Prevention of Obesity and Diabetes

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This is the second of a series of articles reviewing presentations at the 63rd annual scientific session of the American Diabetes Association (ADA), held in New Orleans, Louisiana, June 2003.

The changing shape of childhood

Francine Kaufman gave the outgoing President's Address, discussing our burgeoning societal recognition of obesity as a health problem for children. She traced the differing environments of the child of 40,000 years ago through that experienced today. For the neolithic child, levels of physical activity were high. Approximately one-third of energy intake came from animal protein, typically low in associated fat because animals hunted for meat (as opposed to the high fructose feeds currently used for livestock which greatly increase the saturated fat content of these foods). Half of energy intake was from high-fiber fruits and vegetables, gathered close to home, and the remainder of the diet was high in polyunsaturated fats. Dietary sodium was low. With the advent of agriculture 5,000 years ago, the availability of grain led to greater fat depots in feed animals and began to alter the dietary balance to which humans had evolved. This pattern continued during the development of the civilization of the middle ages and the Renaissance, with the wealthy often exhibiting marked obesity and gluttony being recognized as one of the "seven deadly sins." Although the lower prevalence of diabetes among European ancestry Caucasians may reflect a diminished need for "thrifty genes," Kaufman mentioned a current speculation that diabetes did emerge as a health problem during this period in Europe. According to this hypothesis, the European diabetes gene pool decreased as the food supply increased, while other ethnic groups, particularly with the devastation of the subsequent centuries of European colonial rule, faced periods of extreme hunger for which there was survival advantage to the retention of "thrifty genes" (1).

By 1920, food processing was the largest industry in the U.S. and the legislation of a secure food supply was seen as an important advance. The prohibition of alcohol use at the end of the decade led to increasing popularity of carbonated sweetened beverages. With the development of suburbs and automobiles requiring complexes of highways, and of fast food and frozen foods during the 1950s, imbalance existed between energy intake and energy expenditure and was worsened by subsequent increases in saturated fat intake and decreases in physical activity among children. Total energy intake rose. A typical snack increased from 160 to 250 kcal and a soft drink from 130 to 200 kcal during the period from 1970 to the 1990s. Large sizes became available for the vast majority of food products. Energy expenditure decreased. Television watching, already substantial at 1 h per child per day, increased to 3 h. Physical education in high schools decreased from 2 days to 1 day per week. As a result, rates of obesity increased from 5 to 20% in children, and even more among African Americans and Latinos, with similar statistics available from other countries in the developed world. Considering the "assault" of food and sedentary behavior, Kaufman stated, "Progress has nearly eradicated starvation. . . but no longer makes us healthy and well."

Many parties must be "stakeholders" to reverse these trends. The child's parents "must assume responsibility to offer appropriate foods in appropriate quantities." Schools and communities "must allow safe activity. . . Neighborhood must assure access to nutritious food. . . There must be a healthcare system. . . [that] promotes prevention beyond its own doors." We need appropriate medications, the food industry must promote nutritious foods, and "reasonable portion sizes must be restored." Kaufman also noted that "the media must be used for health promotion. . . [and] must communicate to youth images that are responsible." Furthermore, government "must help set the appropriate agenda." "Everyone in this audience," Kaufman concluded, "has a responsibility to help end this epidemic. . . It is our responsibility to our paleolithic DNA."

Environmental and economic factors leading to the epidemic of obesity

At a symposium on environmental and economic factors leading to the current epidemic of obesity, David Ludwig, Boston, Massachusetts, discussed its epidemiology, noting the recent increases both among adults (2) and children (3), which may be particularly problematic in the latter group, leading to major psychosocial, pulmonary, gastrointestinal, renal, musculoskeletal, renal, cardiovascular, and endocrine effects (4), so that "obesity affects the quality of life in children as severely as cancer." Although excellent advice for treatment of obesity has been available for thousands of years, with Hippocrates stating, "Obese people should perform hard work, eat only once a day, take no baths, and walk naked as much as possible," there must be both genetic factors among individuals who become obese and, given our genetically stable populations, new environmental factors to explain the increased prevalence of obesity.

Physicians are not, Ludwig argued, usually able to help their patients lose weight. Meta-analyses have shown that with intensive diet, there is a maximal weight loss around 11 kg, with substantial regain at 1 year (5), and that in practice, only 15% of people satisfy at least one criterion for successful weight loss (6). Certainly, conventional dietary approaches are not effective (7), with low-fat diets no better than control in some analyses and mixed evidence that high-fat diets are more efficacious. Alternatively, Ludwig stated, adverse environmental in-

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Abbreviations: ADA, American Diabetes Association; DPP, Diabetes Prevention Program; ESRD, end-stage renal disease; FBG, fasting blood glucose; IGT, impaired glucose tolerance; QALY, quality-adjusted life year; UKPDS, U.K. Prospective Diabetes Study.

fluences overwhelm our efforts to maintain healthy lifestyles.

There has been an "invasion" of children's diets by soft drinks, fast food, and high-calorie poor-quality snacks, with per capita soda consumption having increased fivefold over the past 50 years and now comprising >10% of caloric intake for the average adolescent. Fast food has increased from 2 to 15% of calories in children's diets in all aspects of society since the 1970s, leading to food high in refined carbohydrates, high in *trans* fatty acids, low in fiber, and low in vitamins. In a study comparing the daily ingestion of 1,150 ml sugar versus artificially sweetened drinks, the latter decreased calorie intake (8). Over 10 weeks, sugar-sweetened diets led to a 5-lb weight gain (9). Epidemiologic analysis suggests that each additional serving of sugar-sweetened drink per day increases the risk of obesity by 60% (10). In diet recall studies of 6,000 children ages 4–19 from 1994 to 1998, one-third ate "fast food" on any given day, in association with caloric intake of 2,236 cal, as opposed to that of 2,049 cal on days without such food products (11). Fast food eaters have higher BMI (12) and greater risk of developing features of the insulin resistance syndrome. Provision of larger portions leads, not unsurprisingly, to greater calorie intake (13), suggesting the adverse effect of the common sales technique of "supersizing," where for a small additional fee the purchaser can increase caloric intake from, for example, 150 to 600 cal for typical beverages. Worryingly, the proportion of children eating dinner with their families declines with age and has decreased over time, although such meals are associated with healthier nutrient intake (14).

In addition to altered nutritional behavior is the replacement of physical activity by sedentary pursuits, with the risk of obesity increased 12% per weekly hour of television viewing, while it is decreased 10% per weekly hour of moderate physical activity (15).

Ludwig mentioned that the food industry spends $12 billion/year to influence the eating habits of children, encouraging the ingestion of high-calorie low-quality products. Industry-sponsored websites suggest, for example, that soft drinks are useful to prevent dehydration (16). Brand names are linked to toys, games, movies, education tools, and even baby bottles (17). Public schools under financial pressure have curtailed physical education classes, placed fast food and soda vending machines on campus, and contracted school lunch programs to fast food franchises. Government invests inadequately in obesity prevention and underfunds school programs. Ludwig further stated that sugar industry political contributions have exerted influence that led to weakening of U.S. Department of Agriculture nutritional recommendations and that recently threatened the World Health Organization recommendations of lowering dietary sugar.

John C. Peters, Proctor & Gamble, Cincinatti, Ohio, gave a contrasting discussion from the perspective of the food industry. Peters suggested the benefit of partnerships between the public and private industry in addressing the epidemic of obesity, asking, "How did we allow this situation to develop? We rationalize by saying that it's personal responsibility and that because obesity is caused by many factors it is unfair to demonize specific foods [but] this is specious." There are, he stated, diet and exercise behavioral policies and one should improve the environment to influence these positively, but unfortunately these are being influenced in precisely the opposite fashion. "These forces serve to overwhelm our biology. . . [and] place short term over long term. The human costs of obesity are incalculable." Peters suggested that the media should restrict food advertising, in particular that directed at children, and should tax fast food and sugar-sweetened soft drinks, and subsidize fruits and vegetables, instead of making them relatively more rather than less expensive. He agreed that there is need to regulate political contributions from the fast food industry.

It is important, however, Peters noted, to consider the relative contributions of energy intake as opposed to physical inactivity in causing obesity, and to note that what we think are causes may actually be symptoms of deeper social and economic issues. Our society has an abundant, accessible, and affordable food supply, and has strived to reduce the amount of physical labor needed, a productivity effort which has led to increasing demand for more technology and to increased pace of life and time pressure, further causing increased demand for convenience. Our society has undergone major transformation over the past 50 years, with decline in political, religious, and civic participation, loss of informal social connections, dissolution of community, and isolation of individuals. Robert Reich, former Secretary of Labor, has stated that "personal choices about work and life are taking place within a larger set of societal changes. . . work organized and rewarded" (18). The unintentional consequences include obesity. "We have changed our environment more quickly than we know how to change ourselves," said Walter Lippmann in 1915. If proposed solutions are to be based on food disincentives, Peters asked, why not also tax physical inactivity? We need to recognize that our social system rewards productivity and values technology and to provide strong short-term social and individual incentives to make healthy behavior choices.

The western medical model is about being "disease free," but consumers are more interested in happiness than in health; for consumers to call for health, we need to learn how to link this to the perception of happiness. Furthermore, we must provide realistic goals for change to make consumers' management of body weight easier. If the obesity epidemic is caused by weight gain of 1–3 lb/year, requiring only 10–30 kcal/day of excess, the initial goal should be to prevent weight gain in the population. Another way to "close the energy gap" would be to encourage walking a mile daily and/or reducing the amount one eats by 100 kcal daily. Peters described the "America on the move" campaign, which encourages the population to eat less and "move" more, beginning in Colorado, with industry partners including Procter and Gamble, Schwinn Fitness, Kellogg, Coca-Cola, Pepsi, M&M Mars, General Mills, McDonald's, Kraft, and a number of other companies. "Public-private partnerships are key," Peters stated. Furthermore, he continued, private industry can innovate to fill demand for products and services and to reinforce important messages, to help create an environment that supports healthier choices. Private industry, he noted, met the "Healthy People 2000" goal of launching 5,000 new reduced-fat foods 5 years ahead of schedule in 1995. Peters concluded that the health care industry–government collaboration should not lead to perception of conflict of inter-

est but should rather become an accepted approach.

Roland Sturm, from the RAND Corporation, Santa Monica, California, discussed the economics and politics of diet and physical activity, citing as "a puzzle" the question, "Why don't well-intended proposals to improve health receive enthusiastic support?" Every piece of legislation, regulation, or intervention creates winners and losers, he stated, and there are legitimate competing interests, so that the "fast food tax" would be "a real dud" as the public reviles food taxes by a two-third majority, a margin as wide as the approval of cigarette taxes, and industry lobbyists are seen as upholding common sense. He pointed to the internet site, Consumerfreedom.com, which endeavors to encourage people in favor of food industry positions. (Perusal of this site on 18 August 2003 showed articles discussing the harms being done by the "food police" in Texas who are "unilaterally" trying to eliminate "treats" in schools, on how there is an "obesity scare," etc.) Sturm stated, then, that we need to determine what information is required to inform public debate, including data to compare health risks, as not everything (cigarette discontinuation, weight control, exercise, alcohol, illegal drugs, accidents, etc.) can be "the most important," and that we need to determine approaches to pay for any proposed strategy. He stated that the public becomes numbed from "countless health warnings," warning that we must not engage in "single issue advocacy," and that "public health suffers from too much advocacy."

Sturm described a national survey with 10,000 participants that addressed 17 chronic health problems, the main explanatory variables emerging as obesity and age, with cigarettes, overweight (as opposed to obesity), and problem drinking being much less important. If one, then, determines that obesity is the truly important problem that must be brought to the attention of politicians, Sturm further suggested that there is a confusingly large number of hypotheses being advanced as to its causes. He suggested that it is a myth that Americans have less leisure time and exercise less now than they did before the increase in obesity levels 2 decades ago, referring the interested reader to www.ppheal.org for further information on this topic. From 1987 to 2001, he noted, the gross domestic product increased by 50%, while sporting goods sales doubled, although "this is totally dwarfed by the growth of home electronics." Exercise facilities have doubled in membership sales, but sedentary sports-related activities have increased far more. Differential growth may reflect technological innovation, particularly when complementary developments such as the growth of cable television and that of sports viewing coincide. He suggested that it is actually unlikely that advertising can cause the same level of change in preferences.

Since 1965, overall productive activity levels have decreased substantially, while time spent in leisure and, perhaps particularly important, in transportation to and from work, have increased. It is true that most leisure time activity is spent watching television, but this particularly increased between 1965 and 1980, before the increase in mean weight levels. Indeed, leisure time exercise levels have also increased, although one-quarter of the population remains totally inactive and more than half do not meet activity recommendations.

He suggested, then, that it is unclear how one should explain the causes of the epidemic of obesity, and hence what to recommend as a cure, given that exercise levels are not actually decreasing and that the increase in food supply "overexplains" the prevalence of obesity. Strum characterized two competing views of ways to address this as the economic versus public health views. The economist suggests that one intervene only if there is failure of market forces. As examples, he gave "external factors" such as underprovision of public recreational services, making it difficult for children to have outlets for exercise or lack of information about healthful exercise because of changes in education. The public health perspective, in contrast, is that one should intervene based on expert opinions that make it likely that health could be improved.

As an economist, he asked whether obesity trends indeed reflect market failure. Firms will, he suggested, always provide products for which there is demand, whether for physical activity, sedentary entertainment, or water with sugar and flavoring added. Low food prices and the convenience of prepared food do contribute to obesity, but he pointed out that one should not consider easy availability of food, which is necessary for life, as necessarily being bad! He characterized the lack of safe neighborhoods to walk or bicycle, however, as indeed being a "market failure" for which there are not good private substitutes. Urban sprawl, without destinations in walkable distance, may have been caused by zoning laws isolating workplaces from residential areas that were appropriate in past decades when work activity differed substantially from that in which most people are currently engaged. It may, then, be appropriate to increase gasoline and car prices to reflect the social costs of automobile driving.

Increased prevalence of type 2 diabetes in youth

At a symposium addressing the role of physical activity and nutrition in the development of type 2 diabetes among children, Pietro Galassetti, Irvine, California, discussed the impact of physical activity and of fitness on glucose regulation in children. Fitness is defined as "the optimal adjustment to physical activity of a series of systems and tissues including the cardiorespiratory system, the muscle, bone, and connective tissue, the brain. . . and the regulation of energy metabolism." Exercise testing in children is limited by the size of the apparatus, usually a cycle ergometer or treadmill. Oxygen uptake increases linearly at a rate of ~10 ml O_2 consumption per watt per minute, a relationship which holds in males and females and at all ages. Maximal oxygen uptake ($V_{O_{2max}}$) corresponds to the plateau of this level, which children may not be able to achieve. Other assessments of fitness include square wave exercise increments, and children with diabetes may require a longer time to reach steady-state oxygen uptake under such circumstances. With mild exercise at 25% $V_{O_{2max}}$, there is little breakdown of muscle glycogen and most energy comes from plasma fatty acids. With moderate or extreme exercise at 65 and 85% $V_{O_{2max}}$, glycogen breakdown becomes important. In children, the decrease in intercellular pH is less marked with exercise because of lower levels of phosphocreatinine generation.

In "real life," Galassetti noted, people do not maintain constant levels of exercise, but rather exercise intensively but intermittently, with intermediate periods of resting. Fat storage during periods of increased energy intake is normally balanced by periods of fat utilization with

exercise. For example, African Pigmies utilize large amounts of energy when walking away from their villages for hunting. "We maintain the genes for that wide range of foraging," Galassetti stated, and so "humans maintain their fat depots." The regulation of body composition involves fat storage in adipocytes, with exercise involving the physiologic reduction in insulin levels and release of epinephrine and growth hormone resulting in lipolysis. If a high-fat meal is ingested before intense exercise, the growth hormone response is reduced, which may have effects on long-term growth and development in children. In obese children, the physiologic growth hormone response is markedly reduced and the epinephrine response attenuated, potentially further modifying energy balance. Fat is present within muscle fibers, in both obese and nonobese adults and children, presumably with more marked autocrine and paracrine effects of this tissue in obese than nonobese children, who have higher interleukin-6 and tumor necrosis factor-α and lower adiponectin levels. In children, there appears to be a body composition threshold at 70% of age-adjusted body weight, above which fitness levels decrease. Ongoing exercise increases insulin sensitivity via increasing GLUT4-mediated muscle glucose transport. In a sense, there is early aging of the system with obesity, which attenuates multiple beneficial effects of exercise. There is, however, an exponential inverse correlation between fitness and insulin sensitivity, suggesting that a small improvement in fitness may have important effects in improving overall metabolism, so "the targets are accessible."

Bernard Gutin, Augusta, Georgia, discussed physical activity and body composition during growth and development, contrasting epidemiologic and physiologic studies, the former allowing more long-term follow-up assessment. Exercise and diet influence general and visceral adiposity, as well as fitness, with potential effects on numerous cardiovascular risk factors. Using dual-energy X-ray absorptiometry for analysis of fat mass, fat-free soft tissue, and bone mineral density and MRI for measurement of visceral adipose tissue, he showed that the ratio of subcutaneous-to-visceral abdominal fat in children is ~6, while in adults a ratio of 2 is more typical. $V\text{O}_{2max}$ is difficult to use in assessment of fitness in children, as noted by Galassetti, with approximately half of children not achieving this level. The increase in heart rate versus O_2 consumption may be a better way of measuring fitness in children. Cross-sectional studies show that lower adiposity and higher fitness are associated with reducing type 2 diabetes risk. Leaner adolescents have "higher energy throughput," with more exercise but paradoxically with greater caloric intake than in obese children. Vigorous physical activity leads to protein turnover and synthesis and then to a greater partitioning of ingested energy into fat-free mass. This is also associated with higher cardiovascular fitness. This in turn tends to encourage greater physical activity, further leading to greater energy throughput with lower body fat. Under such circumstances, adequate nutrient intake is more likely, with, for example, calcium intake important and dieting therefore less desirable for children than exercise.

Gutin described a study in children over the 85th percentile in body weight participating in an exercise program for 4 months, 5 days per week for 40 min daily. Heart rate monitoring was used to assess and encourage intensity of exercise. The exercise program was associated with reduction in body fat levels, in association with decreases in insulin levels, with increase in body fat noted after cessation of the exercise program.

Another study comparing lifestyle education without exercise with moderate-intensity (65% $V\text{O}_{2max}$) long-duration or high-intensity (>75% $V\text{O}_{2max}$) shorter-duration physical training found the latter somewhat more effective in improving fitness despite similar caloric expenditure, with visceral adipose tissue decreasing similarly and improvements in lipids (HDL, triglyceride, and LDL size) with both physical training interventions. "If you are obese and have an unfavorable level [of fitness] at baseline," Gutin stated, "you are most likely to show a favorable effect." Addressing prevention, a study of nonobese adolescent girls participating in 90-min exercise sessions showed reduced accretion of fat mass.

Robert Berkowitz, Philadelphia, Pennsylvania, discussed weight management programs for children, addressing behavioral and pharmacological treatment. He pointed out the enormous increases in obesity that have occurred over the past decade. Programs that endeavor to modify behavior by setting goals, monitoring behavior, and reinforcing behavior change can result in significant weight loss and weight loss maintenance for children, suggesting benefit. Family participation is essential to implement these protocols, and often the overweight parent is actively trying to also lose weight. Portion-controlled diets that are low in fat and high in vegetable content are important, as is "behavioral hygiene," i.e., making sure that the child has a balanced diet and does not skip meals and planning for high-risk situations such as social eating situations. Other approaches, including reduction of food stimuli in the home, trying to reduce foods of high caloric density, and encouraging children to eat more slowly.

In 10-year studies, either treating both the child and parent or treating the child alone with such an approach was beneficial. Treatment of the child alone stabilized weight, and the family approach was associated with actual weight loss. Structured lifestyle exercise programs show that building exercise into the "everyday life" (e.g., encouraging children to walk to school), has long-term benefits, while not requiring the same investment in facilities of actual exercise programs. "The problem is," Berkowitz stated, "when you do nothing [after completion of an intervention], 6 months later they're all back to baseline."

For obese adolescents, like adults, relapse rates are high, and pharmacologic approaches may be reasonable. In a study of adolescents with mean BMI 38 kg/m^2 treated with a comprehensive family-based behavioral intervention, placebo was compared with the serotonin and norepinephrine reuptake inhibitor sibutramine 15 mg daily for 6 months. Those receiving placebo had 4% weight loss, while those treated with sibutramine had 8.5% weight loss. Waist circumference decreased by 3 vs. 8 cm. Fifteen vs. 40% of the placebo versus sibutramine groups lost 10 and 3% vs. 20% lost 15% of baseline weight. Hunger scores were decreased with sibutramine. Adherence to the behavior program was associated with 6% weight loss in placebo group and with 12% weight loss in the sibutramine group. In a subsequent open-label study, weight loss was maintained in the intervention group through 12 months and increased in the placebo group to levels achieved in those receiving sibutramine

for 12 months. Triglyceride, HDL, and LDL cholesterol improved, as did fasting insulin levels. Blood pressure and pulse were slightly higher with sibutramine. The adverse effects of sibutramine include increased blood pressure and pulse, seen in ~15% of treated individuals. Orlistat is now being studied in obese adolescents and appears to show benefit. Interestingly, interventions appear to be equally successful in lower and higher income and socioeconomic groups. Thus, for children, both family-based behavioral intervention and pharmacologic intervention may be useful.

Robert McMurray, Chapel Hill, North Carolina, discussed the use of school- and community-based programs to implement these endeavors. "The kids are there most of the day," he pointed out, providing opportunities to address both activity and nutrition. Presently, there is little effective physical activity occurring during physical education classes, and these classes are often being reduced or eliminated in schools. It is certainly possible to improve this, "but it is going to take a lot of work." Not all studies, including some of the largest ones, have shown an effect of school-based interventions. Approaches can include increasing exercise in physical education and nutritional counseling and encouraging afterschool activities, with girls showing better response than boys. A risk-based approach keeping overweight children in their regular classes to stress exercise and nutritional counseling can modify body fat, although not reducing body weight. Addressing glycemic status, insulin levels have been shown to decrease in a number of studies, with suggestion of decrease in glycemic response to a meal, with exercise particularly lowering insulin among those children with highest baseline levels. In a 3-year study of Zuni Indian youth, changes in diet (particularly assisting the children to reduce sweetened beverages) and exercise led to reductions in postload glucose and insulin levels. A proposed program aimed at increasing fruits and vegetables, decreasing soft drinks, and increasing exercise over a number of years in ~60 schools would give important further information about the potential usefulness of this approach.

Is diabetes prevention cost-effective?

A lecture given by Robert Ratner, Washington, DC, at the Mount Sinai Diabetes Seminar Series, New York, New York, on 30 January 2003, offered a useful introduction to a debate at the ADA meeting (*vide infra*) on the economics of diabetes prevention. Ratner suggested that knowledge of the "intermediate states" of impaired fasting glucose or impaired glucose tolerance (IGT) implies that ~17 and 10% of adult men and women, respectively, have "pre-diabetes," with higher prevalence greater in Hispanics. In 1992, 3% of people in the U.S. had diabetes and accounted for 12% of direct health care costs. One-third of Medicare expenditures, Ratner stated, are for individuals with diabetes. Adults with diabetes, compared with those without, lose 8.3 vs. 1.7 days of work annually, must restrict physical activity 21.7 vs. 6.8 days annually, and have 7.8 vs. 3.0 bed-disability days per year. The economic impact in excess of chronic complications and general medical conditions accounted in 1997 for $12 and $25 billion in costs, respectively, while diabetes treatment per se had a cost of ~7 billion dollars.

A number of terms are used in economic analyses. "Cost-savings" refers to reduction in costs, regardless of outcome; "cost benefit" compares benefits from resources in competing uses, "cost-effectiveness" compares cost per health outcome for alternative interventions, and "cost utility" is the incremental cost per quality-adjusted life year (QALY). The QALY scale sets 1 year of perfect health at 1 QALY, 1 year dead at 0 QALY, with representative intermediary values: 1 year with blindness at 0.69 QALY, 1 year with lower extremity amputation at 0.70 QALY, and 1 year with end-stage renal disease (ESRD) at 0.32 QALY. Ratner noted, "Nothing is cheaper than a dead patient," and stated, "We have to accept the fact, we are going to spend more, the question is how much." Acceptable cost, he stated, is <$20,000/QALY, such as the cost of childhood vaccination, while an unacceptable cost (from the perspective public policy) is >$100,000/QALY, such as the cost of performing liver transplantation for alcoholic cirrhosis.

Application of the Diabetes Control and Complications Trial data to all people in the U.S. with diabetes suggests that intensive glycemic treatment would prevent 764,000 person-years of blindness, 87,000 person-years of renal failure, and 556,000 person-years with amputation, leading to 700,000 additional years of life, with an increase in QALY by 1 million years, for an incremental cost/QALY gained of $16,002 (19). This compares favorably with treatment of hypertension, at a cost of $20–60,000/QALY, depending on the blood pressure at which one starts treatment (20). The cost of diabetes treatment/QALY is less with worse control at baseline, at $135,000, $35,000, and $15,000/QALY for those with initial HbA_{1c} 8, 9, and 12%. The U.K. Prospective Diabetes Study (UKPDS) showed even greater evidence of cost-effectiveness, with total costs of diabetes treatment plus treatment of complications similar for intensive versus conventional treatment. If the later costs of complication treatment than diabetes treatment are discounted, glycemic treatment remains highly cost-effective (21).

The Diabetes Prevention Program (DPP) was designed with prospective assessment of economic factors for the 3,234 participants with IGT, whose fasting blood glucose (FBG) and 2-h blood glucose levels were 95–125 and 140–199 mg/dl, respectively, with mean age 51 years, BMI 34 kg/m^2, 68% women, and 45% from minority populations. Specific costs included those of the intensive lifestyle intervention with monthly follow-up ($3,198), 850 mg metformin twice daily and quarterly follow-up ($2,960), and placebo with quarterly follow-up ($497), while total per-person medical costs for the three groups during the period of study were $27,334, $26,216, and $23,804, respectively. Diabetes decreased 58 and 31% over 2.8 years in the two intervention groups, leading to respective costs per case of diabetes prevented of $15,665 and $31,338 (22). The lifestyle and metformin interventions, compared with placebo, led to gains of 0.072 and 0.022 QALYs per patient treated, respectively, for costs per QALY of $51,582 and $99,171. Ratner noted that with generic metformin, cost decreases to ~$14,000, and that the use of group (rather than "one-on-one") lifestyle intervention with 10 people at each session would decrease cost to ~$13,000, decreasing cost per QALY to $29,000 and $35,000 for lifestyle and metformin. To be fair, one might add the cost of identification of individuals with pre-diabetes, which involved screening of 158,037 people and performance of 30,984 glucose tolerance tests to randomize 3,819 people, for a recruitment cost of

~$1,200 per person randomized. Algorithms such as those using FBG with history, examination, and lipids to better diagnose diabetes and IGT might lessen this cost (23).

At the ADA meeting debate, William Herman, Ann Arbor, Michigan, used the DPP data to argue that both the lifestyle and metformin interventions are cost-beneficial (in the sense given above), not merely during the period of observation but actually over the lifetime of a person at risk of developing diabetes, using 55 and 30% respective decreases in diabetes over 3.2 years (slightly different from the 2.8-year follow-up results) and giving a lifetime simulation of the effects of the DPP recommendations. For treatment of IGT, lifestyle cost was greatest in year 1 and discounting at 3% annually was used to compare these costs with the later costs incurred for metformin treatment and with development of diabetes (based on the DPP experience) and with development of diabetes complications (based on a variety of existing studies). In the simulation, Herman stated that metformin cost $1,400 more than placebo, with a gain of 0.3 QALY, while the lifestyle intervention cost $3,500 less, with a gain of 0.8 QALY, based on the projection that 66, 77, and 85% of subjects in the lifestyle, metformin, and placebo interventions, respectively, would develop diabetes, with projection of decreased microvascular and macrovascular complications and increased life expectancy for the lifestyle and metformin interventions. This analysis, then, suggested that the identification of individuals with IGT and use of lifestyle intervention is cost-saving, reducing diabetes 26%, increasing life expectancy 1.1 years, decreasing blindness 36%, ESRD 42%, amputation 35%, stroke 6%, and coronary heart disease 8%. Metformin would be projected to cost ~$6,000 per QALY, decreasing diabetes 9%, increasing life expectancy 0.4 years, and reducing cumulative blindness 18%, ESRD 17%, amputation 15%, stroke 6, and coronary heart disease 3%.

Herman described a variety of changes made in the simulation to assess the robustness of the conclusions. If the DPP intervention were implemented for just 3 years, lifestyle intervention would still be cost-saving and the cost of metformin would decrease slightly to $4,000 per QALY. If lifestyle used a group rather than individual intervention and metformin costs were calculated with generic pricing, both interventions became cost-saving. A 20% lower effectiveness in routine clinical practice reduced but did not eliminate the cost-saving of the lifestyle intervention, while the cost of metformin increased to $12,000/QALY. With both lower cost and lower effectiveness, both interventions were still cost-saving, resulting in net improvements in QALY. Thus, he suggested that a policy change to promote both interventions in high-risk individuals with IGT was appropriate, although pointing out the need to evaluate the long-term effectiveness and sustainability of the interventions.

David Eddy, Aspen, Colorado, "came to a very different conclusion" with a simulation model he used to analyze approaches to prevention of diabetes. "The interventions themselves are rather expensive," he noted, giving a variety of perspectives from which to view potential costs and benefits. He used a simulation entitled the "Archimedes model," which attempts to simulate patients and illnesses with "physiology models," and each part of the health care system separately and in detail with "models of care processes" over a continuous rather than intermittent simulation of time to assess potential costs (24).

In simulations, Eddy showed evidence that the model was highly effective in predicting the actual results of the DPP, the UKPDS, and many other controlled studies, with an overall correlation coefficient of 0.993. Using this model, it was possible to simulate a continuation of the DPP protocol for 30 years, including long-term outcomes and costs, using a diabetes treatment approach similar to that in the UKPDS. He noted that weight loss appears to be the main "driver" of the benefit of the DPP lifestyle intervention, and stated that this is "more than just prevention," and if continued after the point of development of diabetes, it would be an important ongoing portion of diabetes treatment. He projected that relative diabetes reduction, however, decreased from 58% at 3 years to 46% at 4 years, 19% at 20 years, and 16% at 30 years, with overall absolute reduction in diabetes of 11%, "so you can see what's happening, it's gradually decreasing over time." Further, he noted that the rate of development of diabetes depends on the definition used. If the FBG alone rather than a glucose tolerance test were used in the DPP for the definition of diabetes, the rates of diabetes development would be substantially decreased, so that the absolute decrease would be 9, 6, or 2% with cutoff FBG levels >125, >140, or (for symptomatic diabetes) >180, respectively, used in defining diabetes. Thus, based on the Archimedes model, Eddy stated, "We believe that continuing the DPP would have a power of 8%" at 20 years for determining differences in CVD outcome. As, he pointed out, "it is unlikely that the [long-term] effectiveness of this program will ever be demonstrated in a controlled trial," he analyzed the potential outcome benefit that would be seen with this effect. At 30 years, he suggested that 50% of placebo participants will have had a diabetes complication and 13% will have died as a result. However, with lifestyle intervention there is a potential for an ~8% decrease in these outcomes, so that "every pound will decrease risk by about 1%."

From the perspective of a health plan enrolling 100,000 individuals, of whom 3.5% have "pre-diabetes," 550 vs. 500 myocardial infarctions might then be expected to occur with no intervention versus lifestyle intervention, while he suggested that the cost for the cohort would be $200 million with no intervention and would increase by ~$50 million over 30 years with the lifestyle intervention. The savings, he stated, would only offset ~15% of the cost of the intervention, and the cost to prevent one myocardial infarction would be ~$900,000. For cost-saving, a plan must spend only ~$100/person/year.

From the perspective of the country overall, with ~10 million pre-diabetic individuals, there would be a cost of ~$5 billion annually. The lifestyle group would gain ~0.2 QALYs at a cost of $10,000 per person. "The real benefits and the savings," he stated, are however "out into the future." In the first year, the cost is $2,500,000/QALY, at year 10 it is $250,000/QALY, and only at year 30 does the cost decrease to $67,000/QALY. Eddy summarized, "Losing weight is effective, [but] the issue is the cost." He suggested that intensive lifestyle intervention might best be initiated when the FBG exceeds 125 mg/dl, rather than at the pre-diabetes stage.

Although there may be weaknesses in the models proposed by the two discussants (as argued in a subsequent question-and-answer session), one is left believing

that as a society, we are indeed developing approaches that will lead to the prevention of both diabetes and obesity.

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