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COMPARISON OF THE 9/11/01 TRAGEDY TO THE FREQUENCY OF DEATH FROM OTHER CAUSES

The November/December 2002 issue of *World-Watch* compared the September 11 tragedy with the magnitude of other deaths (1). In the USA, the numbers of persons dying or killed each year on average are as follows: by cigarette smoking, 431,000; by obesity, 300,000; by alcohol abuse, 110,000; by motor vehicle accidents, 43,000; by guns, other than war, 34,000; by adverse reactions to prescription drugs, 32,000; by suicide, 31,000; by accidental falls, 15,000; by accidental poisoning, 9000; by aspirin and nonsteroidal antiinflammatory drugs (NSAIDs), 8000; by drowning, 4000; by choking on ingested objects, 3000; and by the September 11 attacks in 2001, 3000.

In other countries, the numbers of people dying or killed each year on average are as follows: by ongoing civil war in Sudan, 2,000,000; by the Khmer Rouge massacre in 1975 to 1978 in Cambodia, 1,700,000; by the ongoing war in Congo, 1,700,000; by US secret bombings in 1970 to 1973 in Cambodia, 150,000; by pesticide suicides of despairing farmers in China, 125,000; by 2 atomic bombs dropped by US planes in 1945 in Japan, 103,000; by obesity in the United Kingdom, 30,000; by the Bhopal chemical spill in 1985 and its aftermath in India, 20,000; by venomous snakes in India, 10,000; by malaria in Brazil, 8000; and by Serbian army massacres of Bosnian Muslim prisoners, 7000.

INFECTIONS

If you want to get frightened, I suggest Madeline Drexler's new book, *Secret Agents. The Menace of Emerging Infections* (2). She begins this way: "Infection is an inescapable part of life. All creatures feast on other creatures and in time are feasted upon in a kind of Escheresque food chain. When humans are the meal, we call it infectious disease." The book is about today's new and emerging infections—those that have increased in attack rate or geographic range or have threatened to do so. It explores why these infections are materializing now and why they will never go away. Each chapter looks at a different threat: animal- and insect-borne diseases, foodborne pathogens, antibiotic resistance, pandemic influenza, infectious causes of chronic disease, and bioterrorism.

Early on she quotes the famous bacteriologist and historian, Hans Zinsser, who wrote in 1934: "However secure and well-regulated civilized life may become, bacteria, protozoa, viruses, infected fleas, lice, ticks, mosquitoes, and bedbugs will always lurk in the shadows ready to pounce when neglect, poverty, famine, or war lets down the defenses. And even in normal times they prey on the weak, the very young, and the very old, living along with us, in mysterious obscurity waiting their opportunities."

Drexler describes the swine food debacle of February 1976, when the US government pulled out all stops preparing for a repeat—which never occurred—of the deadly 1918 influenza pandemic. The summer of 1976 brought legionnaires' disease, which struck in Philadelphia, killed 34 people, and stumped the infectious disease experts for nearly 6 months. Other outbreaks followed and a new vocabulary arose: Lyme disease, toxic shock syndrome, *Escherichia coli* O157:H7, sexually transmitted diseases, Ebola virus. In June 1981 came the now landmark report from the Centers for Disease Control and Prevention (CDC). Nine brief paragraphs described a strange cluster of fatal symptoms among 5 gay men in Los Angeles: AIDS, which has already infected 250,000 persons in the USA. Before the recent headline accounts of avian flu, a silent hepatitis C epidemic, parasite-contaminated water slides, new-variant Creutzfeldt-Jakob disease, and anthrax, we had smallpox, typhus, polio, cholera, rabies, and the Black Death. We still have them. None have been consigned to history. Small human populations suffer the oldest diseases of humankind: either chronic, such as leprosy or herpes, or those that have reservoirs in animals or in soil, such as yellow fever, the virus of which circulates in monkeys. Only when a community is dense and filthy enough to keep spreading germs and big enough to keep supplying new susceptibles do such infections as measles, smallpox, typhoid, and influenza—crowd diseases or "zymotics"—stay in circulation.

And the "plagues" of history are still with us. In AD 79, an outbreak believed to be malaria contributed to the Roman Empire's fall. The plague of Antoninus (AD 166–180), probably smallpox, killed about 30% of Italy's population. The plague of Justinian (AD 542–543), one of the first documented cases of rat-borne bubonic plague, killed 10,000 people daily in Constantinople and eventually spread as far north as Denmark, annihilating much of the human race in its path. Between 1346 and 1350, one third of Europe's population died of bubonic plague, spread from Asia to Europe by Mongol armies, whose retinues of rodents carried infected fleas that subsequently bit

humans. In the 16th and 17th centuries, slave ships from West Africa brought yellow fever and its mosquito vector to the New World. Smallpox, transported to the Americas by Spanish conquistadors, killed one third of the relatively disease-free native population and was followed by a similar lethal onslaught of measles. Diseases introduced from Europe killed an estimated 95% of the pre-Columbian Native American population, and exotic infections attacked the other direction also. European colonials succumbed to malaria, yellow fever, and other endemic infections in tropical Africa, India, Southeast Asia, and New Guinea. Syphilis appeared in 1494, perhaps with Columbus' returning soldiers. The industrial revolution of the 19th century amplified such diseases as tuberculosis, an ancient bacterial infection that thrives in squalid close quarters. Illnesses from contaminated food and water, such as typhoid fever and cholera, also went on a spree.

Beginning in the late 1870s, the new discipline of bacteriology found the agents that caused cholera, tuberculosis, gonorrhea, typhoid, and scarlet fever. By 1900, most scientists agreed that microorganisms—spread by casual contact, food and water contamination, insects, and even (in the cases of typhoid and tuberculosis) healthy human carriers—caused communicable diseases. These discoveries spurred expansion of government health initiatives such as water purification, food inspection, and rodent control, as well as more awareness of individual hygiene measures such as covering a cough or washing hands before eating.

In the later 1930s and 1940s came specific antimicrobial therapies such as sulfa compounds and penicillin, and by the mid 1960s numerous antibiotics were available to treat such infections as gonorrhea, syphilis, pneumonia, tuberculosis, bacterial meningitis, typhoid fever, and even bubonic plague, while new vaccines prevented epidemics of measles, rubella, and polio. The study of infectious disease became unfashionable between 1970 and 1975. The National Institutes of Health (NIH) budget increased 100%, but the budget for infectious diseases increased only 30%. Cancer and heart disease got most of the money. When HIV came along in the early 1980s, the government initially looked the other way. Public health agencies had already stopped surveillance for drug-resistant tuberculosis just as the disease started to rise. In the 1980s and 1990s, the US infectious disease mortality rate jumped 58% even after removing AIDS from the tally during that period, and infectious disease deaths in the USA rose 22%. In 1998, the CDC issued a detailed 5-year plan to prepare the nation for emerging infections, but congressional funding has lagged.

And microorganisms (viruses, bacteria, fungi, protozoa) play the survival game exceedingly well. They adapt far more quickly than do humans as the environment changes. Humans produce a new generation every 20 years or so; bacteria do it every 30 minutes, and viruses even faster. Natural selection, whereby genetically better adapted individuals leave more progeny and thus transmit those desirable characteristics, operates far more efficiently in the microbial world. Because they assemble in enormous numbers, viruses and bacteria can support considerable variety in their communities, including mutated oddballs that further proliferate when circumstances change. When an enterovirus like polio goes through the human intestinal tract in 3 days, its genome mutates about 2%. That level of mutation—2%

of the genome—takes the human species 8 million years to accomplish!

Compared with humans, microorganisms are relatively simple. A virus (the word comes from a Latin term for “poisonous substance”) is nothing more than nucleic acid, DNA or RNA, surrounded by a shell of protein and sometimes lipids. Viruses range in size from about 20 to 400 nanometers in diameter, such that millions can fit in a period at the end of a sentence. Outside a living cell, a virus is a dormant particle, lacking the raw materials for synthesis. Only when it enters a congenial host cell does it explode into action, hijacking the cell's metabolic machinery to produce copies of itself that may burst out of infected cells or simply bud off a cell membrane. Viruses cannot be cultured in artificial media. They can be propagated only in live cells, fertilized eggs, tissue cultures, or bacteria. Viruses hurt us by killing the host cells. Viral infections are harder to fight once the process is under way because our immune responses usually kick in too late to subdue them.

Bacteria, one-celled organisms that are more self-sufficient, are about 1000 times larger than viruses and are generally visible under a light microscope. Bacteria are known as prokaryotic—so primitive they lack a membrane-bound nucleus with neatly linear chromosomes inside. Instead, bacteria usually carry a tangled necklace of DNA joined at the ends and sometimes smaller rings of DNA known as plasmids, which contain genes that enable them to manufacture proteins. Bacteria carry only 1 set of chromosomes instead of 2, an arrangement that means that every gene counts and every selected advantage must be conserved.

Over eons, bacteria have learned tricks to help them cleave to cells, make paralyzing poisons, allude or suppress our bodies' defenses, and shrug off drugs and antibodies. They pick up genes from almost everywhere: from other bacteria, viruses, plants, and even from yeast. When a virus picked up a toxic gene from a deadly *Shigella dysenteriae* and inserted it into a harmless *E. coli*, it created *E. coli* O157:H7, a bacterial hybrid that clings to mucosal surfaces in the intestine and produces toxins that trigger hemolytic uremic syndrome, the most common cause of acute kidney failure in children. Bacteria inflict damage in a different way than viruses. Sometimes they multiply so rapidly they crowd out host tissues and disrupt normal function. Sometimes they kill cells and tissues outright. Sometimes they manufacture toxins that can paralyze, destroy metabolic pathways, or generate a massive immune reaction that is itself toxic. Drug-resistant bacteria often make an enzyme that destroys antibiotics or spits them out. Bacteria don't attack until their numbers are high enough to establish an infection (“quorum sensing”). Nevertheless, bacteria remain easier to treat than viruses. Because they are free living and because their structure differs from that of mammalian cells, they are more susceptible to drugs delivered via the bloodstream.

The newly discovered infectious agents such as bovine spongiform encephalopathy (BSE or mad cow disease)—and its human counterpart, new-variant Creutzfeldt-Jakob disease—apparently repealed the laws of biology. Called prions, these proteins are folded in an unusual way: when they come into contact with other proteins, they turn them into prions, setting off a chain reaction that eventually riddles the brain with holes. A cow can contract BSE by eating 1 g of prion-infected tissue—the size of a peppercorn—from another cow. Unlike viruses or

bacteria, prions cannot reproduce and evoke no immune response. More frightening, they resist heat, ultraviolet light, radiation, and sterilization.

Traditional wisdom about emerging pathogens is that they are noxious because they are new and therefore ill adapted to a human host. Animal viruses, such as the Ebola virus or the Sin Nombre virus that causes hantavirus pulmonary syndrome, can trigger unusual symptoms because our immune response has not evolved with the virus. Over the long haul, microorganisms in humans usually reach a subtle accommodation. Humans acquire resistance to the infectious agent while the parasite becomes milder, permitting us to survive its assault and permitting it to transmit its genes to someone else. Microorganisms need their host to survive: a dead host is a dead end. The reason the lethal spore-forming bacillus *Clostridium botulinum*—the cause of botulism—has not leveled our species is because when it kills us with its toxins, it kills its prospect for spread.

In the case of emerging infections, the collision is between pathogens and people. Emerging infections come because change is everywhere, not only for humans but also for nonhuman animals, plants, seeds, and insects. Virtually every aspect of American culture—from where we live to where we play, from how we raise livestock to how we raise children—is changing, and change creates new markets, so to speak, for pathogens, which have a knack for leveraging the slimmest advantage. Every day, >2 million people worldwide cross national borders; every year, >1.5 billion people travel by air. The USA hosts 47 million visitors yearly. With air travel today, people in India are like neighbors. Just as in the 19th century when cholera traveled on steamships to Europe and Africa, so in the early 1990s cholera reached the oyster beds of Mobile Bay by stowing away in the bilge water of ships from Latin America. Trucks, freighters, and airplanes have replaced caravans and steamships. Our stores are now filled with foods from all over the world. Any pathogen, not just those present in food, can be virtually anywhere in the world within 48 hours. Lyme disease came to us courtesy of 19th-century deforestation in the Northeast, followed by patchy and less-diversified second-growth forests. Coastal population growth has led to contamination of shellfish beds with human waste, fostering the transmission of viral and bacterial pathogens. Human encroachment on the tropical rain forest may open the way for hemorrhagic fever viruses and perhaps even HIV's mysterious retroviral cousins.

Communing with nature is not the only path to pathogens: microbes also love crowds. In 1900, only 5% of the world's population lived in cities with >100,000 residents. By 2025, 65% of the population in developing regions will inhabit cities. Dense urban enclaves are magnets for infections from isolated rural areas and launchpads that allow pathogens to reach other fast-growing populations. Overwhelmed by unsafe water, poor sanitation, and widespread poverty, tomorrow's megacities will become cauldrons for new infections. The devastating 1998–1999 Nipah virus outbreak in Malaysia that killed nearly a third of infected people probably sprang from intensive pig raising, which permitted a novel virus (probably carried by fruit bats) to propagate and then jump to farmers. Pig farms thus acted as megacities for the deadly agent, and pig farmers became sentinel cases. In industrialized countries, day care centers are notably noxious set-

tings in which the combination of frequent infections, susceptible children, poor hygiene, and high antimicrobial use breeds diarrheal diseases and antibiotic-resistant microbes.

Keeping ourselves alive longer also increases our susceptibility to infection. In 1900, only 4% of the US population was over age 65; in 2040, it will reach almost 25%. Elderly individuals, with their fading immunity, are at the mercy of microorganisms that are normally benign. While chemotherapy and other immunosuppressive treatments have enabled people to live with cancer and other illnesses, they also increase our susceptibility to ubiquitous pathogens such as cytomegalovirus and West Nile virus. And modern technologies intended to make our lives easier may also make life easier for microbes. The bacterium of legionnaires' disease, which is normally a habitué of moist soil in lakes, not only thrives in water of narrowly warm temperature ranges, but also must be misted into tiny particles to penetrate deep into human lungs—and so is neatly accommodated by cooling towers, whirlpool spas, and even hot water pipes. One major worry about organ transplants from pigs is that these organs could infect humans with porcine endogenous retroviruses, which are in the same class as HIV. These viruses, which are insinuated in the donor pig's DNA, could interact with human viruses to create new, potentially dangerous species that might spread to the general population.

Bugs themselves are changing. In 1954, the USA produced 2 million pounds of antibiotics. Today it makes tens of millions of pounds per year, half or more administered to livestock. As a result, 70% of bacteria that cause the infections patients acquire in hospitals are resistant to at least one antibiotic, and the animals we eat have become favorites for drug-resistant microbes. If vancomycin-intermediate *Staphylococcus aureus*, or VISA, defies our most powerful antibiotic, simple scrapes could become mortal wounds, and surgery could be as dangerous as it was 100 years ago. It takes 17 years to produce a new antibiotic, but a bacterium can develop resistance in minutes!

What many biologists fear most is a new deadly virus. Viruses, of course, are harder to fight with drugs and are intimately entangled with the genes and metabolic machinery in our cells. Viruses also seem to stimulate our immune systems more violently and self-destructively than do bacteria. And, unlike with bacteria, it's harder to predict whether a particular virus will radiate quickly or will be especially savage. In the 1930s during the Great Depression, Hans Zinsser wrote, "Infectious disease is one of the few genuine adventures left in the world." Even the most extreme sports wouldn't produce the adrenaline of a race against pandemic influenza or a cloud of anthrax at the Super Bowl. In the field of infectious disease, reality is stranger than anything a writer could dream up. The most menacing bioterrorist is Mother Nature herself!

Madeline Drexler has written a splendid book!

SMALLPOX

From 1878 until 1978, when the virus was eradicated—the first eradication of an infectious disease—smallpox killed 1 billion people. Smallpox is undoubtedly the worst disease of human beings! If it went global, smallpox could kill as many human beings in 15 to 20 weeks as AIDS has done in 20 years! Smallpox virus could have been entirely eliminated from the planet,

but that choice was not made. The World Health Organization in Geneva, Switzerland, decided to keep 1 dose of the vaccine for every 12,000 people in the world in a freezer. The smallpox virus now resides officially in only 2 high-security freezers—at the CDC in Atlanta and at Vector, a Russian virology institute in Siberia. Today, smallpox is a weapon of mass destruction. The virus is alive and it knows how to make copies of itself in the human body. Ironically, to keep ourselves safe from the virus we have to keep the virus around.

Humans are the only animals who naturally get smallpox. Researchers are desperately looking for a nonhuman animal to infect with smallpox so attempts could be made to develop a smallpox drug. Monkeys are now being infected with human smallpox! The Food and Drug Administration (FDA) requires that any drug or vaccine be used in a nonhuman animal before being tried in a human.

The “demon in the freezer” has been set loose. It is almost certain that hostile states including Iraq and North Korea have illegal stocks of smallpox. Peter Jahrling, a prominent biologist, fears that biologists in secret labs are using genetic engineering to create a new “superpox” virus, a smallpox virus resistant to vaccines. One reason for developing an antismallpox drug is that approximately 20% of the US population cannot be vaccinated: they are immune compromised or they have eczema or they are pregnant women or they are very young children. That’s a large number of people who will have no protection if smallpox comes back. That’s why a drug is so important.

These above facts were obtained from the book *The Demon in the Freezer* by Richard Preston (3), who also wrote *The Hot Zone* and *The Cobra Event*, both *New York Times* bestsellers.

DEXAMETHASONE IN BACTERIAL MENINGITIS

De Gans and colleagues (4) from several medical centers in the Netherlands conducted a trial comparing dexamethasone with placebo in adults with acute bacterial meningitis. Dexamethasone (10 mg) or placebo was administered 15 to 20 minutes before or with the first dose of antibiotic and given every 6 hours thereafter for 4 days. Of the 301 patients, 157 received dexamethasone and 144 received placebo. Treatment with dexamethasone was associated with a 41% reduction in the risk of an unfavorable outcome and with a 52% reduction in mortality. Among the patients with pneumococcal meningitis, an unfavorable outcome occurred in 26% of the dexamethasone group and in 52% of the placebo group. Thus, early treatment with dexamethasone improves outcomes in adults with acute bacterial meningitis and does not increase the risk of gastrointestinal bleeding.

FISH AND METHYLMERCURY

For years I have limited my flesh eating to fish for a number of reasons. The November 5, 2002, *USA Today* had a first-page lead story entitled “People who eat a lot of fish may run health risk” with a subtitle “Study finds elevated consumption can lead to high intake of mercury” (5). Mercury is in all of our bodies. It’s only when too much is in our bodies that potential danger exists. The most common sources of mercury in air are coal-burning power plants, municipal waste combustors, medical waste incinerators, and hazardous waste combustors. Tiny particles of mercury in the air fall onto soil and water. As a conse-

quence, mercury can accumulate in fish and wildlife. Small fish are eaten by big fish, so big fish and fish-eating birds generally have the highest levels of contamination.

Methylmercury is an organic form of mercury that is different from what is in mercury thermometers or what goes up smokestacks when coal is burned. Mercury is converted to methylmercury by bacteria in water. So when we talk about mercury in fish, we are really talking about the toxic methylmercury. Since methylmercury is hard for the body to eliminate, it builds up and may affect the nervous system. Most human exposure to methylmercury is through fish consumption.

In an article published in the November 2002 issue of *Environmental Health Perspectives*, an online journal of the National Institute of Environmental Health Services, part of the NIH, a physician in the San Francisco area, Jane Hightower, MD, reported high levels of methylmercury in blood and hair samples taken from dozens of her patients, including men, women, and children. The Environmental Protection Agency and the National Academy of Sciences have long recommended keeping mercury levels in blood at $\leq 5 \mu\text{g/L}$. In Hightower’s study, patients’ blood levels ranged from 2 to nearly 90 $\mu\text{g/L}$. Symptoms varied widely and did not correlate well with the amount of methylmercury in the blood. Some patients with elevated blood mercury levels had no symptoms, and others with low levels had symptoms. Thus, whether the symptoms were due to direct effects of mercury or to a reaction to it or to something else is unclear.

The FDA ceased its large methylmercury sampling program in 1998. Women of childbearing age have long been warned to limit their fish intake to reduce the risk of exposing an unborn baby to mercury. The amount of fish safe to eat each week is based on body weight. For example, the amount of canned tuna that is safe to eat each week would be 10 oz for a 200-lb person, 9 oz for a 175-lb person, 5 oz for a 100-lb person, but only 1 tablespoon for a 25-lb person. In July 2002, an FDA advisory committee recommended that the agency do research to assess the risk to women and young children who eat canned tuna. The amount of methylmercury per can is generally low, about 0.17 parts per million, but it varies widely. Tuna is the most consumed fish in the country. One expert recommended that pregnant women not eat >2 cans of tuna per week. The FDA currently recommends that women who are or could become pregnant limit all fish to 12 oz a week.

But all fish do not contain the same amount of methylmercury. Fish with high levels of mercury include swordfish, shark, tile fish, king mackerel, and tuna steak. Fish that generally have low levels of mercury include salmon, flounder, cod, catfish, trout, pollock, clams, shrimp, scallops, and lobster. I am sorry to see tuna on the high-level list because that is my favorite fish, but I am grateful that salmon, trout, shrimp, and lobster are on the low-mercury list. It appears that fish that are high in omega-3 fatty acids such as salmon and sardines are low on the mercury scale. Thus, people should not be encouraged to avoid fish but simply to eat those with lower levels of mercury in them.

CHILDHOOD OBESITY AND SOFT DRINKS

It is estimated that about 60% of adults in the USA are overweight (body mass index roughly 25–30 kg/m^2) and half of them are obese (body mass index >30). Obesity may soon replace ciga-

rette smoking as the leading cause of preventable death in the USA. Obesity may be responsible for about 300,000 deaths in the USA in adults per year and, unlike the trend with smoking, the prevalence of obesity is increasing. The total cost of overweight and obesity in 2000 in the USA is estimated to have been \$117 billion, nearly 10% of the US health care expenditure (6). Obesity is both undertreated and underreported in the USA. Only about 40% of patients classified as obese are reported as obese by their physicians. And treatment is enormously difficult. Lifestyle modification, diet, and pharmacotherapy result on average in only a 5% to 10% weight loss overall with a maintenance of weight loss for only 1 to 2 years, and 95% of all patients who lose weight regain the lost weight within 7 years. Nevertheless, weight loss as little as 5% can lower blood glucose, blood lipids, and blood pressure.

Childhood obesity is rising, and schools are helping (7, 8). Soft drink companies frequently aim advertising campaigns at children. In 1997, American children obtained 50% of their calories from fat and sugar (35% and 15%, respectively), and only 1% of US children regularly ate diets conforming to the recommendations of the food guide pyramid. Indeed, nearly 50% failed to achieve any of the pyramid recommendations.

The consumption of soft drinks is of special concern because of their high sugar content. Nearly 25% of adolescents drink >26 oz of soft drinks each day, and that provides nearly 15% of their daily calories. About 60% of US middle schools and high schools sell soft drinks in vending machines. In 2002, an estimated 240 US school districts had entered into exclusive "pouring rights" contracts with soft drink companies. Typically, the companies give the schools cash and other incentives in return for the right to sell sodas in vending machines and to advertise on scoreboards, in hallways, on book covers, and other places. These contracts reward schools for selling more soda to students, and some even directly link the school's revenues to the amount of sodas sold. A few school districts are beginning to ban deals with soft drink companies. Banning sales of sodas to junior high and high schools in the USA would certainly be a start to decreasing body weight in these teenagers.

COFFEE DRINKING AND DIABETES

The caffeine of coffee has been shown to acutely reduce sensitivity to insulin. No studies of coffee consumption and risk of adult-onset (type 2) diabetes mellitus have been reported until van Dam and Feskens (9) from the Netherlands studied 17,111 Dutch men and women aged 30 to 60 years. During 125,774 person-years of follow-up, 306 new cases of type 2 diabetes developed. After adjustment for potential confounders, individuals who drank ≥ 7 cups of coffee a day were half as likely as those who drank ≤ 2 cups of coffee a day to develop type 2 diabetes. Thus, coffee consumption was associated with a substantially lower risk of type 2 diabetes. As a rather heavy coffee drinker, I am delighted.

COMPARISON OF C-REACTIVE PROTEIN AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL AS PREDICTORS OF FIRST CARDIOVASCULAR EVENT IN WOMEN

The November 14, 2002, issue of *The New England Journal of Medicine* had an article by Ridker and colleagues (10) comparing the usefulness of C-reactive protein (CRP) and low-

density lipoprotein (LDL) cholesterol in predicting first cardiovascular events. Three days later an unsigned editorial in the *New York Times* picked up on the usefulness of CRP in predicting cardiovascular events, and numerous newspapers followed. Ridker and colleagues' study included nearly 28,000 apparently healthy American women who had baseline CRP and LDL cholesterol measurements. These women were followed for a mean of 8 years for the occurrence of acute myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. CRP and LDL cholesterol correlated poorly, but baseline levels of each correlated well with the occurrence of first cardiovascular events. Compared with the women in the lowest quintile (1.0), the relative risks of first cardiovascular events according to increasing quintiles of CRP were 1.4, 1.6, 2.0, and 2.3. The corresponding relative risks in increasing quintiles of LDL cholesterol, compared with the lowest (1.0), were 0.9, 1.1, 1.3, and 1.5. Similar effects were observed among the users and nonusers of hormone replacement therapy. Overall, 77% of all events occurred among women with LDL cholesterol levels <160 mg/dL, and 46% occurred among those with LDL cholesterol levels <130 mg/dL. Screening for both biologic markers provided better prognostic information than screening for either alone. These data suggest that the CRP level is a stronger predictor of first cardiovascular events in women than is the LDL cholesterol level.

C-REACTIVE PROTEIN AND CORONARY ARTERY DISEASE AFTER CARDIAC TRANSPLANTATION

A major problem following cardiac transplantation has been the development of narrowing in the coronary arteries of the donor heart. Numerous studies have been done trying to determine risk factors in these heart transplant recipients for development of coronary artery narrowing. Labarrere and colleagues (11) from Indianapolis, Indiana, and Cleveland, Ohio, prospectively studied 109 consecutive patients who received heart transplants and had CRP concentrations determined 3 months after cardiac transplantation. The mean and median CRP concentrations in the 109 patients were 4.8 and 3.9 mg/L, respectively, and the upper quartile of CRP concentrations was >7.2 mg/L. The median CRP concentration during the first 3 months after transplantation for allografts that remained free of coronary artery disease was 2.6 mg/L, and for allografts that developed angiographically detectable coronary disease in a mean of 40 months, 5.3 mg/L. The concentrations of CRP determined 3 months after transplantation were associated with increased severity and enhanced rate of progression of coronary artery disease, heightened frequency of myocardial ischemic events, and graft failure. Unfortunately, the concentrations of CRP before cardiac transplantation were not apparently determined.

ASPIRIN AND CORONARY ARTERY BYPASS GRAFTING

Mangano (12), for the Multicenter Study of Perioperative Ischemia Research Group from 40 centers in 17 countries, prospectively studied 5065 patients who underwent coronary artery bypass grafting (CABG), of whom 5022 survived the first 48 hours after operation. During hospitalization, 164 patients died (3.2%) and 812 others (16%) had nonfatal cardiac, cerebral, renal, or gastrointestinal ischemic complications. Among pa-

tients who received aspirin (up to 650 mg) within 48 hours after CABG, subsequent mortality was 1.3% (40/2999) compared with 4.0% among those who did not receive aspirin during this period (81/2023). Aspirin therapy was associated with a 48% reduction in frequency of acute myocardial infarction (2.8% vs 5.4%), a 50% reduction in stroke (1.3% vs 2.6%), a 74% reduction in renal failure (0.9% vs 3.4%), and a 62% reduction in bowel infarction (0.3% vs 0.8%). No other factor or medication was independently associated with reduced rates of these outcomes, and the risk of hemorrhage, gastritis, infection, or impaired wound healing was not increased with aspirin use. Thus, early use of aspirin after CABG is safe and is associated with a reduced risk of death and ischemic complications involving the heart, brain, kidneys, and gastrointestinal tract. Another plus for this 100-year-old drug!

ALZHEIMER'S DISEASE, ASPIRIN, AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Data from the Cache County Study on Memory, Health, and Aging show that elderly people who took NSAIDs or aspirin for at least 2 years were half as likely to develop Alzheimer's disease as those who did not take such compounds (13). Two previous population-based studies—the Baltimore Longitudinal Study on Aging and the Rotterdam Study—found that long-term use of NSAIDs can delay or prevent onset of the disease as long as use of these drugs starts before symptoms of Alzheimer's disease appear. These 3 studies together provide compelling epidemiologic evidence that NSAIDs are neuroprotective. These studies also show that the use of NSAIDs several years prior to the onset of clinical dementia may provide greater protection than use near the time of onset. The mechanism of how these drugs act against Alzheimer's disease is unclear.

DIGITALIS, GENDER, AND HEART FAILURE

Rathore and colleagues (14) from New Haven, Connecticut, studied 6800 patients with systolic heart failure to see if the effect of digitalis was similar or different in men vs women. All patients received diuretics and angiotensin-converting enzyme inhibitors. Digoxin (0.25 mg/day) was not associated with a significant reduction in the rate of death from any cause (35% in both groups). There was a 12% reduction in the rate of death due to pump failure with digoxin that was offset by an increase in the rate of death presumed to have resulted from arrhythmia. Digoxin was associated with a significant reduction in the rate of death or hospitalization for worsening heart failure. The greatest benefit was to those who had cardiomegaly on chest radiograph, an ejection fraction <25%, or severe symptoms.

Women had a lower overall rate of death than men (31% vs 36%). The rate of death was also lower among women in the placebo group than among men in this group (29% vs 37%) and among women in the digoxin group than among men in the digoxin group (31% vs 35%). Digoxin also was associated with a 5% smaller absolute reduction in the rate of hospitalization for worsening heart failure among women compared with men. This study is important not only because it shows a difference in the effect of digoxin in men vs women with heart failure but also because it underscores the importance of investigations of sex-based variations in effects of drugs.

RONALD MALT, MD, AND ARM REIMPLANTATION

Ronald Malt was born in Pittsburgh in 1932 and died in Massachusetts in October 2002 at age 70 from complications of Alzheimer's disease (15). He was professor of surgery at Harvard Medical School and worked at the Massachusetts General Hospital. He was coeditor of the *Oxford Textbook of Surgery* and an associate editor of the *New England Journal of Medicine*. On May 23, 1962, when Malt was 30 years old and chief surgical resident at the Massachusetts General Hospital, a 12-year-old boy named Everett Knowles was admitted to the emergency room. When Knowles had tried to hop on a freight train to hitch a ride to a baseball game, he was thrown against a wall, and his right arm was ripped off cleanly at the shoulder. Until that point successful reimplantation of an arm had never been performed. Malt assembled a team of 12 specialists; they agreed on a protocol to follow and reattached the severed limb. Their success made Malt and the other team members celebrities. Malt's team first reattached the bone with a special pin, then reconnected the arteries, and then grafted the skin and muscle together. They decided against reattaching the nerves until some healing had occurred.

Not long after the first operation, the boy's hand regained color and the radial pulse was palpated. Several months elapsed before the connections to the brachial nerve trunks were restored. After extensive physiotherapy, a year after the accident, Knowles could move all 5 fingers and bend his wrist. Two years later, he was playing baseball and tennis and, some years later, he worked for a haulage company driving a 6-wheel truck and shifting sides of beef. During the past 5 years, refinements to the pioneering work started by Malt have made successful reimplantation possible after amputation of multiple digits, a thumb, a hand severed through the palm or carpus, and a wrist or forearm.

LUMPECTOMY VS MASTECTOMY FOR BREAST CANCER

Fisher and colleagues (16) from Pittsburgh studied 1851 women with breast tumors up to 4 cm in maximal diameter. In over a third of the cases the cancer had spread to axillary lymph nodes. The women were randomly assigned to one of 3 treatments: total mastectomy, lumpectomy alone, or lumpectomy followed by radiation. The women had the same chance of being alive after 20 years, with or without cancer, regardless of whether the breast had been removed or only a lumpectomy had been done. Radiation treatment significantly reduced the chance of another cancer's arising in the same breast, sparing many women a mastectomy—the usual treatment for a second cancer in the same breast. The risk of a second cancer developing in the same breast was about 40% in women who had a lumpectomy without irradiation and 14% in women who had lumpectomy plus radiotherapy. Thus, lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer provided the surgical margins of the resected specimen are free of cancer.

TANNING AND HEALTH

Despite awareness of the risks associated with ultraviolet light exposure, university students continue to use tanning lamps to get a so-called "healthy" tan, and these are a highly educated segment of the society! A study by Farmer and colleagues (17) from Indianapolis included 489 students seeking walk-in care for

a medical condition at the student health center. They were quizzed about their knowledge of skin cancer and their tanning habits: 47% had used a tanning lamp during the previous year, and 39% reported never having used a tanning lamp. More than 90% of current and past users were aware that premature aging and skin cancers were associated with tanning-lamp use. Yet, 92% of current users said they used tanning lamps because they “enjoyed a tanned appearance”; 71% said they “had no time” to tan in natural sunlight; 61% used tanning lamps for “vacation preparation” (despite the fact that such use affords no protection against subsequent sun exposure); and 42% said they used tanning lamps for “relaxation.” Students with a positive family history of skin cancer were 1.5 times more likely to use tanning lamps than those without such a family history!

DRINKING ALCOHOL WHILE ON CALL

Ahmad and colleagues (18) from 3 US medical centers developed a survey with 10 questions to probe doctors’ perceptions about their own and their colleagues’ use of alcohol. They took a 20% random sample of physicians from each specialty and mailed up to 3 rounds of surveys over a 6-month period. Of the 206 surveys sent out, 135 (65%) responses were returned. Most doctors (86%) were against drinking any alcohol while on call, but 14% felt that social drinking was acceptable and 25% thought that in their specialty some alcoholic use was safe. In response to asking how many drinks a doctor in their specialty could safely drink while on call, 73% answered 0, 9% answered 1, 4% answered 2, 5% answered 3, and 10% answered 4 or more. A quarter admitted to drinking alcohol while on call, and 64% and 27% reported having encountered colleagues whom they suspected had used or were impaired by alcohol while on call, respectively. Almost all doctors believe that patients care whether they use alcohol while on call, but doctors were divided about their obligation to inform patients before seeing them. It might be wise for medical societies to include stronger declarations about drinking alcohol while on call in their ethical codes before the issue is decided for them.

MAYOR MICHAEL BLOOMBERG AND SMOKING

New York City’s mayor, a very wealthy one, fondly likened his college fraternity to the one in *Animal House*, and he still enjoys a party (19). On tobacco he has surprised many constituents. First, he increased the city tax on cigarettes, raising the price of a pack of cigarettes in New York City to around \$7. Now, he proposes to outlaw smoking in every bar and restaurant in the 5 boroughs of New York. Mr. Bloomberg is a convert from a pack-a-day habit. He sells his smoking ban as an issue of workplace safety. Although he strongly defends a person’s right to smoke to death, that right does not allow the smoker to spray that toxic effluent into the airspace of innocent bystanders, in particular, waiters and bartenders.

Basically 3 arguments are being raised against him: science, economics, and personal liberty. Two of them Mr. Bloomberg wins hands down, and one is open to debate. The city health commissioner of New York says that in 2002, about 1000 New Yorkers will die from other peoples’ cigarettes. The economics argument is that no-smoking statutes hurt business at bars and restaurants. In California, smoking has been barred from bars and

restaurants since 1998, and since then there has been increased spending of nonsmokers in these establishments, which easily compensates for the smokers who stay home. The personal freedom argument holds that smoking is a social pleasure and that the right to congregate over drinks and cigarettes should be not be denied to consenting adults. Interestingly, Adolf Hitler banned smoking in public places! Smoking is more of an addiction than a choice, and most smokers stay smokers because they simply can’t quit. Mr. Bloomberg gave up smoking cold turkey, and he expects New York nightspots to do likewise.

LAUGHING IN THE DOCTOR’S OFFICE

Some researchers from the University of Helsinki videotaped 250 consultations of patients with physicians to count the number of instances of laughter, smiles, and “smiling voices” involving the physician, the patient, or both (20). In 70% of cases of a patient’s laughing, there was no response from the doctor! In 20% of cases the doctor did smile, but in only 10% of cases did he or she laugh. Patients laugh an average of 4 times during an average consultation with a doctor. Laughing is good for doctors as well as for patients.

NURSING SHORTAGE

According to the Department of Health and Human Services, about 1 million nursing positions will need to be filled by 2010 (21). The average age of nurses in the USA now is 45, and most retire in their 50s. The US government in its last budget allocated \$93 million for nursing education and \$8 billion for physician education. California Congresswoman Lois Capps, a registered nurse, was the one behind the recent establishment of a National Nurse Service Corps that would provide scholarships to nurses willing to serve in a public or private nonprofit health facility where there is a critical shortage of nurses. The bill sailed through Congress last winter and the president quickly signed it.

NEW LEADERSHIP AT THE FOOD AND DRUG ADMINISTRATION

The FDA has a new commissioner, Mark McClellan, a 39-year-old physician-economist who, as a member of the President’s Council of Economic Advisors, has been one of President Bush’s top aides on health policy (22). The FDA regulates not only all prescription and nonprescription drugs marketed in the USA but also all medical devices, blood products, vaccines, tissues used for transplantation, animal feed and drugs, cosmetics, and 75% of food (everything except meat and poultry!). Commissioner McClellan thus will have regulatory authority over products that account for roughly 25% of all US consumer spending.

In September 2002, the US General Accounting Office analyzed approval time for drugs from 1993 to 2001 and found that these times for “standard” drugs had dropped from a median of 27 months to 14 months, and approval for new drugs had dropped from 21 to 6 months. At the same time, the percentage of drugs that had to be withdrawn from the market after approval because of safety-related reasons had risen from 3.1% to 3.5% in the 8 years following the initiation of pharmaceutical companies’ paying for the review of the drugs they wanted to bring to market. Apparently the morale in the FDA is quite low, and there is a need to restore the independence of the FDA from industry funding.

MEASURING THE METER

The metric system changed the world! It was a radical innovation. It made possible free trade, the open market, and globalization. Before the metric system was developed, a pint in one community was quite different than a pint in another community, and therefore trade among communities was a bit hazardous. Ken Alder has written a book entitled *The Measure of All Things. The Seven-Year Odyssey and Hidden Error That Transformed the World* (23). In the midst of the French Revolution, 2 astronomers set out in opposite directions from Paris, one going north to Dunkirk, the other south to Barcelona, for the purpose of measuring a portion of the north-south meridian to define the meter as one ten-millionth of the distance between the pole and the equator so that all countries would have a specific unit of measure. Jean-Baptiste-Joseph Delambre led the northern portion and Pierre-Francois-André Méchain led the southern portion of the meridian expedition. Ken Alder located the long-lost correspondence between these 2 men along with their mission logbooks, and he stumbled upon a 200-year-old secret and that is that the meter is in error! Méchain, one of the 2 astronomers, made contradictory measurements from Barcelona and, in a panic, covered up the discrepancy. The guilty knowledge of his misdeed drove him to the brink of madness and ultimately to his death. Only then, after the meter had already been publicly announced, did his partner, Delambre, discover the truth and face a fateful choice: to disclose the error or cover it up.

The measurement brought back by Delambre and Méchain not only made science into a global enterprise and made possible our global economy, but it also revolutionized our understanding of error. Their error, interestingly, was the equivalent of the thickness of 2 sheets of paper. These 2 astronomers made a meter in platinum, and that platinum bar still resides in Paris. Today, 95% of the people on the earth live in countries that use the metric system. The only countries that do not use the metric system are Myanmar (Burma), Liberia, and the USA. Interestingly, Napoleon banned the metric system in 1812 because his people got annoyed with the measurements. It was not until 1920 that the metric system returned to France. When he was secretary of state in 1770, Thomas Jefferson first proposed that the USA adopt the metric system but was not successful. He did persuade Congress to use decimal coinage rather than pounds, shillings, and pence. Measuring the meridian from Dunkirk to Barcelona was the first state sponsorship of science. These 2 astronomers were the first to be called "scientists." Before that, scientists were called "natural philosophers."

These 2 astronomers worked at a time when scientists believed they could redefine the foundations of space and time. The French Revolution created the 30-day month, the 10-day week, and the 10-hour day with each hour 100 minutes and each minute 100 seconds. Of all the changes associated with the metric system, the date and time changes were the most unpopular, and they were quickly rescinded.

The November 25, 2002, issue of *Barron's* had a piece by Thomas G. Donlan entitled "Measure for measure. It's time for the United States to join the world in using the metric system" (24). Americans buy liquor, wine, and soft drinks by the liter but beer by the fluid ounce. We buy medicines by the milligram but meat by the pound. In some ways the USA has been officially

on the metric system for more than a century. Using metric measurements has been legal in the USA since 1866. The USA signed an international metrification treaty in 1875. In 1890, the National Bureau of Standards took delivery of the official national kilogram, a precise duplicate of the world's standard kilogram enshrined in Paris. And in 1893, the US pound was officially defined as 0.4535924277 kg and the yard as 3600/3937 of a meter. In 1906, Congress rejected a bill to put the metric system into general use. A metrification law enacted in 1975 required the federal government to use the system wherever "practical," and many reasons have been found to declare it impractical to buy things in metric sizes.

Things "scientific" have gone metric with occasionally mixed results: food packages are usually in the antique system; nutrition labels are in metric. Thus, the nutrition label on a 1.5-ounce bag of potato chips reveals that the contents include 12 mg of fat. A footnote offers a conversion table for grams to calories, but not grams to ounces. The US Metric Association claims that by not going metric, US industry loses billions of dollars in lost export business annually.

But metrification hasn't been easy anywhere. The European Union still permits dual labeling in the metric and the antique system. Canada went metric in 1971, putting its speed limit signs in kilometers per hour along with nearly all measurements the government uses. But in 1984 a new government made further metrification optional, leaving the process in a state of suspended animation. Frozen turkeys, for example, in Canada are sold by the kilogram and fresh turkeys by the pound, even in the same store.

The United Kingdom, formally the land of the 20-ounce imperial pint, went the other way, ending the shilly-shallying of a voluntary system and imposing metrification in concert with the European Union. Freeborn Englishmen rebelled, and in a test case last year a grocer was fined for selling bananas by the pound, but otherwise enforcement has ground nearly to a halt.

Having both the metric system and the antique system in contemporaneous use has its drawbacks. One disaster occurred in 1999 when NASA lost a spacecraft intended to orbit Mars. Some data on rocket thrust that the jet propulsion laboratory thought was in metric was actually in pounds, so a rocket burned for orbital insertion was drastically mistimed. An Air Canada jetliner ran out of fuel in 1983 because it was loaded with thousands of pounds of fuel instead of thousands of kilograms. Fortunately, the pilot was able to glide to an emergency landing strip.

In the USA, the blame must go to Congress. Fixing the standard of weights and measures is one of its enumerated powers in the Constitution. Since 1975, however, Congress has only attempted a conversion to the metric system. The government buys and builds in the metric system, hoping to jump-start the free market. All it has done is raise the cost of doing business with the government! There are few places in the economy where the government can actually legislate American efficiency. The system of weights and measures is one of them. Congress can and should convert the country to the metric system!

COLMAN MCCARTHY AND PEACE

For many years, Colman McCarthy wrote editorials for the *Washington Post*, and I was fond of his pieces when I lived in that area. In the last few years, he has headed an organization called

Center for Teaching Peace. He is against killing of all varieties and seeks solutions to violence wherever it may occur. He has always asked, "Are there nonviolent ways to deal with violence?" He advises, "Be humble, praise people, say positive things, don't attack others, treat everybody warmly, don't try to change the world but don't let the world change you." The cost of war and violence is enormous. Our Department of Defense (he calls it the Department of Offense) spends \$11,000 per second or \$900 million per day. The cost to kill each enemy soldier in the Korean War was \$500,000. Four times more is spent on our military each day than on the Peace Corps for an entire year. About 40,000 people are killed each month by wars around the earth, and they are mostly poor fighting poor. He stresses that the best thing we can do in life is to raise good, decent, and honorable teachers. He advises, "Do what you love and the money will follow." (That certainly has been the way with me.) He stresses, "Don't bring your adversaries to their knees; bring them to their senses." He is, of course, against killing animals. "Honor life in all forms," he stresses.

He distinguishes between hot violence and cold violence. The World Trade Center tragedy and the Oklahoma City tragedy are examples of hot violence that produce outrage. Cold violence is something most of us never feel or never see. About 40,000 people die each day of hunger. We kill 12 million animals each day for food. The USA sells weapons to almost anybody who will buy them. He stresses early prevention rather than later intervention as the cure for violence. "We sell more weapons to other nations than any nation and then these weapons are often used against us." He is against the death penalty, emphasizing, "We kill people who kill people to show that killing is wrong." He believes that violence is a learned behavior. Colman McCarthy is an interesting man and deserves an ear. His address is Center for Teaching Peace, 4501 Van Ness Street, NW, Washington, DC 20016. His most recent book is *I'd Rather Teach Peace*.

"JOHNNY U" (1933–2002)

It wasn't always easy for Johnny Unitas, probably the best National Football League (NFL) quarterback in history (25). His father died when he was 4, and his mother supported the 4 children thereafter by working 2 jobs. Football success did not come easily. When the first-team quarterback at St. Justin's High School in Pittsburgh broke his ankle, Johnny Unitas inherited the job. He learned the entire offense in less than a week. After high school, he wanted to go to Notre Dame, but that college was wary of a 6' quarterback who weighed only 138 lb. The University of Pittsburgh offered a scholarship, but Unitas failed the entrance examination. He accepted an offer from the University of Louisville and did well enough to be taken in the ninth round (102nd overall) of the NFL's 1955 draft by the Pittsburgh Steelers. As the fourth-string quarterback, Unitas never got into a preseason game, and the Steelers dropped him. He took a construction job but played football at \$6 a game for the Bloomfield Rams, a semipro team in the Pittsburgh area that played on dirt, not grass, and the field had to be sprayed with oil before the game to keep the dust down. The next year he was signed by the Baltimore Colts and given a \$7000-a-year contract with the condition that he had to survive the entire season to earn it all. He

got his chance in the fourth game of the season after the starting quarterback suffered a broken leg against the Chicago Bears. Unitas' first pass was intercepted and returned for a touchdown! He fumbled on his next 2 possessions, but the starter was hurt and the other backup chose law school over football, and Unitas kept the job. By now he was bigger (he would eventually weigh 200 lb) and soon he was a star.

His career extended from 1956 until 1973. In his career he completed 2830 passes for 40,239 yards and a record 290 touchdown passes. He threw a touchdown pass 47 consecutive games, setting a NFL record. He was voted the player of the decade for the 1960s and was named the greatest player in the first 50 years of pro football. Raymond Berry, Unitas' main receiver, said, "What made Unitas so good was his uncanny instinct for calling the right play at the right time, his icy composure under fire, his fierce competitiveness, and his utter disregard for his own safety."



—William Clifford Roberts, MD

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