

Facts and ideas from anywhere



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LIFE'S MASTER MOLECULE

The year 2003 represents the 50th anniversary of the discovery of the structure—the fabled double helix—of deoxyribonucleic acid, or DNA, by Watson and Crick (1, 2). Earlier experiments by others had shown that DNA from 1 strain of bacteria could permanently alter another, and this observation convinced Watson and Crick that it might hold the secret of heredity. They had also seen some x-

ray pictures done by Rosalind Franklin. On February 28, 1953, Watson cleared off his desk and began fiddling with cardboard models of 4 key parts of DNA: adenine, guanine, cytosine, and thymine. Suddenly, the puzzle pieces fit into place: *a* linked with *t* and *c* with *g*. The 2 pairs looked identical, and Watson realized they could form the steps of a spiral staircase. This double helix could duplicate itself by unzipping into 2 strands, each a template for building another helix with the same sequence of letters. DNA has achieved superstar status, and its lovely double spiral is an icon of science. DNA has cured deadly diseases and allowed labs to create animals with new features. It has freed the innocent from death row and caught a president in a tawdry lie. Now, 50 years later, the finishing touches are being put on the full 3-billion-letter sequence of our DNA.

Many scientists believe that DNA evolved from another long-chain molecule, namely RNA. Like DNA, RNA has 4 “letters” that store information. But it has an extra oxygen unit that makes it highly reactive. That oxygen unit even attacks RNA itself, making it unreliable for long-term information storage.

DOLLY DEAD

Dolly, the cloned sheep, was put to death on February 14, 2003, after disease and premature aging (she was 6, about half the life expectancy of her breed) marred her short existence. Dolly, a Finn Dorset sheep named after the singer Dolly Parton, bred normally twice (3). The birth showed that clones could reproduce. In 1999, when she was 2, scientists noted that the cells in Dolly's body—cloned from the breast cell of a 6-year-old ewe—were showing signs of wear more typical of an older animal. In January 2002, her creators announced she had developed arthritis at the age of 5.5 years. Dolly's body has been promised to the National Museum of Scotland and will eventually be put on display in Edinburgh.

DIETARY INTAKE OF FRUITS, VEGETABLES, AND FAT

Dietary guidelines for reducing cardiovascular disease and cancer risk have been widely promoted by national groups. Dietary guidelines from the American Heart Association and the dietary goals outlined in the health objectives for *Healthy People 2010* recommend a diet with 5 or more servings of fruits and vegetables per day and no more than 30% of calories from fat. A 16-state survey in 1996 showed that only 23% of adults reported consuming 5 or more servings of fruits and/or vegetables per day, and national data suggest that approximately 33% of persons ≥ 2 years of age consumed no more than 30% of calories from fat, well below the goal of 75% set in *Healthy People 2010*.

DeBoer and colleagues (4) from the Mayo Clinic performed a community survey to assess the prevalence of cardiovascular disease risk factors among residents of Olmsted County, where the Mayo Clinic is located. They conducted a random-digit-dial telephone survey during 50 days in 1999 by calling 1232 adults. They then mailed a structured questionnaire to the survey respondents, and 732 individuals responded. Only 16% of the adult population of Olmsted County reported meeting standard dietary recommendations for consuming both 5 or more servings of fruits and/or vegetables per day and no more than 30% of calories from fat. Fifty-one percent of the population met neither recommendation. Women more often met both goals than did men (22% vs 8%), but still more women met neither than met both goals (40% vs 22%). The following factors predicted adherence to both goals: being a woman, having a relatively low body mass index, being a nonsmoker, having a high serum cholesterol level, and exercising daily. We must do better to produce a healthier population.

USEFULNESS OF STATINS FOR PREVENTING CARDIOVASCULAR EVENTS IN PERSONS WITH MILD CHRONIC RENAL INSUFFICIENCY

Tonelli and colleagues (5) for the Cholesterol and Recurrent Events (CARE) Trial Investigators found 1711 participants who had chronic renal insufficiency with a creatinine clearance ≤ 75 mL/min. These patients were a subgroup of the 4159 patients in the trial that compared pravastatin (40 mg daily) to placebo in patients with previous myocardial infarction and total plasma cholesterol levels < 240 mg/dL. After a mean follow-up of 59 months, the incidence of death from coronary artery disease or nonfatal acute myocardial infarction was lower in participants receiving pravastatin than in those receiving placebo. Likewise, pravastatin was associated with a lower frequency of other coro-

nary events and coronary revascularization but not with total mortality or stroke. These data indicate that pravastatin is effective and safe for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency.

FOOD PORTION SIZES

While many believe that food portion sizes are increasing, no data have documented actual increases. Neilsen and Popkin (6) from Chapel Hill, North Carolina, compared food portion sizes consumed in the USA in 1977–1978 with those consumed by individuals in 1996. Consumption by over 63,000 individuals aged ≥ 2 years were sampled. Portion sizes varied by food source, with the largest portions consumed at fast food establishments and the smallest at other restaurants. Between 1977 and 1996, food portion sizes increased both inside and outside the home. The energy intake and portion size of salty snacks increased by 93 kcal (28 to 45 g), soft drinks by 49 kcal (387 to 588 mL), hamburgers by 97 kcal (162 to 198 g), French fries by 68 kcal (88 to 102 g), and Mexican food by 133 kcal (179 to 227 g). Thus, portion sizes and energy intake for specific food types have increased markedly during these 20 years, with greatest increases for food consumed at fast food establishments and in the home.

FAT CITY

For the third year in a row, *Men's Fitness* magazine has awarded Houston the dubious title of the fattest city in the USA among a list of 25 cities (7). The other 4 in the top 5 were Chicago, Detroit, Philadelphia, and St. Louis. Dallas ranked number 9.

PRO "GURGITATORS"

In 2002, there were fewer than 50 eating contests in the USA (8). This year, "gurgitators" expect nearly 100 different events, covering everything from anchovy pizza to zeppole, and many of the events will be televised. Prizes can be as high as \$50,000. Competitive eating is a test of stomach capacity, jaw strength, and hand speed, all of which require training but not gluttony. The 2002 champions ate the following: Buffalo wings, 74 in 12 minutes (2.65 lb of chicken meat); cabbage, 6 lb 9 oz in 9 minutes; cannoli, 21 in 6 minutes; chili, 1.5 gallons in 10 minutes; conch fritters, 45 in 6 minutes; hard-boiled eggs, 38 in 10 minutes; hot dogs, 50.5 with buns in 12 minutes; and oysters, 168 (hands free) in 10 minutes. Winners, we will see you on the autopsy table.

SLEEP-DISORDERED BREATHING AMONG PROFESSIONAL FOOTBALL PLAYERS

Sleep-disordered breathing means apnea and hypopnea during sleep, and it affects about 4% of the general population. George and colleagues (9) from 3 different cities did full overnight polysomnographic studies in 52 National Football League football players. Offensive and defensive linemen accounted for 85% of the cases of sleep-disordered breathing. The linemen also had the largest neck circumference (19 ± 1 in) and highest body mass index ($37 \pm$

3 kg/m^2). Both systolic blood pressure (129 ± 11 vs 122 ± 9 mm Hg) and diastolic blood pressure (84 ± 9 vs 77 ± 8 mm Hg) were significantly higher in the linemen than in the other players. The authors estimated that the prevalence of sleep-disordered breathing among all professional football players was 14% overall and 34% within the high-risk group, mainly the linemen. This estimated prevalence is much higher than that found in men of similar age. The presence of sleep-disordered breathing is a known risk factor for the development of systemic hypertension, and treatment of sleep-disordered breathing will presumably reduce the risk of cardiovascular disease. The offensive linemen in the National Football League now average well over 300 lb, and the defensive linemen are not far behind. Professional football is not healthy for the heart or the joints.

CONTINUING DECREASE IN DEATH RATES FROM CORONARY HEART DISEASE

Fewer people are dying from coronary heart disease in most developed countries. Between 1988 and 1998, the death rate from heart disease in the USA fell approximately 30%; in the United Kingdom, 38%; in Denmark, 49%; in Norway, 45%; and in Australia, 45% (10). The improved outcomes are attributed to quicker diagnoses and treatment of recent-onset chest pain, more prompt use of thrombolytic agents and angioplasty, and greater use of preventive drugs. More information from additional countries can be found at <http://www.heartstats.org>.

CHANGING INCIDENCE OF OUT-OF-HOSPITAL CARDIAC ARREST

Since the overall mortality from coronary heart disease in the USA has been decreasing, it follows that the incidence of out-of-hospital cardiac arrest must also be decreasing. A study from Finland described a marked decrease in out-of-hospital cardiac arrest in a 5-year period (1994–1999), and another study in Sweden showed a decrease in a 17-year period. Cobb and colleagues (11) compared out-of-hospital cardiac arrest cases during 21 years (1979–2000) in Seattle, Washington (*Figure*). The annual incidence of cardiac arrest with ventricular fibrillation as the first identified rhythm decreased by about 56% and was most evident in men. When all treated arrests (including asystole) with presumed cardiac etiology were considered, the incidence decreased by 43% in men but negligibly in women. Thus, in Seattle and hopefully in other parts of the country, there has

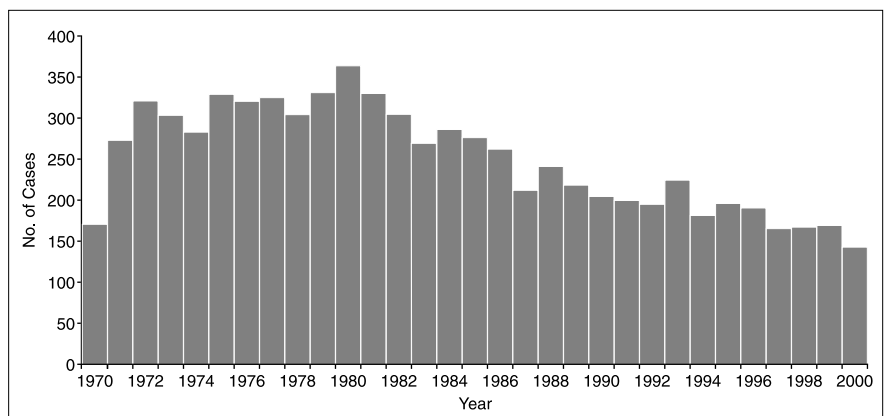


Figure. Annual numbers of all patients treated for out-of-hospital ventricular fibrillation, 1970–2000. Reprinted with permission from reference 11.

been a major decline in the incidence of out-of-hospital ventricular fibrillation and in all cases of cardiac arrest presumably due to heart disease.

TREATING SYSTEMIC HYPERTENSION WITH DIURETICS, ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS, AND CALCIUM ANTAGONISTS

In late 2002, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) involved >42,000 patients from the USA and Canada and compared the diuretic *chlorthalidone* with the ACE inhibitor *lisinopril* and the calcium antagonist *amlodipine* (12). (The alpha-adrenergic receptor inhibitor arm was stopped early because of adverse events.) ALLHAT concluded that chlorthalidone was more effective for blood pressure control and for outcomes than was lisinopril or amlodipine.

In early 2003, the Second Australian National Blood Pressure Study (ANBP2) trial was reported (13). It involved just over 6000 patients who were followed by 1594 family practitioners in Australia for a median of 4.1 years. The ANBP2 trial indicated that *enalapril*, the ACE inhibitor used, had an outcome advantage over *hydrochlorothiazide*, the diuretic used. Thus, the conclusions of these 2 trials are diametrically opposed to one another (14). The ALLHAT trial used chlorthalidone; the ANBP2 trial, hydrochlorothiazide. No head-to-head trials have compared the efficacy of and outcomes with these 2 diuretics. ALLHAT used lisinopril whereas ANBP2 used enalapril as the ACE inhibitor. Likewise, no head-to-head comparisons have been done of the long-term efficacy of and outcomes with these 2 ACE inhibitors. In both trials other antihypertensive medicines were also frequently used to achieve blood pressure goals, and the use of these additional agents compounds the complexities of comparisons between these trials. In the ALLHAT trial, the diuretic-based regimen was more efficacious in blood pressure lowering and in the percentage of patients in whom the blood pressure goal was achieved compared with the lisinopril and amlodipine arms. In the ANBP2 trial, there were similar reductions in blood pressure in the chlorothiazide and in the lisinopril arms. In the ALLHAT trial, the primary outcome of death from coronary causes or nonfatal myocardial infarction was similar in the 3 treatment arms, but when the primary and secondary cardiovascular events were combined, the outcomes favored chlorthalidone. The primary outcome in the ANBP2 trial was the total number of fatal and nonfatal cardiovascular events, and here enalapril performed better than chlorothiazide. So take your choice. I take an ACE inhibitor, an aldosterone receptor blocker, and hydrochlorothiazide (12.5 mg), and my blood pressure is 120/80 mm Hg.

ALCOHOL, STROKE, AND ACUTE MYOCARDIAL INFARCTION

Stroke is the third leading cause of death and a major cause of disability in the USA. Approximately 30% of stroke survivors are permanently disabled, and 20% require institutionalized care. Stroke also, of course, is a huge financial burden for patients, their families, and the health care system. The direct and indirect cost of stroke in the USA in 2002 is estimated to be \$50 billion. Over the past 20 years, many observational epidemiologic studies have examined the role of alcohol as both a risk factor and a potential protective factor for stroke.

Studies investigating the association between moderate consumption and stroke have reported conflicting results. Reynolds and colleagues (15) from New Orleans, Louisiana, performed a metaanalysis of 35 observational studies (cohort or case control) to examine the relative risk of stroke at various levels of alcohol consumption. Compared with abstainers, those who consumed >60 g of alcohol per day had an increased relative risk of total stroke (64%↑), ischemic stroke (69%↑), and hemorrhagic stroke (18%↑), while consumption of <12 g per day was associated with a reduced relative risk of total stroke (17%↓) and ischemic stroke (20%↓), and consumption of 12 to 24 g per day was associated with a reduced relative risk of ischemic stroke (28%↓). These results indicate that heavy alcohol consumption increases the relative risk of stroke, while light or moderate alcohol consumption may protect against total and ischemic stroke.

Although moderate consumption of alcohol confers a decreased risk of acute myocardial infarction, the role of the type of beverage consumed, the pattern of drinking, and the consumption with meals is unclear. Mukamal and colleagues (16) from Boston, Massachusetts, studied the association of alcohol consumption and acute myocardial infarction among 38,077 male health professionals who were free of cardiovascular disease and cancer at baseline. During the 12-year follow-up (1986–1998), there were 1418 cases (4%) of acute myocardial infarction. Compared with men who consumed alcohol less than once per week, men who consumed alcohol 3–4 or 5–7 days per week had decreased risks of acute myocardial infarction (32%↓ and 37%↓, respectively). The risk was similar among men who consumed <10 g of alcohol per drinking day and those who consumed ≥30 g per drinking day. No single type of beverage conferred additional benefit, nor did consumption with meals.

Thus, among men, consumption of alcohol at least 3 to 4 days a week was inversely associated with the risk of acute myocardial infarction. Neither the type of beverage nor the portion consumed with meals substantially altered this association. Men who increased their alcohol consumption by 12.5 g daily during a 40-year period had a further decreased risk of acute myocardial infarction. (A 5-oz [150-mL] glass of wine contains about 20 g of alcohol, a 12-oz [355-mL] container of beer contains approximately 14 g of alcohol, and a 50-mL bottle of spirits contains 20 g of alcohol.)

EFFECTS OF ANTIRETROVIRAL THERAPY ON CARDIOVASCULAR RISK FACTORS

The advent of potent combination antiretroviral therapy has led to a profound decrease in the rate of illness related to AIDS and has significantly improved survival among patients with HIV infection. The success of antiretroviral therapy, however, has been tempered by the occurrence of drug-related toxic effects in many patients. Improvements in AIDS-free survival mean that many people face the prospect of decades of therapy, and concern about long-term toxic effects has now come to the fore. Combination antiretroviral therapy increases serum levels of triglycerides, low-density lipoprotein cholesterol, apolipoprotein B, high-sensitivity C-reactive protein, fibrinogen, insulin, and plasminogen-activator inhibitor type 1 and decreases levels of high-density lipoprotein cholesterol. This therapy increases visceral fat and the thickness of the carotid arteries and decreases

flow-mediated arterial vasodilatation. The therapy also alters fat distribution such that there is peripheral lipoatrophy and visceral adiposity (“lipodystrophy”). All of these metabolic abnormalities may affect cardiovascular risk.

Bozzette and colleagues (17) did a retrospective study of 36,766 patients who received care for HIV infection at Veterans Affairs facilities from January 1993 to June 2001. Approximately 1000 patients received combination therapy with a protease inhibitor for at least 48 months, and approximately 1000 patients received combination therapy with a nonnucleoside reverse-transcriptase inhibitor for at least 24 months. Between 1995 and 2001, the rate of admissions for cardiovascular or cerebral vascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21 to 5 deaths per 100 patient-years. Thus, use of newer therapies for HIV was associated with a large benefit in terms of mortality that was not diminished by any increase in the rate of cardiovascular or cerebral vascular events or related mortality. Fear of accelerated vascular disease, therefore, need not compromise antiretroviral therapy over the short term.

The finding of stable or declining rates of cardiovascular disease concurrent with the introduction of potent combination antiretroviral therapy is particularly noteworthy in light of the fact that approximately 25% of the patients had previously received treatment for conditions known to be associated with increased cardiovascular risk. Importantly, however, the median duration of antiretroviral therapy in the cohort was only 15 months. Therefore, these results do not rule out an increased cardiovascular and cerebral vascular risk that becomes evident only with longer follow-up.

NEPHRON NUMBER AND SYSTEMIC HYPERTENSION

Brenner and colleagues (18–20) proposed nearly 20 years ago that a low number of nephrons increases the risk of both systemic hypertension and progressive renal disease. This hypothesis was based on observations that rat strains with a high complement of nephrons were less susceptible to progressive renal disease. Conversely, in both nonhuman animals and in humans, a reduction in the number of nephrons is associated with systemic hypertension and increased risk of progressive renal disease. Keller and colleagues (21) from Germany designed a study to test the hypothesis that a reduced number of nephrons contributes to essential hypertension in the general population. Using a 3-dimensional stereologic method, they compared the number and volume of glomeruli in 10 white patients aged 35 to 59 years with a history of essential hypertension or left ventricular hypertrophy or both and with renal arteriolar lesions with the number and volume of glomeruli in 10 normotensive subjects matched for sex, age, height, and weight. All 20 subjects had died in accidents. Patients with hypertension had significantly fewer glomeruli per kidney than matched normotensive controls (median 702,379 vs 1,429,200). Patients with hypertension also had a greater glomerular volume than did the controls (median $6.50 \times 10^{-3} \text{ mm}^3$ vs $2.79 \times 10^{-3} \text{ mm}^3$) but very few obsolescent glomeruli. These data thus support the hypothesis that the number of nephrons is reduced in white patients with essential hypertension.

Finding obsolescent glomeruli in the hypertensive kidneys implies ongoing nephron loss, meaning that persons with hypertension most likely had not lost glomeruli over time but rather had a smaller number at birth.

What determines nephron number? All studies to date according to Ingelfinger (22) show that there is a variation among phenotypically normal persons, with some having more nephrons than others. “Perinatal programming,” the term coined to describe the observation that events during gestation can have far-reaching effects in adulthood, was first proposed by Barker and colleagues in 1989 when they observed an inverse relation between birth weight and cardiovascular disease in a cohort of middle-aged British men. Clinical and experimental data amassed since that observation suggest that alterations in intrauterine nutrition, especially protein calorie restriction, may “program” the fetus for later susceptibility to systemic hypertension, cardiovascular disease, and stroke. Studies in experimental models show directly that relatively minor insults, such as protein restriction, can result in fewer nephrons.

The concepts of perinatal programming and hyperfiltration fit well together: persons who undergo intrauterine stress, even fairly subtle, may not develop a full complement of nephrons. Over time, the compensatory efforts of the kidney go awry, leading to increased filtration by each nephron, then subtle dysfunction and scarring and, ultimately, hypertension. Improved nutrition for pregnant women might prevent decreased nephron endowment, which in turn might decrease the frequency of systemic hypertension in susceptible offspring during their adult lives.

VITAMIN A AND BONE FRACTURE

Vitamin A (retinol) in high doses stimulates bone resorption and inhibits bone formation. In addition, a high dietary intake of vitamin A increases the risk of skeletal deformities in human fetuses. The incidence of hip fracture has been shown to be much higher in countries where the intake of vitamin A is very high compared with countries where its intake is low. At least 3 studies have indicated an increased risk of hip fracture and low bone density in women with a high dietary intake of vitamin A.

Michaëlsson and colleagues (23) from Sweden investigated the relation between serum retinol levels and the subsequent risk of fracture among men. They enrolled 2322 men aged 49 to 51 years and analyzed serum retinol and beta carotene levels at enrollment. Fractures were documented in 266 men during 30 years of follow-up. The risk of fracture was highest among men with the highest levels of serum retinol. Men with retinol levels in the 99th percentile had an overall risk of fracture 7 times higher than that of men with lower levels of retinol. The level of serum beta carotene was not associated with a risk of fracture.

Vitamin A is present in liver, kidney, and milk (24). Dairy foods are fortified with small amounts of vitamin A and D in many countries. The provitamin beta carotene is widely distributed in plants and is cleaved to form retinol. Symptoms may occur with either too little or too much vitamin A. The first symptom of vitamin A deficiency is maladaptation to darkness (night blindness), followed in later stages by dryness of the conjunctiva, corneal ulceration, and blindness. Vitamin A deficiency in children is a major cause of blindness in some developing

countries. Acute vitamin A toxicity produces severe illness, and chronic vitamin A toxicity, caused by a high intake of vitamin A (25,000–50,000 IU per day or more) over a long period, is characterized by bone and joint pain, anorexia, nausea and vomiting, and weight loss. In the Nurses' Health Study, a total vitamin intake of ≥ 1.5 mg/day was associated with a 64% increase in hip fracture compared with an intake < 0.5 mg/day.

The Rancho Bernardo study suggested that bone mineral density was optimal when the vitamin A intake was 2000–2800 IU/day (0.6–0.9 mg/day), indicating that both low and high intakes of vitamin A may compromise bone health. The current recommended intake of vitamin A is 0.7 mg/day for women and 0.9 mg/day for men, amounts similar to the optimal intake in the Rancho Bernardo study. The maximal intake considered to be safe is 3 mg/day. The study by Michaëlsson and colleagues suggests that vitamin A supplementation and fortification of food with vitamin A may be harmful in Western countries where the life expectancy is high and the prevalence of osteoporosis is increasing. Serum retinol increases with age, and older persons may be at increased risk for hypervitaminosis A. Supplements containing vitamin A were used by 28% of the participants in the third National Health and Nutrition Examination Survey and by 46% of the women and 38% of the men in the Baltimore Longitudinal Study of Aging. These data suggest that supplements containing vitamin A should not be routinely used by men or women, at least in the Western world, and that fortification of cereals with vitamin A should be questioned. On the other hand, in Africa and Asia where malnutrition in children is common, vitamin A supplementation and fortification of food with vitamin A have been used to prevent xerophthalmia.

PROGNOSTIC SIGNIFICANCE OF COMMUNITY-ACQUIRED PNEUMONIA IN PERSONS ≥ 65 YEARS OF AGE

Kaplan and colleagues (25) from several US medical centers compared all Medicare recipients (age ≥ 65 years) hospitalized with community-acquired pneumonia and controls matched for age, sex, and race hospitalized for reasons other than community-acquired pneumonia. The authors identified 158,960 community-acquired pneumonia patients studied in the first quarter of 1997 and 794,333 hospitalized controls. Hospital mortality rates for the pneumonia group and hospitalized controls were 11.0% and 5.5%, respectively. One-year mortality rates for the pneumonia group and hospitalized controls were 41% and 29%, respectively. One-year mortality rates in hospital survivors of the pneumonia and control cohorts were 34% and 25%, respectively. Almost half of these older patients admitted for community-acquired pneumonia died in the subsequent year, with most deaths occurring after the initial hospital discharge. The mortality was considerably higher than that of either the general population or a control population hospitalized for reasons other than community-acquired pneumonia. Thus, pneumonia in older people is a bad prognostic sign for longevity.

PREVALENCE OF ARTHRITIS OR CHRONIC JOINT SYMPTOMS AMONG ADULTS IN THE USA

In 2001, the estimated prevalence of arthritis/chronic joint symptoms among US adults was 33%, representing approximately 70 million adults, including 11% (22 million) of the adult

population with physician-diagnosis arthritis only, 10% (21 million) with chronic joint symptoms only, and 12% (27 million) with both (26). Prevalence increased with age, and women had a higher prevalence than men. The prevalence ranged from 18% in Hawaii to 43% in West Virginia (median, 33%).

EFFECT OF LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION ON PROGNOSIS IN HYPERTROPHIC CARDIOMYOPATHY

Maron and associates (27) from several large worldwide medical centers assessed the effect of left ventricular outflow tract obstruction on morbidity and mortality in patients with hypertrophic cardiomyopathy (HC) who were followed for a mean of 6 years. Of the 1101 consecutive patients, 273 (25%) had obstruction to left ventricular outflow under resting conditions with a peak instantaneous pressure gradient ≥ 30 mm Hg. Of the 273 patients, 127 (47%) died of HC, and the 146 surviving patients (53%) had a much higher frequency of severe, disabling symptoms of progressive heart failure (functional class III or IV) and stroke than did the 828 patients without outflow obstruction (gradient < 30 mm Hg). The probability of death due to HC and the risk of progression to New York Heart Association class III or IV heart failure or death specifically from heart failure or stroke was significantly greater among patients with obstruction, particularly among those aged ≥ 40 years. Surprisingly, the likelihood of severe symptoms and death related to outflow tract obstruction did not increase as the gradient increased above 30 mm Hg. Thus, among patients with HC, left ventricular outflow tract obstruction at rest is a strong independent predictor of progression to severe symptoms of heart failure and of death.

DEATH DURING CHILDHOOD

In February 2003, a meeting was held in Bellagio, Italy, to refocus the world's attention on child mortality and to establish working groups to fight for resources (28). According to World Health Organization figures, the world's average child mortality rate in the year 2000 was 67 deaths per 1000 live births, a marked improvement from 1990, when the average rate was 85 per 1000. But in Africa, the child mortality rate averages 150 deaths per 1000 live births, a rate 8 times that seen in Europe, and there has been little or no change in child mortality rates over the past 50 years in 7 African countries—Burundi, Lesotho, Madagascar, Mauritania, Nigeria, Sierra Leone, and Tanzania. In 2003, nearly 11 million children will die before they reach the age of 5 years. Of this number, about 6 million will die of diseases that could have been easily prevented or treated: diarrhea (2 million), pneumonia (2.1 million), malaria (1 million), and measles (nearly 1 million). Many of these lives could be saved with the implementation of simple measures.

COMPARISON OF MORTALITY, SEVERE MORBIDITY, AND INJURY IN CHILDREN LIVING WITH ONE PARENT VS THOSE LIVING WITH BOTH PARENTS

Weitof and colleagues (29) from Stockholm, Sweden, assessed overall cause-specific mortality between 1991 and 1998 and risk of hospital admission between 1991 and 1999 for 65,085 children with single parents and 921,257 children with both parents. After adjustment for compounding factors, such as socio-

economic status and parents' addiction or mental disease, children in single-parent households had increased risks compared with those in 2-parent households for psychiatric disease in childhood, suicide attempt, alcohol-related disease, and narcotics-related disease. Boys in single-parent families were more likely to develop psychiatric disease and narcotics-related disease than were girls, and they also had increased risk of all-cause mortality. Thus, growing up in a single-parent family is disadvantageous to the health of the child. Children of single parents have increased risks of mortality, severe morbidity, and injury.

PARENTAL MORTALITY AFTER OFFSPRING MORTALITY

One of life's greatest tragedies is for parents to bury their child. Li and colleagues (30) from Aarhus, Denmark, compared 21,062 parents in Denmark who had a child who had died with 293,745 parents whose children were alive. The authors found an increased overall mortality rate in mothers whose child had died. An excess mortality from natural causes was noted in mothers only during the tenth to eighteenth year of follow-up. Mothers had increased mortality rates from unnatural cause throughout follow-up, with the highest rate recorded during the first 3 years. Bereaved fathers had only an excess mortality from unnatural causes. Thus, the death of a child is associated with an overall increased mortality from both natural and unnatural causes in mothers and an early increased mortality from unnatural causes in fathers.

TWENTY PRIORITIES IN HEALTH CARE

A new report issued by the Institute of Medicine, a division of the National Academy of Sciences that advises the US Congress on medical issues, has recommended to the US government and to private health care organizations that they should focus on 20 medical problems having the broadest impact on the US population, including tobacco addiction, obesity, evidence-based cancer screening, complications such as bed sores and falls associated with the frailty of old age, systemic hypertension, immunization, depression, medical errors, nosocomial infections, pain management, stroke prevention, severe mental illness, diabetes mellitus, asthma, and risk factors for conditions such as coronary heart disease (31).

US POPULATION

The US population as of July 1, 2001, was 285 million persons. The number included 230 million whites, 37 million Hispanics or Latinos (of any race), 196 million whites (not Hispanic or Latino), 36 million blacks or African Americans, nearly 3 million American Indians or Alaska natives, and 0.5 million native Hawaiians and other Pacific Islanders. Latinos accounted for nearly 13% and blacks also nearly 13% of the nation's population. Non-Hispanic whites made up 69% of all US residents. The Hispanic population is growing faster than any other group in the USA. Hispanics in Texas represent 32% of the state's population, while blacks account for slightly less than 12%. By 2005, the state's population will become majority minority, and by about 2030, Hispanics will account for >50% of the state's population (32).

CITIES WITH THE BEST MANNERS

Etiquette expert Marjabelle Young Stewart started compiling her annual list of America's best-mannered cities 26 years ago. The winner in 2002 was Charleston, South Carolina, followed by San Diego, New York, Philadelphia, San Francisco, and Chicago; Dallas came in as number 7, followed by Detroit, Minneapolis, and Seattle (33). Doctors with the best manners seem to have the most patients and the fewest lawsuits.

HEAD TURNING WHILE KISSING

A researcher observed 124 couples kissing in airports, railway stations, parks, and beaches and found that twice as many couples turned their heads to the right as to the left (34).

PHYSICIANS ON STRIKE

In July 2001, a walkout by surgeons forced Las Vegas' only trauma center to close for 10 days. In January 2002, >800 physicians in Florida stayed home from work on a specified Monday, ostensibly saying they were attending a 2-day seminar on insurance costs (35, 36). In Mississippi, physicians from 4 hospitals took leaves of absence, causing county and city officials to declare a state of emergency. Ambulances shuttled patients to hospitals in Alabama and Louisiana. In West Virginia, 24 surgeons took 9-day leaves of absence. Physicians in New Jersey in February began an indefinite work slowdown to protest soaring malpractice costs. Thousands of New Jersey's 22,000 physicians participated. These walkouts were held to protest the medical malpractice crisis. At issue, of course, are pain and suffering damages in malpractice cases. The Bush administration has proposed capping such damages at \$250,000, a position strongly supported by the American Medical Association.

VICTOR HERBERT, MD (1927–2002)

On Christmas Day 1961, Victor Herbert, a young hematologist training at Harvard's Thorndike Memorial Laboratory, awoke feeling nearly paralyzed. He had been starving himself of folic acid for >2 months in an attempt to prove that such a diet, even in the absence of alcoholism or intestinal malabsorption, would induce megaloblastic anemia (37). But Herbert did not believe the folic acid deficiency was causing his paralysis. He thought it was due to the elaborate preparations of his food, which included boiling chicken and applesauce 3 times before eating, procedures that remove most of the potassium. He took some potassium iodine and brought himself to the hospital, where his potassium level was 2.77 mmol/L, far below normal. After potassium supplementation, his paralysis disappeared. After 133 days on his folic acid-depleted diet, his hematocrit had dropped from 48% to 42%, and during that time he had undergone 9 bone marrow aspirations and 1 small intestinal biopsy.

Victor Daniel Herbert was named after his father's cousin, the famous operetta composer. His childhood was spent mainly in orphanages and foster homes. His father died in the Spanish Civil War when Victor was 10, and his mother died from breast cancer when he was 13. In 1948, he graduated from Columbia University with a bachelor's degree in chemistry. He earned his keep during medical school by selling life insurance to his professors. He graduated from medical school in 1952 and after an internship at Walter Reed Army Medical Center, he served in Korea

and then later was on the staff at several medical centers. Later in his career he became an outspoken critic of quackery and fraud in medicine, and in 1974 he obtained a law degree from Columbia to make him a more effective antiquackery activist. He also served as a paratrooper in the Green Beret in World War II, the Korean War, the Vietnam War, and Operation Desert Storm (Kuwait).



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1. Boyce N. Triumph of the helix. *US News & World Report*, February 24/March 3, 2003.
2. Senior K. From the standing start to human genome sequence in 50 years. What was biology really like before Watson and Crick discovered the DNA double helix 50 years ago? *Lancet* 2003;361:580–581.
3. Ross E. Cloned sheep's death raises more questions. *Atlanta Journal-Constitution*, February 15, 2003.
4. DeBoer SW, Thomas RJ, Brekke MJ, Brekke LN, Hoffman RS, Menzel PA, Aase LA, Hayes SN, Kottke TE. Dietary intake of fruits, vegetables, and fat in Olmsted County, Minnesota. *Mayo Clin Proc* 2003;78:161–166.
5. Tonelli M, Moyé L, Sacks FM, Kiberd B, Curhan G, for the Cholesterol and Recurrent Events (CARE) Trial Investigators. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 2003;138:98–104.
6. Nielsen SJ, Popkin BM. Patterns and trends in food portion sizes, 1977–1998. *JAMA* 2003;289:450–453.
7. Lozano JA. Houston gains its 3rd “fat city” title. *Dallas Morning News*, January 3, 2003.
8. Puente M. The right “stuff.” Competitive gluttons belly up to the table to gorge for glory, prizes and charity. *USA Today*, January 31, 2003.
9. George CFP, Kab V, Levy AM. Increased prevalence of sleep-disordered breathing among professional football players. *N Engl J Med* 2003;348:367–368.
10. Kmietowicz Z. UK lags behind many European countries in reducing deaths from heart disease. *BMJ* 2003;326:242.
11. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980–2000. *JAMA* 2002;288:3008–3013.
12. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981–2997.
13. Wing LMH, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GLR, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348:583–592.
14. Frohlich ED. Treating hypertension—what are we to believe? *N Engl J Med* 2003;348:639–641.
15. Reynolds K, Lewis LB, Nolen JDL, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. *JAMA* 2003;289:579–588.
16. Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. *N Engl J Med* 2003;348:109–118.
17. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;348:702–710.
18. Hakim RM, Goldszer RC, Brenner BM. Hypertension and proteinuria: long-term sequelae of uninephrectomy in humans. *Kidney Int* 1984;25:930–936.
19. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure: less of one, more of the other? *Am J Hypertens* 1988;1:335–347.
20. Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 1994;23:171–175.
21. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003;348:101–108.
22. Ingelfinger JR. Is microanatomy destiny? *N Engl J Med* 2003;348:99–100.
23. Michaëlsson K, Lithell H, Vessby B, Melhus H. Serum retinol levels and the risk of fracture. *N Engl J Med* 2003;348:287–294.
24. Lips P. Hypervitaminosis A and fractures. *N Engl J Med* 2003;348:347–349.
25. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, Angus DC. Pneumonia: still the old man's friend? *Arch Intern Med* 2003;163:317–323.
26. Bolen J, Helmick GG, Sacks JJ, Langmaid G. Prevalence of self-reported arthritis or chronic joint symptoms among adults—United States, 2001. *MMWR Morb Mortal Wkly Rep* 2002;51:948–950.
27. Maron MS, Olivetto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295–303.
28. Lancet editorial staff. The world's forgotten children. *Lancet* 2003;361:1.
29. Weitoft GR, Hjern A, Haglund B, Rosén M. Mortality, severe morbidity, and injury in children living with single parents in Sweden: a population-based study. *Lancet* 2003;361:289–295.
30. Li J, Precht DC, Mortensen PB, Olsen J. Mortality in parents after death of a child in Denmark: a nationwide follow-up study. *Lancet* 2003;361:363–367.
31. Gottlieb S. US health care should focus on 20 areas. *BMJ* 2003;326:182.
32. Mittelstadt M. Census: Latinos surpassing blacks. *Dallas Morning News*, January 22, 2003.
33. Associated Press. Charleston wins again, thank you very much. *Dallas Morning News*, January 25, 2003.
34. Güntürkün O. Human behaviour: adult persistence of head-turning asymmetry. *Nature* 2003;421:711.
35. DePaolis M. Physicians' strikes could be contagious. *Star Tribune*, January 31, 2003.
36. Appleby J, Rubin R. New Jersey doctors begin protest. *USA Today*, February 3, 2003.
37. Oransky I. Victor Herbert. *Lancet* 2003;361:353.