EDITORIALS

TODAY — A Stark Glimpse of Tomorrow

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Caloric intake that exceeds energy expended and its consequences, particularly development of type 2 diabetes mellitus, is emblematic of a climate change for modern medicine — a phenomenon so complex, embedded in culture and economics, and intertwined with conflicts between individual freedom and societal health that solutions are difficult to envision. Chronic caloric surplus (rather than obesity itself) is a central cause of epidemic type 2 diabetes,[1] but differences in response to energy excess,[2-4] disproportionately present among disadvantaged youth, increase susceptibility to type 2 diabetes in early life. Indeed, the percentage of type 2 diabetes in cases of new-onset diabetes in adolescence has increased from 3% a few decades ago to approximately 50% today.[5] Because complications increase with the duration of diabetes, it is critical to improve prevention and treatment strategies for affected youth.

In an impressive effort, the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study, now reported in the *Journal*, randomly assigned 699 young people with type 2 diabetes to test how well metformin alone, metformin plus rosiglitazone, and metformin plus an intensive lifestyle-intervention program maintained glycemic control (a glycated hemoglobin level of <8%) for a minimum of 2 years.[6] The recruitment and retention of demographically representative participants and the implementation of a lifestyle-intervention program in children and adolescents is laudable. However, the results of the study were discouraging — 52% of participants treated with metformin alone had treatment failure, metformin plus lifestyle intervention did not significantly improve glycemic control and achieved targeted weight loss in only 31% (and this weight loss was apparently transitory in many participants), and the addition of rosiglitazone to metformin improved durable glycemic control, but 39% still had treatment failure. Furthermore, the failure rate with metformin monotherapy appeared higher than that in recently diagnosed adult patients. Thus, these data imply that most youth with type 2 diabetes will require multiple oral agents or insulin therapy within a few years after diagnosis.

Do these results put a nail in the coffin of lifestyle modification and endorse add-on drugs to treat type 2 diabetes in children? Reasons to resist this notion may lie in the study design and analysis. The study's focus on the comparison of metformin alone with metformin plus lifestyle change or metformin plus rosiglitazone, without comparison of the two combination treatments, overshadows the fact that failure rates of the metformin-plus-lifestyle and metformin-plus-rosiglitazone groups did not differ significantly. With regard to secondary outcomes, participants in the metformin-plus-lifestyle group gained less fat mass than those in the metformin-plus-rosiglitazone group, a result that could reduce the risk of other diseases associated with obesity. In addition, possible sex[7] and racial differences in the effect of lifestyle change on glycemic control hint that effective strategies to prevent type 2 diabetes and slow its progression may vary.

Critics may conclude that the lack of meaningful weight loss in most participants in the metformin-plus-lifestyle group points to poor adherence, rather than representing an indictment of lifestyle change itself. Because changes in eating and activity habits were calculated to decrease baseline weight by 7 to 10%,[8] most participants clearly did not adopt these habits, and the feasibility of lifestyle change was evaluated

more than its effect. But this result is still informative, since the assertions that lifestyle change by definition works and that any lack of effect is therefore due to poor adherence constitute a tautology. Indeed, this is the essential, maddening conundrum of the epidemic of type 2 diabetes — collective failure to adhere to a lifestyle healthy enough to prevent the disease. A critical point is that the participants in the TODAY study were not adults, but youth immersed from a young age in a sedentary, calorie-laden environment that may well have induced and now aggravates their type 2 diabetes. Fifty years ago, children did not avoid obesity by making healthy choices; they simply lived in an environment that provided fewer calories and included more physical activity for all. Until a healthier "eat less, move more" environment is created for today's children, lifestyle interventions like that in the TODAY study will fail.

Solace can still be found in the TODAY study, if its larger message transcends its worrisome findings. Illness from childhood overnutrition is a societal and cultural problem that current medicines treat but cannot resolve. For a substantial proportion of those millions of children at risk for largely preventable type 2 diabetes, the findings of the TODAY study reinforce the idea that medications and even procedures[9] will not stave off a lifetime of illness. Furthermore, lifestyle changes for youth are undermined by immersion in an obesogenic world, in which personal responsibility appears to be invalidated by the limits of willpower[10] with respect to overnutrition. The stark message from the TODAY study is that, tomorrow and beyond, public-policy approaches — sufficient economic incentives to produce and purchase healthy foods[11] and to build safe environments that require physical movement — and not simply the prescription of more and better pills will be necessary to stem the epidemic of type 2 diabetes and its associated morbidity.

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Hormonal Contraceptives and Arterial Thrombosis — Not Risk-free but Safe Enough

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The link between combined estrogen–progestin oral contraceptives and venous and arterial thrombosis was made soon after these products were marketed, in the early 1960s.[1-3] By 1970, the doses of estrogen in combined estrogen–progestin oral contraceptives had already been lowered on the basis of epidemiologic data showing that formulations with higher estrogen doses were associated with increased vascular risks.[4] Studies published in 1995 and 1996 showed that increases in the risk of venous thromboembolism were greater with newly marketed estrogen–progestin oral-contraceptive formulations containing desogestrel and gestodene than with formulations