

Facts and ideas from anywhere



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ANOTHER WIN FOR STATINS

The results of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) were published in April 2003 (1, 2). This trial involved nearly 20,000 hypertensive patients aged 40 to 79 years with at least 3 other cardiovascular risk factors. The patients were randomized to 1 of 2 antihypertensive regimens, one arm treated with a calcium antagonist (*amlodipine*) plus an angiotensin-

converting enzyme inhibitor (*perindopril*) and the other arm treated with a beta-blocker (*atenolol*) plus a diuretic (*doxazosin* gastrointestinal therapeutic system). One half of the patients in each hypertensive arm—about 5000 patients per arm—were also treated with 10 mg of *atorvastatin* daily, and the other half received placebo.

The criteria for inclusion in the study were an untreated systolic blood pressure ≥ 160 mm Hg or diastolic pressure ≥ 100 mm Hg or both, or a treated systolic blood pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg or both. Total cholesterol concentrations had to be ≤ 250 mg/dL (≤ 6.5 mmol/L), and patients could not be taking a statin drug or a fibrate upon enrollment. All patients also had to have at least 3 of the following 11 risk factors: left ventricular hypertrophy, other electrocardiographic abnormalities, type II diabetes mellitus, peripheral arterial disease, previous stroke or transient ischemic attack, male sex, age ≥ 55 years, microalbuminuria or proteinuria, smoker, ratio of plasma total cholesterol to high-density lipoprotein (HDL) cholesterol ≥ 6 , or family history of premature coronary heart disease.

The study stopped after 3.3 years for the 5000 subjects in each arm of the study who were receiving atorvastatin because by that time 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group (36% \downarrow). This benefit emerged in the first year of follow-up. In each of the 2 atorvastatin arms, the relative risk reduction in fatal and nonfatal stroke was 27% (89 atorvastatin vs 121 placebo), total cardiovascular events were reduced 21% (389 atorvastatin vs 486 placebo), and total coronary events were reduced 29% (178 atorvastatin vs 247 placebo). There were 185 deaths in the atorvastatin group and 212 in the placebo group (13% \downarrow). Atorvastatin lowered the mean serum total cholesterol from 212 to 162 mg/dL (26% \downarrow) and the low-density lipoprotein (LDL) cholesterol from 131 to 90 mg/dL (31% \downarrow).

This study is important for atorvastatin because the only previous long-term study of atorvastatin included a small number

of patients (about 300). The ASCOT-LLA study shows that atorvastatin has long-term outcome benefits similar to those provided by simvastatin, pravastatin, and lovastatin.

STATIN-ASSOCIATED MYOPATHY

Thompson and colleagues (3) from Hartford, Amherst, and Boston reviewed numerous published articles on statin myopathy as well as the Food and Drug Administration (FDA) MedWatch database; Ballentyne and colleagues conducted a similar review (4). *Myalgia* was defined by Thompson and associates as muscle pain that affected patients' quality of life and their compliance with taking the statin drug. Myalgia has rarely been reported in clinical trials and has infrequently led to statin discontinuation in trials. In the recently published Heart Protection Study, there was no difference in muscle pain or weakness between patients treated with simvastatin 40 mg/day or placebo for 5 years, and there was no difference in the number of patients who discontinued treatment for musculoskeletal complaints between the treatment and the placebo groups. In trials, both treatment and placebo groups had a 1% to 5% rate of myalgia. Thus, there is no consensus that statins are responsible for myalgic complaints, although many clinicians believe that statins can induce myalgia without creatine kinase (CK) elevations.

Myositis was defined as muscle pain with CK levels >10 times the upper limit of normal. Thompson and colleagues collected 1440 cases of rhabdomyolysis reported to the FDA from January 1, 1990, through March 31, 2002. This number, which excluded cases due to cerivastatin, included 612 cases secondary to simvastatin, 383 to atorvastatin, 243 to pravastatin, 147 to lovastatin, and 55 to fluvastatin. CK elevations <10 times the upper level of normal are not known because this information is rarely reported in clinical studies. Statins can magnify the increase in CK levels that can occur following exercise.

Skeletal muscle weakness is frequent in association with clinically important myositis and rhabdomyolysis but can also occur in patients with little or no CK elevation. The frequency of symptomatic weakness, however, has never been reported, and the only study to examine muscle strength in patients treated with statins was limited to 4 subjects.

There are rare clinical anecdotes of patients who take statins and complain of persistent muscle discomfort, occasionally associated with CK elevations, both of which persist after withdrawal of the statin drug. Such patients, of course, need to be evaluated for other conditions such as polymyalgia rheumatica and temporal arteritis, which may have been unmasked by statin therapy, as well as hypothyroidism, which can also elevate CK levels.

The frequency of fatal rhabdomyolysis has been estimated using the FDA and National Prescription audit to be as low as 0.15 deaths per million prescriptions. The estimated incidence rates (per million prescriptions) for the various statins are as follows: pravastatin, 0.04; simvastatin, 0.12; fluvastatin, 0; and atorvastatin, 0.04 (differences insignificant). The death rate for cerivastatin was about 50 times greater than that for the other statins. A compilation of all randomized controlled statin trials identified 83,858 patients randomly assigned to receive either statin treatment or placebo, and there were only 49 cases of myositis and 7 cases of rhabdomyolysis in the statin treatment group compared with 44 cases of myositis and 5 cases of rhabdomyolysis among placebo controls.

The Heart Protection Study randomized 20,536 patients to simvastatin 40 mg/day or placebo. CK was measured in patients with unexplained muscle complaints and in those using a non-study statin during the 3 first-year visits. Over the mean 5 years of the study, 33% of the simvastatin and 33% of the placebo participants complained of unexplained muscle pain or weakness during at least 1 of 3 first-year or subsequent biannual visits. Nevertheless, only 49 (0.48%) of 10,269 statin patients and 50 (0.49%) of 10,267 control patients discontinued treatment because of muscle symptoms. Rhabdomyolysis, defined in this study as CK values >40 times the upper limit of normal, occurred in 5 statin and 3 placebo participants. Persistent CK elevations of >4 times the upper limit of normal occurred in 7 (0.07%) statin patients and in 1 (0.01%) placebo patient. Thus, these controlled study results document the low frequency of important muscle complaints with statin therapy.

Certain concomitant medications, of course, increase the risk of statin-associated myopathy, and they include the fibrates, particularly gemfibrozil; niacin; cyclosporine; azole antifungals; macrolide antibiotics; HIV protease inhibitors; nefazodone; verapamil and diltiazem; amiodarone; and grapefruit juice (>1 quart/day).

Much has been made of the risk of myopathy among the statins based on their water solubility or potency in reducing LDL cholesterol. No clinical or epidemiological evidence permits differentiation among the statins as to their myotoxic potential. The estimated incidence of fatal rhabdomyolysis in the FDA database is 0.04 cases per million prescriptions for both pravastatin and atorvastatin, despite the fact that pravastatin is the most hydrophilic and atorvastatin is the most powerful of the presently available statins. This observation suggests that factors other than hydrophilicity or potency in reducing LDL cholesterol affect the myopathic process.

Combining a statin with another lipid-lowering agent known to increase the risk of myopathy is not contraindicated if the benefits of combined therapy are likely to outweigh the risks. Such combination therapy with a statin and a fibrate or niacin is often required in patients with high serum levels of both LDL cholesterol and triglycerides or low levels of HDL cholesterol. Similarly, transplant recipients and patients with HIV infection frequently develop hyperlipidemia from immunosuppressive or antiviral therapy. These patients may require statin therapy and even therapy with a statin and a fibrate or niacin, despite the fact that cyclosporine and protease inhibitors increase the risk of rhabdomyolysis. Ezetimide can be used in combination with

statins without increasing the risk of myopathy. By itself, it lowers LDL cholesterol by about 18%; when combined with a statin, it lowers LDL cholesterol by about 25%. It also lowers serum triglycerides an average of 14% and has no significant effect on HDL cholesterol.

Routine measurement of CK levels in asymptomatic patients before or during statin treatment is not required. There is no need to discontinue statin therapy in asymptomatic patients whose CK levels are elevated <10 times the upper limit of normal. If, however, patients become symptomatic or their urine darkens, the drug should be stopped promptly. Patients complaining of myalgias without elevated CK levels can continue the medication if the symptoms are tolerable. If the symptoms are intolerable or progressive, the statin should be stopped. Then, when the patient is totally asymptomatic again, statins can be restarted, but probably a different statin should be used.

The number of serious adverse events and the rate of liver enzyme abnormalities did not differ between patients assigned atorvastatin (10 mg daily) or placebo in the ASCOT-LLA study of about 20,000 patients (1, 2). One nonfatal case of rhabdomyolysis was reported in a man receiving atorvastatin who had had a very high alcohol intake and a recent febrile illness. Thus, the 5 presently available statins are incredibly safe drugs.

NEW GUIDELINES FOR HEALTHY EATING

The Food and Agriculture Organization (FAO)/ World Health Organization (WHO) Expert Report on Diet, Nutrition, and Prevention of Chronic Diseases, compiled by 30 independent experts, recommends limiting daily fat intake to 15% to 30% of total daily energy intake; saturated fats, to <10%; free sugars, to <10%; and iodized salt, to <5 g. Carbohydrates should make up 55% to 75% of daily energy intake; protein, 10% to 15%; and fruits and vegetables, ≥400 g (5). The report also recommends 1 hour of moderate-intensity activity, such as walking, every day.

EFFECTS OF CEREAL, FRUIT, AND VEGETABLE FIBER INTAKE ON RISK OF CARDIOVASCULAR DISEASE IN PATIENTS ≥65 YEARS OF AGE

Mosaffarian and colleagues (6), from 4 US medical centers, studied 3588 men and women aged >65 years and free of known cardiovascular disease at baseline in 1989–1990. They followed these patients until June 2000 and assessed their dietary fiber consumption. The average consumption of cereal fiber was 4.2 g/day; fruit fiber, 5.2 g/day; vegetable fiber, 6.9 g/day; and total fiber, 16.2 g/day. The main foods contributing to cereal fiber intake were dark breads and high-fiber or bran cereal; to fruit fiber intake, apples, oranges, and bananas; and to vegetable fiber intake, beans, broccoli, peas, corn, and cauliflower. During the 8.6 years mean follow-up, there were 811 cardiovascular events. After adjustment for age, sex, education, diabetes mellitus, smoking at any time, pack-years of smoking, daily physical activity, exercise intensity, alcohol intake, and fruit and vegetable fiber consumption, cereal fiber consumption was inversely associated with cardiovascular events, with a 21% lower risk in the highest quintile of intake compared with the lowest quintile. Neither fruit fiber intake nor vegetable fiber intake were associated with decreased cardiovascular disease. Higher cereal fiber intake also was associated with lower risk of stroke and a trend toward lower

risk of coronary death. Dark breads such as wheat, rye, or pumpernickel were associated with the lowest risk of cardiovascular disease. Thus, cereal fiber consumption in the Medicare-aged group decreases the risk of cardiovascular disease.

OBESITY'S EFFECT ON LIFESPAN

We all know the dangers of obesity, and we also know the difficulties of maintaining ideal body weight. Fontaine and colleagues (7) from Baltimore, Maryland, and Birmingham, Alabama, attempted to quantify the effect of obesity in terms of the expected number of years of life lost (YLL), defined as the difference between the number of years a person would be expected to live if he or she were not obese and the number of years a person would be expected to live if he or she were obese. The authors used 4 large databases to derive YLL estimates for adults aged 18 to 85 years. Body mass index, divided into various categories, was used. BMI of 24 was used as the reference category. They found the optimal BMI (associated with the least YLL or greatest longevity) to be 23 to 25 kg/m² for whites and 23 to 30 kg/m² for blacks. For any degree of overweight, younger adults generally had greater YLL than did older adults. The maximum YLL for white men and white women aged 20 to 30 years with a severe level of obesity (BMI >45) was 13 and 8 years, respectively. For men, this represented a 22% reduction in expected remaining lifespan. Blacks at younger ages with severe levels of obesity had a maximum YLL of 20 years for men and 5 years for women. Thus, obesity lessens life expectancy considerably, especially among younger adults.

RELATION OF OVERWEIGHT AND OBESITY TO MORTALITY FROM CANCER

Calle and colleagues (8) from Atlanta prospectively studied >900,000 US adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982. During the 16 years of follow-up, there were 57,145 deaths from cancer. The authors examined the relation in men and women between BMI in 1982 and the risk of death from all cancers and from cancers at various sites while controlling 4 other risk factors. The heaviest of the subjects studied (BMI \geq 40 kg/m²) had death rates from all cancers combined that were 52% higher for men and 62% higher for women than the rates in men and women of normal weight. In both men and women, BMI also was significantly associated with high rates of death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney; the same was true for deaths due to non-Hodgkin's lymphoma and multiple myeloma. Significant trends of increasing risk with higher BMI index values were observed for death from cancers of the stomach and prostate gland in men and for death from cancers of the breast, uterus, cervix, and ovaries in women. The authors estimated that current patterns of overweight and obesity in the USA could account for 14% of all deaths from cancer in men and 20% of all deaths from cancers in women. Thus, increased body weight is associated with increased death rates for all cancers combined and for cancers at multiple specific sites. Maintaining ideal body weight is the hardest thing for most of us, but it is clearly the road to better health.

OBSTRUCTIVE SLEEP APNEA AND HEART FAILURE

Sleep apnea occurs almost entirely in overweight persons, and heart failure is far more common in overweight persons than in those at ideal body weight. Thus, the combination of obstructive sleep apnea and heart failure is not uncommon. Kaneko and colleagues (9) from Toronto studied 24 patients with obstructive sleep apnea and heart failure. Patients underwent polysomnography, and the following morning their blood pressure and heart rate were measured by digital photoplethysmography, and their left ventricular dimensions and ejection fractions were assessed by echocardiogram. The subjects were then randomly assigned to receive medical therapy alone (12 patients) or with the addition of continuous positive airway pressure (12 patients) for 1 month. In the control group who received only medical therapy, there were no significant changes in the severity of obstructive sleep apnea, daytime blood pressure, heart rate, left ventricular end-systolic dimension, or left ventricular ejection fraction during the study. In contrast, continuous positive airway pressure markedly reduced obstructive sleep apnea, reduced the daytime systolic blood pressure (126 to 116 mm Hg), reduced heart rate (68 to 64 beats per minute), reduced left ventricular end-systolic dimension (54 to 52 mm), and improved left ventricular ejection fraction (25% to 34%). Thus, continuous positive airway pressure is useful in patients with heart failure combined with obstructive sleep apnea.

C-REACTIVE PROTEIN

An expert panel convened by the American Heart Association and the Centers for Disease Control and Prevention has issued recommendations about when to do the high-sensitivity C-reactive protein (hs-CRP) test, which costs between \$15 and \$20 (10). Their recommendations were as follows. 1) Widespread use of hs-CRP testing to screen the entire adult population to assess cardiovascular risk is inappropriate. 2) Physicians should first assess traditional cardiovascular disease risk factors and calculate an absolute Framingham score before considering hs-CRP testing. 3) Testing hs-CRP should be considered for patients at intermediate risk (10% to 20% risk of developing coronary heart disease in the next 10 years) as determined by the Framingham risk score. 4) Two hs-CRP tests, averaged, fasting or nonfasting, optimally taken 2 weeks apart, provide a more stable estimate of hs-CRP than a single test. 5) A serum hs-CRP level of <1 mg/L is considered low risk; 1.0 to 3.0 is considered average risk, and >3.0 mg/L is regarded as high risk. 6) Search should be made for an obvious source of infection or inflammation in patients with an hs-CRP level >10 mg/L; hs-CRP should then be measured again in 2 weeks.

ASPIRIN, COLORECTAL ADENOMAS, AND COLORECTAL CANCER

Two recent articles provided data on the relation of aspirin to colorectal adenomas and colorectal cancer. One study by Sandler and colleagues (11) from multiple US medical centers randomly assigned 635 patients with previous colorectal cancer to receive either 325 mg of aspirin a day or placebo. Approximately 1 year after randomization, at least 1 colonoscopic examination was performed. One or more adenomas were found in 17% of patients in the aspirin group and in 27% in the placebo group. The mean number of adenomas was lower in the aspirin group

than in the placebo group. The relative risk of any recurrent adenoma in the aspirin group was 35% less than in the placebo group. The time to the detection of the first adenoma also was longer in the aspirin group than in the placebo group. The authors concluded that daily use of 325 mg of aspirin is associated with a significant reduction in the incidence of colorectal adenomas in patients with previous colorectal cancer.

In the other study, Baron and colleagues (12) from multiple North American medical centers randomly assigned 1121 patients with a recent history of histologically documented colorectal adenomas to receive placebo (372 patients), 81 mg of aspirin (377 patients), or 325 mg of aspirin (372 patients) daily. Follow-up colonoscopy was performed at least 1 year after randomization in 1084 patients. The incidence of ≥ 1 adenoma was 47% in the placebo group, 38% in the group given 81 mg of aspirin daily, and 45% in the group given 325 mg of aspirin daily. The relative risks of any adenoma compared with the placebo group were 19% less in the 81-mg group and 4% less in the 325-mg aspirin group. For advanced neoplasms (adenomas measuring ≥ 1 cm in diameter or with tubulovillous or villous features as well as severe dysplasia and invasive cancer), the respective relative risks were 41% less in the 81-mg aspirin group and 17% less in the 325-mg aspirin group. The authors concluded that 81-mg aspirin had a moderate chemoprotective effect on adenomas in the large intestine.

RELATION OF MAMMOGRAPHY SCREENING TO DEATH FROM BREAST CANCER

Several randomized controlled trials with long-term follow-up support the effectiveness of mammography screening in reducing deaths from breast cancer. Some researchers, however, continue to doubt the effectiveness of mammography screening in women aged 40 to 49 years. Tabar and colleagues (13) compared deaths from breast cancer diagnosed in the 20 years (1958–1977) before screening was introduced with those from breast cancer diagnosed the 20 years after the introduction of screening (1978–1997) in 2 Swedish counties in 210,000 women aged 20 to 69 years. The risk of death from breast cancer was 23% less in the second screening period compared with the first in women aged 40 to 69 years. No such decline was seen in 20- to 39-year-olds. After adjustment for age, self-selection bias, and changes in breast cancer incidence in the 40- to 69-year age group, breast cancer mortality was reduced by 44% in women who were screened and by 16% in those who were not screened. After adjustment for age, self-selection bias, and changes in incidence in the 40- to 49-year age group, deaths from breast cancer fell 48% in those who were screened but not in the unscreened women. Thus, mammography screening is contributing to substantial reductions in breast cancer mortality.

A similar study was carried out in the Netherlands. The nationwide mammography screening program for women aged 50 to 69 years was launched in 1988–1989 in 2 cities in the Netherlands. Between 1990 and 1997, the program was extended to the entire country. Otto and colleagues (14) examined data for 27,948 women aged 55 to 74 years who died of breast cancer between 1980 and 1999. Compared with rates in 1986 to 1988, breast cancer mortality rates in women aged 55 to 74 years fell significantly in 1997 (20%↓). Mortality rates had been increasing by an

annual 0.3% until screening was introduced; thereafter, mortality rates declined 1.7% per year in women aged 55 to 74 years and 1.2% per year in those aged 45 to 54 years. These authors also concluded that routine mammography screening reduces breast cancer mortality rates in women aged 55 to 74 years.

ALCOHOL CONSUMPTION AND RISK OF DEMENTIA IN OLDER ADULTS

Because moderate alcohol consumption is associated with a lower risk of cardiovascular disease in the elderly, such consumption might be expected to lower the risk of dementia. But, even moderate alcohol consumption may increase dementia risk. A blood alcohol level as low as 0.02% impairs driving ability, and moderate alcohol use is associated with increased risk of cerebral hemorrhage. Also, moderate alcohol consumption is associated with greater brain atrophy, as determined by magnetic resonance imaging (MRI), but also with fewer silent cerebral infarcts and less white matter disease. Previous studies of alcohol consumption and cognitive decline or dementia have reported conflicting results.

To address the relation of alcohol consumption and risk of dementia, Mukamal and colleagues (15) from Pittsburgh, Seattle, and Boston studied 373 patients with dementia and 373 controls who were among 5888 adults aged ≥ 65 who participated in the Cardiovascular Health Study. Participants in the study underwent MRI of the brain and cognitive testing between 1992 and 1994, and they were followed up until 1999. Compared with the odds for dementia in abstainers, the odds among those whose weekly alcohol consumption was >1 drink were 0.65; 1 to 6 drinks, 0.46; 7 to 13 drinks, 0.69; and >14 drinks, 1.2. A trend toward greater odds of dementia was associated with heavier alcohol consumption, and this was most apparent among men. Thus, compared with abstention, consumption of 1 to 6 drinks weekly is associated with a lower risk of dementia among adults ≥ 65 years of age.

SILENT BRAIN INFARCTS, DEMENTIA, AND COGNITIVE DECLINE

Vermeer and colleagues (16) from Rotterdam, the Netherlands, studied the association between silent (unrecognized) brain infarcts and the risk of dementia and cognitive decline in 1015 participants aged 60 to 90 years and free of dementia and stroke at baseline. The participants underwent neuropsychological testing and MRI at baseline in 1995–1996 and again in 1999–2000 and were monitored for dementia throughout the study. During 3697 person-years of follow-up (mean per person 3.6 years), dementia developed in 30 of the 1015 participants. The presence of silent brain infarcts at baseline more than doubled the risk of dementia and was associated with worse performance on neuropsychologic tests and a steeper decline in cognitive function. Silent thalamic infarcts were associated with a decline in memory performance, and nonthalamic infarcts were associated with a decline in psychomotor speed. When the participants with silent brain infarcts at baseline were subdivided into those with and without additional infarcts at follow-up, the decline in cognitive function was restricted to those with additional silent infarcts.

Whether or not a stroke is silent depends on its location, size, time of occurrence (asleep or awake), and also what the patient

is asked to do by others and what the patient demands of himself or herself. Large neuroanatomical defects can exist without the detection of functional abnormalities on standard neurological examinations or without recognition of deficits by family or friends.

Blass and Ratan (17), from White Plains, New York, had some recommendations for patients whose clinically unrecognized or silent brain infarcts were discovered on imaging studies. They stated that cardiovascular health should be optimized, which means reaching or maintaining ideal body weight, quitting smoking (if applicable), controlling elevated blood pressure and blood lipids, and taking daily baby aspirin and maybe extended-release dipyridamole (200 mg twice a day).

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

An outbreak in atypical pneumonia in Guangdong Province, People's Republic of China, occurred in November 2002 and was reported to have affected 792 people and caused 31 deaths (18). Soon thereafter, the disease was identified in adjacent Hong Kong. The pulmonary disease did not respond to empirical antimicrobial treatment for acute community-acquired typical or atypical pneumonia. Bacteriological and virological pathogens known to cause pneumonia were not identified. Thus, the new disorder was called severe acute respiratory syndrome (SARS), and subsequently SARS has spread worldwide to involve patients in North America, Europe, and other Asian countries. As of May 10, 2003, according to the World Health Organization, 7296 cases have been recognized worldwide and 526 patients (7%) have died.

The first patient in Hong Kong was admitted February 22, 2003, and as of April 6, 2003, a total of 842 cases had been identified in Hong Kong with fatal complications in 22 (3%). Peiris and colleagues (19) from Hong Kong analyzed case notes and microbiological findings in 50 patients with SARS. The patients ranged in age from 23 to 74 years. Fever, chills, myalgia, and cough were the most frequent complaints. When compared with chest radiographic changes, respiratory symptoms and auscultatory findings were disproportionately mild. Patients who were household contacts of other infected people and had older age, lymphopenia, and hepatic dysfunction more likely had the more severe disease. A virus belonging to the family *Coronaviridae* was isolated from 2 patients. By use of serological reverse transcriptase polymerase chain reaction specific for this virus, 45 of the 50 patients with SARS had evidence of infection with this virus, which was absent in all controls. Of the 50 cases, 19 were severe, requiring intensive care and ventilatory support, and these patients were older and had severe lymphopenia and impaired alanine amino transferase. The 31 patients with uncomplicated disease recovered or improved, whereas 8 patients with complicated disease either worsened or died.

The family *Coronaviridae* includes the genera *Coronavirus* and *Torovirus*. They are enveloped RNA viruses that cause disease in human beings and animals. The previously known human coronaviruses, types 229E and OC43, are a major cause of the common cold. They can occasionally cause pneumonia in older adults, neonates, or immunocompromised patients. Coronaviruses have been reported to be an important cause of pneumonia in military recruits. Human coronaviruses can infect neurons, and

viral RNA has been detected in the brain of patients with multiple sclerosis. Phylogenetically, human pneumonia-associated coronavirus was not closely related to any known human or animal coronavirus or torovirus. These authors believe that the coronavirus is the primary agent associated with SARS.

CARLO URBANI AND SARS

Dr. Carlo Urbani first examined Johnny Chen, a Chinese American businessman, on February 28, 2003, 2 days after Chen had been admitted to Hanoi's Vietnam-France Hospital for a suspected avian flu infection that turned out to be SARS (20). Urbani is widely credited as the World Health Organization officer who identified the new disease. But a month and a day after first meeting Chen, Urbani himself died of SARS in a hospital in Bangkok. Urbani earned his medical degree in 1981 from the University of Ancona, Italy, and then trained in infectious diseases at the University of Messina for 3 years. During medical school, he also traveled to Africa to study malaria and other parasites. In 1990, he became deputy chief of the department of infectious diseases in Macerata, Italy's general hospital in Ancona, a position he held off and on while going on other missions around the world for the World Health Organization. Urbani wrote many journal articles on parasites and their control. He died at age 46.

MOST DOWNLOADED ARTICLES

The Lancet started a new monthly feature beginning in the April 12, 2003, issue (21). *The Lancet* is part of Science Direct (<http://www.sciencedirect.com>), which is Elsevier's Web database of >1700 science, medical, and technical peer-reviewed journals. The 10 most downloaded articles from Science Direct in January 2003 included 3 articles on bone marrow transplantation for heart disease; one on the Heart Protection Study comparing 40 mg of simvastatin with placebo in just over 20,000 patients; one on the PROSPER trial comparing effectiveness of pravastatin in older patients; one on thrombolysis vs angioplasty in acute myocardial infarction; one on angiotensin-converting enzyme inhibitors vs adrenergic receptor binders in nondiabetic renal disease; one on dietary supplements; one on the common cold; and one on dementia. Thus, of the 10 articles, 6 concerned cardiac disease.

MERIWETHER LEWIS, WILLIAM CLARK, THOMAS JEFFERSON, BENJAMIN RUSH, AND THE DISCOVERY OF THE WEST

Steven E. Ambrose's 1996 book, *Undaunted Courage*, tells the incredible story of the Lewis and Clark expedition of 8000 miles: up the Missouri River from St. Louis to the Rockies, over the mountains, down the Columbia River to the Pacific Ocean, and back (22). The crew of 30 endured incredible hardships and saw incredible sights, including vast herds of buffalo and Indian tribes that had had no previous contact with white men. Lewis and Clark made the first map of the West, provided valuable scientific data on its flora and fauna, and established the American claim to Oregon, Washington, and Idaho. The trip took 28 months beginning in 1804 and ending in 1806. During that period, only 1 of the 30 explorers died; the death was probably the result of an intestinal infection. Lewis himself died of a gunshot

wound to the head 3 years after returning, and that probably represented suicide.

Before leaving for the adventure, Captain Meriwether Lewis, who had been President Thomas Jefferson's personal secretary, had been schooled in the medicine of the times by the eminent Dr. Benjamin Rush at the advice of President Jefferson, who had engineered the Louisiana Purchase. In the spring of 1803, Jefferson wrote to Rush and tasked him with the education of the 28-year-old Lewis. After completing his lessons, Lewis visited the apothecary using \$90.69 of the expedition's \$2500 budget, filling the medicine cabinets with emetics, diuretics, laxatives, salves, lancets, penis syringes, and a half-pound of Turkish opium.

Two hundred years after Lewis purchased these medical provisions, Gretchen Worden, the director of exhibits at the American College of Physicians in Philadelphia, reconstructed Gillespie and Strong's medicine kit (23). Two years ago, Worden and her curator colleague Charles Greifenstein celebrated the bicentennial of the expedition and its connection to the college for a new exhibit entitled "Only One Man Died: Medical Adventures on the Lewis and Clark Trail," which opened in February 2003 and will run through February 2006. The exhibit features a list of medicines Lewis and Clark carried, a menacing 9' bear, and a reconstructed "sweat pit"—a small tent covering a shallow hole in the ground—that was instrumental in curing a paralyzed Indian chief. Members of the expedition endured snakebites, frostbite, malaria, dysentery, syphilis, gonorrhea, conjunctivitis, chronic boils, frequent constipation, heat stroke, metal poisoning, tick fever, bear attacks, and other hazards.

AND HE WAS A PHYSICIAN TOO

Erik Larson, who wrote *Isaac's Storm*, has now written a frightening book entitled *Devil in the White City. Murder, Magic, and Madness at the Fair that Changed America* (24). This new book is about 2 men, one a great architect and the other a psychopath physician. The architect, Daniel Hudson Burnham, built some of America's most important structures, among them the flatiron building in New York City and Union Station in Washington, DC, and he designed and built the Chicago World's Fair of 1893, officially called "The World's Columbian Exposition," its official purpose being to commemorate the 400th anniversary of Columbus' discovery of America. Burnham made the fair enchanting; it was known throughout the world as "the White City." The fair lasted just 6 months, yet during that time it had 27.5 million visits at a time when the country's total population was only 65 million. On its best day, the fair drew >700,000 visitors.

That the fair had occurred at all was something of a miracle. To build it Burnham confronted a legion of obstacles, any one of which could have and should have killed it long before opening day. Together he and his architectural and construction colleagues built a dream city whose grandeur and beauty exceeded anything anyone could have imagined. The fair occupied over 1 square mile and filled >200 buildings. A single exhibit hall had enough interior space to have housed the US Capitol, the Great Pyramid, Westminster Cathedral, Madison Square Garden, and St. Paul's Cathedral all at the same time. The Ferris wheel became the fair's emblem, a machine so huge and terrifying that it instantly eclipsed the tower of Alexandre Eiffel that had so wounded America's pride 5 years earlier.

That something magical had occurred in that summer of the world's fair was beyond doubt. But darkness too had touched the fair. Scores of workers had been hurt or killed in building the dream, their families consigned to poverty. Fire had killed 15 more, and an assassin had transformed the closing ceremony from what was to have been the century's greatest celebration to a vast funeral. Worse had occurred too, although these revelations emerged only slowly. A murderer had moved among the beautiful things Burnham had created. Young women were drawn to Chicago by the fair and by the prospect of living on their own. Only after the exposition had Burnham and his colleagues learned of the anguished letters describing daughters who had come to the city and then fallen silent. Amid so much turmoil it was understandable that the work of a young and handsome doctor would go unnoticed.

Chicago in 1893 was a dark city. A thousand trains a day entered or left Chicago. Many of these trains brought single young women who had never even seen a city but now hoped to make one of the biggest and toughest their home. Anonymous death came early and often. Each of the thousand trains that entered and left the city did so at grade level. You could step from a curb and be killed by the Chicago Limited. Every day on average 2 people were destroyed at the city's rail crossings. Their injuries were grotesque. There were other hazards. Streetcars fell from drawbridges. Horses bolted and dragged carriages into the crowds. Fires took a dozen lives a day. There was diphtheria, typhus, cholera, and influenza, and there was murder. In the time of the fair, the rate at which men and women killed one another rose sharply throughout the nation, but especially in Chicago, where police found themselves without the manpower or expertise to manage the volume. In the first 6 months of 1892, the city experienced nearly 800 violent deaths, 4 a day. Jack the Ripper's 5-murder spree in 1888 in London had defied explanation and captivated readers throughout America, who believed such a thing could not happen in their own hometowns.

In August 1886, a man calling himself H. H. Holmes walked into one of Chicago's train stations and acquired a ticket to a village called Englewood in the town of Lake, a municipality of 200,000 people that abutted Chicago's southernmost boundary and encompassed the Union Stock Yards (which employed 25,000 men, women, and children and each year slaughtered 14 million animals) and 2 large parks: Washington Park and Jackson Park (where the fair was located). Holmes conjured an impression of wealth and achievement. He was 26 years old, 68 inches tall, and 155 lb. He had dark hair and striking blue eyes.

When he resolved to move to Chicago, he was still using his given name, Herman Webster Mudgett. At 16, Mudgett had graduated from high school and then taught in New Hampshire. At 19, he enrolled in the medicine program at the University of Vermont in Burlington but found the school too small. After 1 year, he moved to the University of Michigan School of Medicine in Ann Arbor. He graduated in June 1884 with a lackluster record and set out to find some favorable location in which to launch a practice. He initially settled in Mooers Forks, New York, where he remained 1 year. There were rumors that a boy seen in his company had disappeared, but no one could imagine charming Dr. Mudgett causing harm to anyone, let alone a child. After other brief periods in Philadelphia and New York, he arrived

in Chicago having passed his license examination in the state capital in Springfield to be a druggist. He registered under the name H. H. Holmes.

It wasn't long before Holmes had acquired property at 63rd Street and Wallace on which he built a hotel that catered only to young women. In the basement of his hotel he built an incinerator to dispose of bodies. At trial in the fall of 1895, Holmes admitted killing 27 people, but exactly how many people he killed will never be known. Estimates ranged as high as 200. If it had not been for a single persistent detective named Geyer, the numerous murders by Holmes, almost all of young women, would have never been confirmed and Holmes would never have been prosecuted. Herman Webster Mudgett, alias H. H. Holmes, was hung on the gallows on May 7, 1896.

In 1997, police in Chicago arrested another physician named Michael Swango at O'Hare Airport. The initial charge was fraud, but Swango was suspected of being a serial killer who murdered hospital patients through the administration of lethal doses of drugs. Eventually, Dr. Swango pled guilty to 4 murders, but investigators believe that he had committed many more. During the airport arrest, police found in Swango's possession a notebook in which he had copied passages from certain books. One passage was from a book about H. H. Holmes, called *The Torture Doctor*, by David Franke. The copied passage sought to put the reader into Holmes' mind: "He could look at himself in a mirror and tell himself that he was the most powerful and dangerous man in the world." Swango's notebook read, "He could feel that he was a god in the skies."

KRAKATOA

The author of *The Professor and the Madman* and *The Map that Changed the World* has now written *Krakatoa* (25). The annihilation in 1883 of the volcano-island of Krakatoa—the name has become a byword for cataclysmic disaster—was followed by an immense tsunami that killed nearly 36,000 people! The eruption in many ways changed the world. Dust swirled round the planet for years, causing temperatures to plummet and sunsets to turn vivid with lurid and unsettling displays of light. The effects of the immense waves were felt as far away as France. Barometers in Bogota and Washington, DC, went haywire. Bodies were washed up in Zanzibar. The sound of the island's destruction was heard in Australia and India and on islands thousands of miles away. Most significant of all, particularly in view of today's new political climate, the eruption helped to trigger in Java a wave of murderous anti-Western militancy among fundamentalist Muslims, one of the first outbreaks of Islam-inspired killings anywhere.

Most volcanoes, of course, continue to exist after erupting. Vesuvius is still there and so are most of the world's best-known volcanoes, such as Etna, Rainier, Kilauea, Paricutin, and Fujiyama. Even Mount St. Helens, the top of which blew off in 1980, is mostly still there. It is rare that an eruption is so great that it destroys the entire mountain. That occurred at Mount Mazama (which left behind Crater Lake in Oregon), Santorini (which may have taken out the Minoan civilization and left a great hole in the Aegean), and Krakatoa, which blew up not only the mountain but also the island the mountain sat on.

Krakatoa was located in the Sunda Strait between the large islands of Sumatra and Java and was composed of 3 peaks: Rakata, at 2600'; Danan, at nearly 1500'; and Perboewatan, at 400'. The volcano began to signal its intentions with violent earthquakes in May 1883. After 3 months of earth tremors, the island blew up with a succession of blasts that were heard 3000 miles away. (If Pike's Peak in Colorado had exploded with the same force, every person in the continental USA would have heard it!) There were 4 detonations over 5 hours; the last that occurred on Monday morning, August 27, 1883, was one of the biggest explosions in recorded history.

At Krakatoa when the earth split asunder, cold sea water contacted the red-hot magma, the steam exploded with catastrophic violence, and 6 cubic miles of rock and ash were hurled >20 miles into the stratosphere. An hour after the explosion, as lightning lit up the blackening skies, a thick muddy rain fell on Batavia (now Jakarta). Boiling-hot debris from the blast, some chunks 3 feet around, fell over hundreds of square miles. Since the island was uninhabited at the time, nobody on Krakatoa was killed, but giant tsunamis rolled out in all directions, flooding the coasts of Java and Sumatra, submerging nearly 300 towns and villages and killing >36,000 people. It was as if a mountain-sized red-hot rock had been dropped into the ocean.

A 72' wave engulfed and totally destroyed the town of Telokbetong at the head of Sumatra's Lampong Bay, killing 2200 people. Water cascaded into the town of Tangerang, and when it swept out again, it carried people, animals, houses, and trees. No one expected the waves to return after they had receded. It is likely that many people believed the worst was over and returned to their shoreside villages, only to experience another, more catastrophic inundation. The town of Merak, which had suffered little damage from the first wave, was destroyed by the second. The huge wave, after traveling at hundreds of miles per hour, entered the narrow bay, and as the shoaling beach slowed down the leading edge of the wave, millions of gallons of water began piling up behind until the wave reached the height of 135', as tall as a 10-story building. This mountain of water rolled over Merak, obliterating everything in its path and drowning all but 2 of 2700 inhabitants. Anjer was drowned by a 33' wave and Tyingin, 24 miles from the volcano, was smashed by a 70' locomotive of rolling water. It was not the lava, noxious gases, flame, smoke, or volcanic bombs that destroyed those unfortunate thousands, it was the power of the water. In most instances death came at the hands of seismic sea waves.

Accompanied by thunderous explosions, the waves swept around St. Nicholas Point on Java and headed for Batavia, 94 miles from the epicenter. At approximately 12:15 PM, 2 hours after the final explosion, the sea roared into the capital city. It receded and then came back. Thousands of ships, ranging in size from steamships to small proas, were destroyed in Batavia's harbor. Nine hours after the eruption, many riverboats were swamped and sunk in Calcutta, 2000 miles away, and ships strained at their anchors in Port Elizabeth, South Africa, 5000 miles from the blast.

What did not remain was the volcano that had caused it all. Krakatoa, after the final concatenation of seismic and tectonic climaxes that occurred just after 10:00 on the Monday morning, had simply and finally exploded itself out of existence. Where

once there had been a tropical peak that was 2600' tall, there was now a hole in the ocean floor that was 1000' deep. Krakatoa's explosion generated a climate-altering ash cloud that produced lurid red, blue, green, and copper sunsets and lowered temperatures around the world.

Krakatoa (the volcano) was not the largest or deadliest of recent Indonesian volcanic eruptions. That dubious distinction goes to Tambora, which erupted with more than twice the power of Krakatoa, killed 10,000 people outright, and caused the deaths of another 82,000 by starvation and disease. *Krakatoa* (the book) must be one of the best books ever written about the history and significance of a natural disaster. And author Simon Winchester, interestingly, is a trained geologist.

WATSON AND DNA

Watson and DNA is the title of Victor K. McElheny's new book on James Watson (26). In 1968, James Dewey Watson published a book called *The Double Helix*. The book presented a picture of science as something thrilling, even obsessive, undertaken by people who were perfectly capable of spite, vanity, and folly but who raced to be the first to offer the world a picture of the universal machinery of conception, growth, and procreation. Reviewers both loved and hated the book. It caused huge offense in the scientific community. Chapter 1 opened with the words "I have never seen Francis Crick in a modest mood." Others have supposed that few people have seen Watson in a modest mood either. But Victor McElheny's life of Watson, published to mark the 50th anniversary of the discovery of the structure of the double helix, confirms a suspicion surely held by anyone who ever met Watson: he rarely felt he had a lot to be modest about.

The book is the story of a thin, bookish, bird-watching boy, the son of a bill collector, who entered the University of Chicago at the age of 15 years and left 4 years later with 3 questions in his head: What is the gene? How is the gene copied? How does the gene function? It was his capacity for putting questions as simply and sometimes as annoyingly as possible that kept Watson in science and in trouble for the next 55 years.

After he, Crick, and Maurice Wilkins won the Nobel Prize in 1962, Watson went on not to do science as such, but to make it happen: at Harvard, at Cold Spring Harbor, New York, and in the power structures of Washington. Watson was at the heart of the first genetic engineering debates. He was one of the handful who made the human genome project happen. He was one of the even smaller handful who then insisted that the data must be freely available to every researcher in the world rather than patented and sold. That stance—along with his capacity to exasperate—cost him the leadership of the human genome project. But Watson went on saying what he thought, in a manner that was almost the antithesis of diplomacy. The book tells the Watson story well and warmly. Watson refused to be interviewed by McElheny at any time.

I recently saw Watson interviewed on television. He used "you know" in every sentence, often more than once per sentence. I guess I should not be annoyed when hearing "you know" by teenagers and athletes when Nobel Prize winners copy them.

SINGAPORE

I visited Singapore for 3 days in March 2003. My 2 favorite places in Asia are Hong Kong and Singapore, so if I get an invitation to either, I try to accept. Hong Kong has 7 million people and Singapore, 4 million. Singapore is not quite as bustling as Hong Kong, but that's not always readily perceivable. Singapore is only about 60 miles from the equator and as a consequence its temperature ranges all year long from 78° to 88°F and its humidity is 90%. Virtually every building is air-conditioned. It takes a long time to get to Singapore from Dallas. The flight from Dallas to Tokyo is >13 hours, and the flight from Tokyo to Singapore is nearly 8 hours. Nevertheless, it's well worth the ride. Singapore is the only place in the world where every flight is an international one.

Singapore consists of just over 60 islands, most of which are uninhabited. The main island is shaped like a flattened diamond and is 26 miles long from east to west and 14 miles long from north to south. Near the northern peak is the causeway leading to the Malaysia Peninsula and the southern foot is Singapore City. To the east is Changi International Airport connected to the city by a beautiful parkway. The airport may be the most magnificent one in the world. Of the islands' total land area, more than half is built up, and the balance is made up of parkland, farmland, plantations, swamp areas, and forest.

Although it may no longer be the richly exotic and romantic city so vividly documented by Conrad and Kipling, Singapore nevertheless is a unique city where the gentle manners of the East peacefully coexist with the comforts, conveniences, and efficiency of the West. It contains some of the world's most luxurious hotels, offering incomparable service and all the amenities. Most major ones are located on or near Orchard Road, where smartly dressed shoppers browse among glittering shop windows, which are so attractive that it's almost like wandering in a museum. Unfortunately, the merchandise is no longer inexpensive. The prices in most shops are about the same as in New York City or London or Paris, and the prices of the hotels are also about the same as in these other cities. But Singapore, in contrast, is easy to explore, and that can be done on foot. It's difficult to get lost in this city. Every street has signposts in English, and most Singaporeans speak English.

In contrast to Hong Kong where about 97% of citizens are Chinese, Singapore is more multicultural. The Chinese make up about 77% of the population, Malays about 14%, Indians about 6%, and others the remainder. The city itself is divided roughly into 4 or 5 sections including Colonial Singapore, Chinatown, the Arab District, and Little India, among others. That division was initiated in 1819 when Sir Thomas Stamford Raffles founded and laid out the city for the East India Company. When he arrived in the early part of the 19th century, Singapura, as it was called then, consisted of jungle and marshes and contained many tigers. Until approximately 1850 or 1860, at least 5 people each year were killed by the tigers that roamed the islands.

Singapore is a nation of contradictions. Except for Japan, it has the best educated, most knowledgeable, and most international society in Asia, but nevertheless the government in many ways regulates its citizens' lives. Although its relations with its immediate neighbors, Malaysia and Indonesia, have improved dramatically over the years, Singapore maintains one of the larg-

est armies in the world proportionate to population and has a ruthlessly efficient and intrusive intelligence agency, the Internal Security Department, which is tireless in its pursuit of dissent. Nevertheless, Singapore is a bastion of capitalism, and the government owns many of the largest local companies. The government is so prudish that it bans *Cosmopolitan*, as well as *Playboy*, yet the national airline promotes itself with slogans on the order of "Singapore Girl, you're a great way to fly." Although Singapore has many of what are called "hawker centers," each with an ethnic *mélange* of food stalls, which offer some of the best street food in the world, young Singaporeans flock to American fast food restaurants.

The city is spotlessly clean, traffic jams are infrequent, and pollution is nearly nonexistent. The airport is so efficient, the taxis are so numerous, and the roads are so good that a visitor arriving at the airport on the eastern tip of the island 12 miles from downtown can reach the hotel within 30 minutes after stepping off the plane. When arriving at the airport, a driver was waiting for me, and on our way into the city, he called the front desk of the Four Seasons Hotel so that when we arrived I was already checked in. Tap water is clean. An international phone call can be direct-dialed as quickly in Singapore as in the USA.

Although 4 languages are spoken in Singapore, the most common one publicly is English. All business is conducted in English and that is the language used in the schools. (Only 1 of 5 Singaporeans, however, speaks English at home. Mandarin is the most common language spoken at home.)

Most Singaporeans live in high-rise flats, over 80% of which were built by the government. Most of these are 10 to 20 stories high and are subsidized by the government, namely the Housing Board. The flats can be anywhere from 1 to 5 rooms in size. The occupants buy a 99-year lease. The 1-room flats cost \$100,000 and 5-room flats, approximately \$500,000. The lease is actually renewed every 10 years and the person has to either renew it or evacuate the flat. The flats in the public housing facilities are owned by the occupants and the high-rises are well maintained by the government. The taxi driver told me that each complex is painted every 5 years.

Despite the high-rise buildings nearly everywhere, Singapore has retained enough greenery to make it a very pleasant city for walking. Every block has trees and flowers. The entire east coast facing the South China Sea is a string of parks and beaches, and only a half hour from downtown Singapore City are nature preserves and some semirural areas with farms. No litter mars a walk through Singapore streets. A litterbug pays a fine, and cigarette butts are counted as litter. Singapore has nearly 50,000 litter baskets throughout the city. Everything in Singapore is clean and everything works.

In a nation known for efficiency, the government is the most efficient of all. When someone calls to report a pothole, the Public Works Department fills it within 48 hours. The Telecommunication Authority will install a new phone the day after the order is received. Secretaries are so conscientious that a journalist gets unsolicited wake-up calls to make sure he or she will be on time for early morning interviews with their bosses. There is no bribing in Singapore. A bribe, whether a small tip to an employee or a large payoff to a high-ranking minister, represents a ticket to jail. Thus, corruption is nonexistent.

The government makes many rules. The walls of buildings are plastered with rules, telling people what they can't do and how much they have to pay if they try to do it. The fines represent considerably more than a slap on the wrist, and they are enforced often enough to make most potential violators think twice. Violations do not always depend on a passing policeman for discovery. Trucks and commercial vans are required to install a yellow roof light that flashes when the vehicle exceeds the speed limit. When a taxi exceeds the maximum speed on a freeway of 48 miles an hour, loud chimes go off inside. The chimes are so annoying that the driver is likely to slow down. At some intersections cameras photograph the license plates of cars that pass through as the light is changing to red. The drivers receive bills for that offense in the mail.

Today Singapore is a city with almost no poverty. In Hong Kong, the gap between rich and poor is visible everywhere. In Singapore, there are no shabbily dressed citizens, and everyone appears to have at least a passable place to live. Food is relatively cheap and plentiful. All have access to high-quality medical care.

Singapore was not always so prosperous or so tidy. When Lee Qwan Yew, prime minister from 1959 to 1990, took power, Singapore represented a mosquito-infested swamp dotted with pig and chicken farms, fishing villages, and squatter colonies of tin-roofed shacks. The streets of the central city were lined with shop houses, mostly 2-story buildings with ornate facades. A family would operate a business on the ground floor and live on the second floor, often without plumbing and electricity and housing as many as 10 people to a room. The shop houses may have represented a picturesque sight for tourists, but they were not very agreeable for their occupants. Living conditions, in other words, were utter filth, and the occupants were poverty stricken. In not much more than a decade, Singaporeans passed from poverty to affluence and the nation's economy from a basket case to the powerhouse of southern Asia. The explanation for this transition, as for nearly everything else that happens in Singapore, rests with Lee Qwan Yew. Lee has put his stamp on Singapore to an extent that few political leaders anywhere in the world have ever matched. He has been tough and authoritarian but uninterested in personal wealth among a people who devote their lives to financial gain and often rude and contemptuous in a country that runs annual campaigns promoting the virtues of courtesy. Lee embodies as many contraindications as does Singapore itself.

I spoke at the Singapore General Hospital, which is the largest hospital among the 11 in Singapore. It has 1400 beds. Singapore has only 1 medical school, the National University of Singapore. The school's primary hospital is the National University Hospital, but many medical students also rotate through Singapore General Hospital, which also has a very large housestaff. Medical students in Singapore, after finishing 12 years of school, take 2 years of preuniversity and then enroll in medical school, which is 5 years. The National University of Singapore has about 215 students in each class. Thus, 215 new physicians each year come out of this medical school. A number of Singapore students go to medical schools in other countries, however, and then return to Singapore to practice. Until this year (2003), the percentage of women in the National University of Singapore Medical School was limited to 20%. In 2003, the quota was lifted.

Training of physicians in Singapore is similar to that in the USA. After medical school they are houseofficers and then registrars. For those going into cardiology, there are 3 years of post-graduate training and then 3 years of a cardiology fellowship. I was told that there are approximately 70 cardiologists in Singapore and about 20 cardiovascular surgeons.

Of the 11 hospitals in Singapore, 7 are considered “restructured” or government-subsidized hospitals and the other 4 are private hospitals. The specialists practice at either the restructured or private hospitals. Those practicing at the restructured hospitals are on salary, although a few of them are allowed private practice. At the private hospitals all of the staff have income entirely from their private practices. The private hospitals are entirely specialty hospitals. The general practitioners practice mainly at what are called “polyclinics” that are subsidized by the government for the less well to do. General practitioners have no hospital connection and do not spend time in the hospitals. The Singapore General Hospital has a heart center that includes cardiologists, cardiac surgeons, cardiac radiologists, and cardiac anesthesiologists. The restructured or government subsidized hospital pharmacies have a formulary that limits drugs the physician can use. The private hospitals have an open formulary.

Patients in Singapore are divided into 3 categories: A, B, and C. Patients in category A pay their entire physician and hospital bills; patients in category C (with annual incomes <24,000 Singapore dollars) are 100% subsidized by the government; and those in category B are partially subsidized by the government. I was surprised to learn that the 3 top drugs prescribed in Singapore are Viagra (sildenafil citrate), Xenical (orlistat), and Lipitor (atorvastatin).

Atherosclerotic disease is very common in Singapore. Coronary heart disease used to be the number 1 killer, but preventive programs have reduced it to number 3; now cancer is the leading cause of death. Obesity and the metabolic syndrome are becoming more prevalent in Singapore just like in the Western world.



—William Clifford Roberts, MD

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