EDITORIALS

Weight-Loss Diets for the Prevention and Treatment of Obesity

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No medical condition has generated as many dietary remedies as obesity. All diets have their followers, but hard data on the efficacy of the diets are scarce. In this issue of the *Journal*, Sacks et al.[1] report the results of a large, long-term trial that tested the efficacy of weight-loss diets that were high or low in carbohydrates, protein, or fat. High-carbohydrate, low-fat diets became popular approximately 20 years ago, when it was thought that calories from carbohydrates were less fattening than the same number of calories from fat. A high-fat, low-carbohydrate diet was popularized by Dr. Robert Atkins in the 1970s[2] and recently enjoyed a revival. The appeal of high-protein diets is that protein is thought to provide more satiation per calorie than fat or carbohydrates.

The trial by Sacks et al. lasted longer than most, the dropout rate was low, treatment was intensive, and compliance was assessed with objective biomarkers.[1] Unfortunately, the dietary goals were only partly achieved. Protein intake was intended to differ by 10% of energy between the high-protein-diet group and the average-protein-diet group, but the actual difference, as assessed by the measurement of urinary nitrogen excretion, was 1 to 2% of energy (according to my calculations, which were based on a diet that provided 1700 kcal per day). Extreme carbohydrate intakes also proved hard to achieve. When fat is replaced isocalorically by carbohydrate, high-density lipoprotein (HDL) cholesterol decreases in a predictable fashion.[3] The authors used the difference in the change in HDL cholesterol levels between the lowest- and highest-carbohydrate groups to calculate the difference in carbohydrate content between those diets. That difference turned out to be 6% of energy instead of the planned 30%.

The reduction in caloric intake was also not sustained. Weight loss averaged 6 kg at 6 months, which fits reasonably with the planned daily deficit of 750 kcal. However, after 12 months, subjects started to regain weight, which suggests that they were eating more than planned. Final weight losses averaged 3 to 4 kg after 2 years. This weight loss is similar to the weight loss that can be achieved with pharmacotherapy, and it is a clinically relevant effect that will slow the onset of type 2 diabetes.[4,5] To that extent, all the diets were successful. But the weight regain during the second year, although slow, suggests that in the end many participants might have regained their original weight even if treatment had continued.

Within each diet group, some participants achieved much better weight loss than others. Participants who lost more weight attended more counseling sessions and adhered more closely to the prescribed dietary composition. These observations led Sacks et al. to conclude that behavioral factors rather than macronutrient composition are the main influences on weight loss. That is a plausible hypothesis, and it has been observed before,[6] but the present data do not allow a firm conclusion to be reached, because differences in macronutrient intake were too small.

Even if the planned differences in macronutrient intake had been achieved, the absence of blinding would have made it difficult to ascribe the effect of a particular diet to protein, fat, or carbohydrate molecules. Weight-loss studies are behavioral studies; they require participants to eat less. Cognition and feelings have a huge impact on such behavior. Participants may eat less not because of the protein or carbohydrate content of a diet but because of the diet's reputation or nov-

elty or because of the taste of particular foods in the diet. Specific effects of fat, protein, and carbohydrates on food intake and body weight can be determined only when all diets look and taste the same. Studies that have accomplished this goal with the use of porridges (similar to oatmeal) and standardized snacks[7] or with covertly manipulated foods[8] have been carried out for short periods, but few subjects would be willing to eat those foods for the several years that would be needed to examine long-term effects. Therefore, this issue is unlikely to be settled soon. If behavior rather than diet composition is the key to weight loss, macronutrient composition may be of secondary importance anyway.

The inability of the volunteers to maintain their diets must give us pause. The study was led by seasoned investigators who were experienced in the performance of diet and drug trials. The participants were highly educated, enthusiastic, and carefully selected. They were offered 59 group and 13 individual training sessions over the course of 2 years. Nonetheless, their body-mass index (the weight in kilograms divided by the square of the height in meters) after 2 years averaged 31 to 32 and was moving up again. Thus, even these highly motivated, intelligent participants who were coached by expert professionals could not achieve the weight losses needed to reverse the obesity epidemic. The results would probably have been worse among poor, uneducated subjects.[9] Evidently, individual treatment is powerless against an environment that offers so many high-calorie foods and labor-saving devices.

It is obvious by now that weight losses among participants in diet trials will at best average 3 to 4 kg after 2 to 4 years[10] and that they will be less among people who are poor or uneducated, groups that are hit hardest by obesity.[9] We do not need another diet trial; we need a change of paradigm.

A little-noticed study in France may point the way.[11] A community-based effort to prevent overweight in schoolchildren began in two small towns in France in 2000. Everyone from the mayor to shop owners, schoolteachers, doctors, pharmacists, caterers, restaurant owners, sports associations, the media, scientists, and various branches of town government joined in an effort to encourage children to eat better and move around more. The towns built sporting facilities and playgrounds, mapped out walking itineraries, and hired sports instructors. Families were offered cooking workshops, and families at risk were offered individual counseling.

Though this was not a formal randomized trial, the results were remarkable. By 2005 the prevalence of overweight in children had fallen to 8.8%, whereas it had risen to 17.8% in the neighboring comparison towns, in line with the national trend.[11] This total-community approach is now being extended to 200 towns in Europe, under the name EPODE (Ensemble, prévenons l'obésité des enfants [Together, let's prevent obesity in children]).[12]

Like cholera, obesity may be a problem that cannot be solved by individual persons but that requires community action. Evidence for the efficacy of the EPODE[12] approach is only tentative,[11] and what works for small towns in France may not work for Mexico City or rural Louisiana. However, the apparent success of such community interventions suggests that we may need a new approach to preventing and to treating obesity and that it must be a total-environment approach that involves and activates entire neighborhoods and communities. It is an approach that deserves serious investigation, because the only effective alternative that we have at present for halting the obesity epidemic is large-scale gastric surgery.

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The Will-o'-the-Wisp of Genetics — Hunting for the Azoospermia Factor Gene

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It has been known for decades that the Y chromosome carries genes required for spermatogenesis and male fertility. But it has been frustratingly difficult to pin down the relevant genes, to such an extent that a finding reported by Luddi et al.[1] in this issue of the *Journal* — that the ubiquitin-specific peptidase 9, Y-linked gene (*USP9Y*) is not essential for normal spermatogenesis — represents a noteworthy advance in the field.

Approximately 15% of couples have difficulty conceiving; the causes are many and include genetic factors. The most common known genetic causes of spermatogenic failure are karyotype anomalies and Y-chromosome microdeletions. Karyotype analysis and screening for Yq deletions are now routine diagnostic tests that are able to help elucidate both the cause of spermatogenic perturbations and their clinical consequences. It is therefore of some interest to know which genes are essential to spermatogenesis; with this information, a more specific diagnosis might be possible, and the clinical management — including genetic counseling — of infertile couples would be greatly improved.

The search for these genes began in 1976, when Tiepolo and Zuffardi[2] reported cytogenetically visible microdeletions in Yq in six azoospermic men. Such deletions must be very large to be visible and are therefore likely to involve the absence of many genes (and unlikely to reveal the causal gene), but this observation provided a starting point for a classic approach to identifying the gene or genes responsible for this phenotype. Smaller deletions within the Yq interval would be sought using molecular methods, leading to the identification of one or a few candidate genes, and inactivating mutations would then be used to confirm which of the candidates was responsible. This strategy has proved successful in the identification of the causal genes underlying countless single-gene disorders since its initial application to chronic granulomatous disease in 1986.[3]

At first, the application of this approach for Y-chromosomal spermatogenic abnormalities seemed promising. Molecular analysis did indeed identify smaller deletions within Yq that were specific to men with spermatogenic failure. These were classified, on the basis of chromosomal location, as three azoospermia factor (AZF) regions: *AZFa*, *AZFb*, and *AZFc*.[4] *AZFb* and *AZFc* were later shown to contain large segments of duplicated sequence and, in fact, to overlap each other. Given the challenge of tracking down specific loci in chromosomal regions enriched in sequence duplications, it is perhaps understandable that the gene or genes responsible for the *AZFb–AZFc* spermatogenesis phenotype have still not been identified.

In contrast, the *AZFa* interval consists of regular single-copy DNA (i.e., DNA that does not contain a supranormal level of repeated sequence) that should not present unusual complications for homing in on the key gene. And in 1999, Sun et al.[5] described what seemed to be a definitive result. They sequenced the two genes in the *AZFa* region (*USP9Y* and the DEAD [Asp–Glu–Ala–Asp] box polypeptide 3, Y-linked gene, *DDX3Y*) in 576 infertile men and discovered exactly the kind of mutation they were looking for, in a man with spermatogenic failure: a de novo deletion of 4 bp within the *USP9Y* gene that destroyed a splice-donor site, resulting in the skipping of the next exon and truncation of approximately 90% of the peptide sequence (Fig. 1). Thus, it appeared that the loss of *USP9Y* was responsible for the observed azoospermia and that one gene underlying spermatogenic failure had been successfully found.