use of selenium supplements does not appear to prevent the recurrence of two other types of skin cancer--basal cell and squamous cell cancer--and may actually raise the risk of squamous cell cancer. The initial results from the Nutritional Prevention of Cancer Trial reported in 1996 showed that selenium use did not influence the rate of nonmelanoma skin cancer in individuals who were at risk for this type of cancer. However, the new findings, which are based on three additional years of follow-up, suggest that use of the selenium, an antioxidant, may promote certain cancers. These findings run counter to the results of animal studies that indicate a protective effect for selenium and other antioxidants. The study involved 1312 patients with a history of nonmelanoma skin cancer who were randomly assigned to receive daily supplementation with selenium 200 micrograms or placebo ("sugar pill"). In agreement with the initial results, selenium use was not associated with the risk of basal cell cancer. However, use

of the antioxidant seemed to raise the risk of squamous cell cancer. Selenium users were 25% more likely to develop this malignancy than nonusers. These findings should be viewed along with the overall impact of selenium supplementation as a potential cancer-preventing agent, the authors note. Prostate cancer prevention trials that are now underway, including one testing selenium supplementation in men with precancerous cells in the prostate.

[J Natl Cancer Inst 2003;95:1477-81]

U.S. FDA approves radiation contamination drug

The U.S. Food and Drug Administration approved a German company's drug treatment for certain kinds of radiation contamination. Radiogardase, known as Prussian blue, could be used to treat people exposed to harmful levels of cesium-137 or thallium. The agency has been asking for companies to come up with treatments for potential chemical, biological and nuclear weapons. The approval of Radiogardase was part of FDA's continuing efforts to provide the American public with medical countermeasures in the event of a terrorist attack. Cesium-137 or thallium can be eaten, inhaled, get into wounds, and fatal in high doses. Lower doses can cause cancer. Its potential use as a component of a conventional explosive device containing radioactive material, commonly called a 'dirty bomb. It had also found that pentetate calcium trisodium (Ca-DTPA) and pentetate zinc trisodium (Zn-DTPA) can safely decontaminate people exposed to radioactive isotopes of the elements plutonium, americium and curium.

[http://www.medscape.com/viewarticle/462519]

Compound slows Parkinson's Disease in mice

An organic chemical called a ketone body protects brain neurons in a mouse model of Parkinson's disease. Parkinson disease occurs when specific kinds of brain cells die. Patients with the disorder develop involuntary movements and tremor that progress over time because the brain cells no longer produce a chemical called dopamine. Although there is no evidence yet that treatment with ketone bodies would be safe or feasible in humans, related strategies may someday be used to slow the progression of Parkinson's disease. According to the report, the neurotoxin MPTP causes symptoms similar to those of Parkinson's disease when injected into mice. It does so by preventing brain neurons from using oxygen. However, when the mice were treated continuously with infusion of the ketone D-beta-hydroxybutyrate (DBHB), beginning prior to treatment with MPTP, the neurons could use oxygen by using a different chemical pathway, and not as many brain neurons died. The mice could keep their balance better and run longer. Another way to increase ketone levels in the body is to follow a "ketogenic" diet that results in production of the compounds and is sometimes used to help treat epilepsy. The diet begins with a period of fasting to simulate starvation during which time water or sugar-free beverages are consumed. After that, a highly restricted diet is started. Because the diet involves eating a lot of fat, patients are at risk for developing dangerously high cholesterol levels, which can trigger heart disease. These diets should only be tried while under the supervision of a doctor

[J Clin Invest 2003;112: 892-901]

Effective methadone dose does not harm newborns

Treating heroin-addicted pregnant women with the most effective dose of methadone does not increase their infants' symptoms of withdrawal after they are born. Instead, methadone appears to reduce risks to both mother and infant by preventing illicit drug use. Methadone is often substituted for heroin and other opiates when patients are treated for their addiction. When the methadone dose is high enough, it blocks the effects of heroin and reduces addicts' craving for the drug. Many physicians believe that methadone doses should be kept no higher than 20 milligrams per day when women are pregnant. But effective doses for pregnant women range from 50 to 200 mg daily. Therefore, the researchers examined the records of 100 mother-newborn pairs treated in their comprehensive program for drug-addicted pregnant women. Methadone doses ranged from 20 to 200 mg per day. Their study differed from previous research, because it examines higher average doses and the last dose prior to delivery. They also scored the newborns' withdrawal problems using an objective measure of clinical signs and symptoms, called the Newborn Abstinence Score (NAS). Birth weight, highest NAS, presence of neonatal withdrawal, and average duration of treatment for withdrawal did not differ significantly between the higher doses and lower doses of methadone. Prior research demonstrated that methadone has no long-term effects on the fetus, just short-term withdrawal, which occurred in 60 percent of the babies. Effective maintenance prevents drug hunger and

craving and blocks the euphoric effect of illicit drugs. As a result, the fetus is not exposed to erratic maternal opioid levels, protecting it from repeated episodes of withdrawal. Furthermore, by preventing drug-seeking behavior, women are less likely to engage in prostitution or other behaviors that increase their risk of HIV, hepatitis infection, and other sexually transmitted diseases. Heroin-addicted women should check into a program that not only helps them with their symptoms of withdrawal, but also addresses psychological and social issues.

[Am J Obstet Gynecol 2003;189:312-7]

Spinal fluid proteins may help identify Alzheimer's

The ratio of one protein to another in spinal fluid may help diagnose Alzheimer's disease (AD). The two proteins, phosphorylated tau protein (phospho-tau) and beta-amyloid peptide-42 (A-beta-42), have already been linked to Alzheimer's disease. Measuring levels of either one in spinal fluid has not proven useful in diagnosing AD. However, it is possible that calculating the ratio of one to the other could be helpful in diagnosing the condition. To investigate, the researchers determined the ratio of phospho-tau to A-beta-42 in 100 patients being evaluated for mental decline and 31 healthy control subjects. 30 patients were diagnosed with non-AD mental decline, 19 with other nerve disorders and 51 with AD. The protein ratio was much higher in AD patients than in the other subjects. At least 80 percent of the time the ratio correctly identified people with AD, while at least 73 percent of the time it correctly identified people without AD. The investigators maintain that multiple areas of research are required before the potential role of the ratio in clinical practice can be defined. If clinical diagnoses and those based on the marker have similar accuracy, the relative cost and convenience of the biomarker and clinical assessment should be compared.

[Arch Neurol 2003;60:1202-6]

Baclofen helpful in GERD refractory to proton pump inhibitors

Baclofen may treat gastroesophageal reflux disease (GERD) refractory to proton pump inhibitor (PPI) therapy, even in patients with duodenal reflux. Acute administration of the gamma-aminobutyric acid$_B$ ($GABA_B$) receptor agonist baclofen can inhibit the occurrence of transient lower esophageal sphincter relaxations, thereby significantly decreasing acid reflux after a meal. It seems conceivable therefore that treatment with baclofen might also reduce exposure of the distal esophagus to duodenal reflux. This study enrolled 16 patients with persistent heartburn or regurgitation for at least three months despite PPI therapy. There were 11 women and five men; mean age was 46 ± 3 years; and seven patients had erosive esophagitis, including five with grade 1 and two with grade 2. While continuing PPI therapy, patients received baclofen 5 mg three times daily, and the dosage was increased by 5 mg every fourth day to a maintenance dose of 20 mg three times daily. During PPI therapy alone, all patients had normal acid exposure (0.3% of the time; range, 0.05%-2.2%) but pathological duodenal reflux exposure (13.8% of the time; range, 11.8%-15.5%). After addition of baclofen 20 mg three times daily, acid exposure was similar (0.4% of the time; range, 0.15%-2.3%; P = N.S.) but duodenal reflux was significantly less (6.1% of the time; range, 0.8%-10.3%; $P < .05$). The total number of duodenal reflux episodes decreased from 23 (range, 14.5-34) to 12 (range, 5-21; $P = .06$), while the number of duodenal reflux episodes lasting longer than five minutes decreased from 5 (range, 3-8) to 2 (range, 0.5-4.5; $P < .05$). The cumulative severity score for 14 reflux symptoms decreased from 10.3 ± 1.7 to 5.8 ± 1.3; $P < .01$). Four patients reported mild adverse events of nausea or drowsiness. The $GABA_B$ receptor agonist baclofen improves duodenal reflux and associated reflux symptoms that persist during PPI therapy. These observations confirm that baclofen can inhibit reflux during repeated administration and suggest a therapeutic potential as an add-on in GERD patients with incomplete relief by acid suppression.

[Gut 2003;53:1397-1402]

Continuous GLP-1 infusion maintains glycemic control in elderly

Continuous infusion of glucagon-like peptide (GLP-1) successfully maintained glycemic control in elderly patients who were previously controlled on oral hypoglycemic agents. The treatment group had fewer hypoglycemic events, greater insulin release in response to glucose, and greater rate of glucose disposal. GLP-1 is an insulinotropic gut hormone that, when given exogenously, may be a useful agent in the treatment of type 2 diabetes. The investigators previously demonstrated that GLP-1 has

insulinotropic activity in elderly diabetic patients and it enhances their insulin- and non–insnlin-mediated glucose uptake. Because of its ability to ameliorate multiple metabolic defects and because hypoglycemia might not be an issue, GLP-1 and its analogs may prove to be valuable therapeutic agents in this population. Of 16 patients with type 2 diabetes who were being treated with oral hypoglycemic agents, eight patients continued on their usual treatment and eight patients discontinued hypoglycemic medications and received a continuous subcutaneous infusion of GLP-1 for 12 weeks at a maximum dose of 120 pmol/kg/hour. Primary end points were HbA1c levels and capillary blood glucose (CBG) determinations. HbA1c levels (7.1%) and body weight were stable in both groups. Although the usual-treatment group had 87 CBG measurements of 3.6 mmol/L during the study, the GLP-1 group had only one such measurement (3.5 mmol/L). GLP-1 infusion did not affect fasting plasma ghrelin levels, but it enhanced glucose-induced insulin secretion (from 119 ± 21 pmol/L to 202 ± 51 pmol/L; $P < .05$) and insulin-mediated glucose disposal (from 29.8 ± 3.3 μmol/kg/min to 35.9 ± 2.3 μmol/kg/min; $P < .01$). A GLP-1 compound is a promising therapeutic optiou for elderly diabetic patients. Long-term administration of GLP-1 by subcutaneous infusion using currently available pumps is impractical for many patients. To allow this therapy to have broader clinical utility, newer delivery systems, dipeptidyl peptidase IV resistant analogs, or agonists of the GLP-1 receptor need to be developed.

[Diabetes Care 2003;26:2835-2841]

Once-daily levofloxacin effective for chronic bacterial prostatitis

Once-daily levofloxacin is as effective as ciprofloxacin taken twice daily for 28 days for the treatment of chronic bacterial prostatitis. Aerobic gram-negative enteric bacteria (eg, *Escherichia coli*) have been recognized as the most prevalent etiologic agents of bacterial prostatitis, and the role of gram-positive bacteria has been controversial. Because of their broad spectrum activity and preferential accumulation in prostatic fluid, fluoroquinolones have become the standard of care for chronic bacterial prostatitis. In this active-control trial, 377 men with a history of chronic bacterial prostatitis, current clinical signs and symptoms, and laboratory evidence of prostatitis were randomized to treatment with levofloxacin 500 mg once daily or ciprofloxacin 500 mg twice daily for 28 days. The primary end point was microbiologic efficacy. The rate of clinical success, defined as cured plns improved patients, was 75% for levofloxacin and 72.8% for ciprofloxacin (95% confidence interval [CI] for the difference in the success rates, -13.27 to 8.87). Microbiologic eradication rates were also similar in both groups (75% for levofloxacin and 76.8% for ciprofloxacin; 95% CI for the difference, -8.98 to 12.58). The most common isolates were *Enterococcus faecalis* and *E. coli*. Both regimens were well tolerated, with similar rates of adverse events and of relapse by six months. Study limitations include contiuued symptoms in some patients in each treatment group despite eradication of the pathogen at the posttherapy visit, and isolation of bacteria in some patients who were considered to have clinical success. This suggests that in chronic bacterial prostatitis, clinical cure and eradication of pathogens may not always correlate. Isolation of a high proportion of gram-positive organisms, as well as gram-negative pathogens, underscores the necessity of choosing an antimicrobial agent with broad-spectrum activity.

[Urology 2003;62:537-541]

Gamma vinyl-GABA may be effective in cocaine addiction

The antiepileptic drug gamma-vinyl-GABA (GVG; vigabatrin) may be effective for the treatment of cocaine addiction. Based on animal models suggesting that GVG blocks the rise in dopamine levels produced by cocaine, nicotine, and other addictive substances, the state of Baja California and the Mexican federal government approved an investigator-initiated clinical trial. In the first week of this eight-week trial, 20 addicts (19 men and one woman) who had been using cocaine five to seven days weekly for three to 15 years received escalating doses of GVG up to a maximum of 3 g daily, followed by a daily maintenance dose of 4 g. To continue in the study, subjects had to remain free of cocaine for 28 consecutive days. The dose of GVG was then tapered by 1 g per day per week for each of the following three weeks. Subjects received twice-weekly urine drug testing and regular psychosocial counseling. Eight subjects dropped out in the first 10 days of the trial to resume cocaine use. Of the 12 remaining subjects, eight (40% of enrollees) completed the trial and were tapered off GVG. All eight of these subjects remained cocaine-free for at least 46 to 58 days after treatment ended, and they reported that their craving for cocaine was eliminated within two to three weeks and did not return even after they tapered off GVG. They showed profound

behavioral improvements in self-esteem, family relationships, and work activities. Of the four subjects who remained in the study more than 10 days but did not withdraw from cocaine, three reduced their cocaine use by 50% to 80%. The results suggested that this drug, in combination with psychosocial therapy, offers a potential treatment for cocaine addiction. Although visual field defects are reported in 30% to 40% of patients on long-term therapy with GVG, none of the subjects in this study developed this adverse event. Daytime sleepiness and headaches associated with GVG use occasionally persisted for several weeks but did not cause subjects to drop out of the study. All subjects who withdrew from cocaine gained weight. A large double-blind, placebo-controlled trial are need to confirm and extend these results.

[Synapse 2003;50:261-265]

Higher dose, longer use of inhaled steroids linked to cataract risk

Higher dose and longer use of inhaled steroids increases the risk of cataracts, according to the results of a population-based case-control study published in the October issue of the British Journal of Opthalmology. The authors emphasize the importance of being aware of this complication and using the lowest effective dose to prevent asthma symptoms. Using the U.K.'s General Practice Research Database, the investigators identified 15,479 patients with cataract older than 40 years and 15,479 control patients without cataract matched for age, sex, medical practice, and observation period. Among those with cataract, nearly 11.5% had been prescribed inhaled steroids compared with nearly 7.5% of controls. The risk of cataract increased in a dose-related fashion, with little or no apparent increased risk for those taking a daily dose less than 400 µg (adjusted odds ratio [OR], 0.99; 95% confidence interval [CI], 0.87 - 1.13), but with an increased risk of 69% for those taking doses greater than 1600 µg a day (adjusted OR, 1.69; 95% CI, 1.17 - 2.43). Risk of cataract also rose with increased duration of inhaled steroid use. These risks need to be considered in the light of the large beneficial effects value of inhaled corticosteroids to many patients with asthma and to some patients with chronic obstructive pulmonary disease. While lower doses have not been shown to be completely without risk, there is good evidence to suggest that lower doses are associated with a reduced risk of adverse effects. The risk of cataract associated with high doses of inhaled corticosteroids needs to be more widely recognized.

[Br J Ophthalmol 2003;87:1247-51]

Alfacon-1 plus steroids leads to rapid improvement in SARS

First use of an interferon drug approved for treating hepatitis C, administered with steroids, led to more rapid improvement in many of the patients among the first 19 who received it during the Toronto outbreak of severe acute respiratory syndrome (SARS). Previous in vitro work by U.S. Army researchers had demonstrated that the consensus interferon alfacon-1 was the most active of the interferons against SARS. So when the second wave of SARS hit, the Toronto team elected "to cautiously treat" patients with probable SARS with alfacon-1 in combination with steroids, and evaluate the drug combination for safety and possible efficacy. Patients had to have progressive deterioration of their respiratory status in the proceeding 48 hours" and confirmed radiologic deterioration during the same period. Dosing consisted of 9 µg of alfacon-1 administered subcutaneously on a daily basis for 10 days. Patients who did not exhibit clinical signs of improvement after day 2 were increased to a dose of 15 µg per day. The steroid component followed the Hong Kong protocol, using a high dose of 500 mg of methylprednisolone for three days, followed by a round of taper. The first nine patients were compared with a historic control group of 13 patients in the first outbreak who had received only steroids. Baseline characteristics of the groups were similar. The researchers presented a Kaplan-Meier analysis of time to 50% resolution from peak chest radiograph abnormality. The group receiving only steroids required 11.5 days to reach that milestone, while those receiving combination therapy took four days (P = .001, Log rank). They also had higher oxygen saturation compared to controls, and had a more rapid resolution of the need for supplemental oxygen (P = .02, Log rank). There was a predictable drop in absolute neutrophil count associated with use of interferon, "which was not clinically significant and resolved after drug cessation. After those positive preliminary results, 10 additional patients were treated with the alfacon-1 and methylprednisolone combination. A salvage effort with six intubated patients in intensive care raised concerns of the risk of cytokine blast. The invesgitors decided to

begin with a low dose and then escalated the dose. Therefore, there was no clinical evidence of cytokine blast or serious adverse events. Four of the six ICU patients treated late in disease died, while those treated earlier survived. So any antiviral used should be used early in disease. No adverse effects commonly associated with the use of interferon concomitant with steroids was not seen. The results suggest that interferon alfacon-1 warrants further prospective investigation as a treatment for SARS. Because the drug is approved for sale as a treatment for hepatitis C, there should be no question of availability for off-label use in the event of subsequent outbreaks of SARS.

[http://www.medscape.com/viewarticle/461698]

Glucose-insulin-potassium infusion saves some lives after myocardial infarctiou

Glucose-insulin-potassium (GIK) infusion saves some lives after myocardial infarction. As adjunctive therapy to primary coronary transluminal angioplasty (PTCA), this treatment reduced mortality in patients without heart failure, but not in all patients. Since the early 1960s, GIK infusion has been advocated as therapy in the early hours after acute myocardial infarction. The main effect of the GIK infusion was considered to be the beneficial effect of administration of glucose to the ischemic myocardium. From April 1998 to September 2001, 940 patients with acute myocardial infarction eligible for PTCA were randomized to receive continuous GIK infusion for 8 to 12 hours or no infusion. Mortality at 30 days was 23 (4.9%) of 476 patients in the GIK group and 27 (5.8%) of 464 patients in the control group (relative risk [RR], 0.82; 95% confidence interval [CI], 0.46 - 1.46). In a subgroup of 856 patients (91.1%) in Killip class 1 who had no signs of heart failure, 30-day mortality was 5 (1.2%) of 426 patients receiving GIK and 18 (4.2%) of 430 patients not receiving GIK (RR, 0.28; 95% CI, 0.1 - 0.75). In 84 patients (8.9%) who had signs of heart failure and were in Killip class 2 or greater, 30-day mortality was 18 (36%) of 50 patients who received GIK infusion and 9 (26.5%) of 34 controls (RR, 1.44; 95% CI, 0.65 - 3.22). Other than possible volume overload in patients with heart failure, there were no adverse effects of GIK infusion. Study limitations include insufficient power to detect a significant difference in mortality based on relatively small sample size in some subgroups, lack of correction for multiple comparisons, and open-label design. GIK as adjunctive therapy to PTCA in acute MI did not result in a significant mortality reduction in all patients. The effect of GIK infusion in patients with signs of heart failure (Killip class >/= 2) at admission is uncertain. In the subgroup without heart failure, a significant reduction was seen. Relatively high infusion rate of GIK may explain the lack of benefit of this therapy in patients with heart failure. Additional research to resolve the issues of whether GIK infusion is beneficial in all patients with acute myocardial infarction and in subgroups with shock or congestive heart failure.

[J Am Coll Cardiol 2003;42:784-91]

Pharmacologic blockade of the renin-angiotensin system: vascular benefits beyond commonly understood pharmacologic actions

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are recognized primarily for their use in hypertension, in heart failure, and after myocardial infarction. New evidence, particularly with ACE inhibitors, has shown their ability to reduce acute coronary events associated with atherosclerosis in patients without a history of the aforementioned cardiac conditions. This is likely due to inhibitory effects on the renin-angiotensin system -- a system that adversely influences fibrinolytic balance, vascular endothelial function, and vascular inflammation, all key components of atherosclerotic progression and adverse coronary outcomes. Results of various studies suggest favorable effects of ACE inhibitors and ARBs on markers of these components, including effects on plasminogen activator inhibitor-1, endothelin-1, and nitric oxide by ACE inhibitors, and effects on vascular cell adhesion molecule-1 and C-reactive protein by ARBs. Although early evidence suggests that ACE inhibitors may provide a greater beneficial effect on some of these markers compared with ARBs, and that certain ACE inhibitors may provide greater vascular benefits than others, further investigation is required to verify such findings. Overall, understanding the distinct coronary vascular benefits of these agents will emphasize the importance of using them, particularly ACE inhibitors, to improve outcomes in patients with coronary atherosclerotic disease.

[Pharmacotherapy 2003;23:1141-1152]

Acetaminophen intoxication and length of treatment: How long is long enough?

The currently recommended dosing scheme for treating acetaminophen overdose in the United States consists of a loading dose of oral *N*-

acetylcysteine 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses, for a total of 72 hours of oral *N*-acetylcysteine therapy. This protocol has been both effective and safe. We critically evaluated the evidence that supports reducing the course of *N*-acetylcysteine therapy from 72 hours to 24 or 36 hours. This shorter regimen offers important benefits for both the patient and the patient's family, such as increased drug tolerability and reduced hospital stay. Patients who intentionally ingested acetaminophen with harmful intent could receive appropriate psychosocial treatment more quickly. In addition, shorter courses of *N*-acetylcysteine therapy have positive financial ramifications by reducing the hospital stay by 1 or 2 days. Clearly, a shorter treatment regimen would not be appropriate for all patients, particularly those who seek treatment late (> 24 hrs after ingestion) and those with evidence of organ toxicity. In order to provide the necessary evidence to support a change in accepted clinical practice, further investigation on the safety and efficacy of a shorter *N*-acetylcysteine regimen should be conducted by clinical researchers in a controlled manner.

[Pharmacotherapy 2003;23:1052-1059]

Smoking marijuaua lowers fertility, study shows

Sperm in men who smoke marijuana regularly lose stamina and burn out which may prevent conception. The study by the State University of New York in Buffalo, New York, is the first to focus on the swimming patterns of sperm in men who smoke marijuana, and found that the sperm from marijuana smokers were moving too fast too early. To attach itself to the egg, the sperm has to swim like mad, that's hyper activation, and they have to be vigorous at the right time. Smoking marijuana messes up the natural regulatory system. These sperm will experience burnout before they reach the egg and would not be capable of fertilization. The study, released at the annual conference of the American Society of Reproductive Medicine in San Antonio, found that men who smoke marijuana have less sperm because of lower quantities of seminal fluid compared to fertile men. One of the ingredients of marijuana, tetrahydrocannabinol, or THC, is the psychoactive chemical that causes people to feel "high." The speed, volume, shape, density, movement and count of sperm were studied in both men whose sperm is fertile and marijuana smokers. A previous study found that the enzyme cap of human sperm changed when exposed to high levels of THC. As a result, the sperm has a harder time attaching to the egg before fertilization. Even if people stop smoking marijuana, THC gets stored in the body fat and may take several months before leaving the body.

[http://www.reuters.com/newsArticle.jhtml?type=healthNews&storyID=3604610]

Stem cells repair heart attack damage

After a heart attack, infusing stem cells into the coronary arteries that supply blood to the heart muscle leads to a reduction in the area of heart damage. Moreover, heart function improves after the treatment. Stem cells are early-stage cells that can go on to become several different types of tissue. The investigators isolated stem cells from the bone marrow or blood of 28 heart attack patients and about four days later infused the cells into the coronary artery that caused the heart attack. The size of the damaged area of the heart fell significantly over the following four months. The reduction in damage size related directly to improvements in cardiac function. Prior to the infusions, the investigators had assessed the capacity of the stem cells to migrate in response to chemical signals produced by the body. They found that migratory capacity, but not the number, of infused cells strongly predicted the reduction in size of the area of heart damage. Therefore, it might be useful to evaluate migratory capacity in order to predict functional improvement after infusion of the cells into patients' hearts. Risk factors for heart disease, such as high cholesterol and age, have a negative effect on the migratory capacity of the circulating stem cells, but lipid-lowering statin drugs can improve cell function. Therefore, current studies are focusing to determine the molecular mechanisms regulating the migratory capacity in order to optimize stem cell function. In addition, the investigators have a large ongoing program to treat patients with chronic heart failure in a similar way. Large randomized trials are required to unequivocally demonstrate long lasting effects of this treatment.

[Circulation 2003 Oct 13 [Epub ahead of print].

Magnesium in diet may alter heart disease risk

Greater intake of magnesium, one of the minerals recommended in a healthy diet, appears to reduce the risk of heart disease, a study of more than

7,000 men shows. Although magnesium deficiency is believed to be detrimental for the heart, the association "has not been clearly identified." In order to do so, the researchers examined dietary magnesium intake in 7172 men who took part in the Honolulu Heart Program. At enrollment, the average daily dietary magnesium intake was 268 milligrams, with a range of 50 to 1138 mg. During 30 years of follow-up, 1431 cases of coronary heart disease were identified. Within 15 years of the first dietary assessment, the rate of heart disease was significantly lower in those with the highest daily magnesium intake (340 mg or more) compared with those with the lowest intake (186 mg or less). The researchers calculate that the rate of heart disease was the equivalent of 4 cases per 1000 people per year for those in the high magnesium group, versus 7 cases among those with the lowest intake. Further work needs to be undertaken to explore the value of magnesium supplementation.

[Am J Cardiol 2003;92:665-9]

Levitra may help when Viagra lets you down

Nearly half of men who did not respond to Viagra achieved successful sexual intercourse when given rival drug Levitra. Results of their 463-patient study showed that 46.1 percent of men who had failed at least four of the last six attempts at intercourse while on Viagra were successful when given Levitra. That success rate was three times greater than the 16.1 percent seen among men taking placebo. Study investigator reported the findings showed many men could rely on Levitra to improve erectile function when other treatments had not worked. Levitra was launched in the United States in September, ahead of another challenger to Viagra, called Cialis, from Lilly-Icos. All three drugs are already competing in Europe, where Cialis was launched ahead of Levitra earlier this year.

[http://www.reuters.com/newsArticle.jhtml?type =healthNews&storyID=3586522]

Antibiotic-resistant infections on the rise

More and more people are becoming infected with antibiotic-resistant "superbugs," even when they have no risk factors that would make them prone to such infections. The reason for the steep increase appears to be improper dosing of antibiotics as well as cumulative exposure to the drugs. The proportion of resistant infections by a bacterium called Streptococcus pneumoniae has increased from 5 percent in 1992 to almost 24 percent in 2002. The problem is even worse for children, among whom resistance is almost 35 percent. Although there are still effective antibiotics available. If resistance to antibiotics continues to increase, within 5 years, it could be that children will die of pneumonia because of resistant strains for which no therapy is available. Another study, looked at 60 otherwise healthy children who were hospitalized between 2000 and 2001 with Staphylococcus aureus infections. 27 infections (45 percent) were resistant to methicillin antibiotics. In the ensuing 2 years, the incidence has just about doubled, to nearly 70 percent. Results of a chart review conducted at the UC Davis School of Medicine and Medical Center are also being presented at the IDSA meeting. In that study, 20.5 percent of 1637 Staph aureus infections were resistant, and nearly 60 percent of these resistant infections were not acquired in the hospital. Moreover, about 20 percent of patients had no identifiable risk factors for becoming infected. The investigators maintain that the most important way to combat the rising rate of resistance is to prescribe antibiotics at the correct dose for the proper duration. The solution is not to restrict antibiotics, but to use them appropriately.

[http://www.reuters.com/newsArticle.jhtml?type =healthNews&storyID=3588382]