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An inconvenient truth about obesity

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The 4-part Home Box Office (HBO) documentary on obesity entitled, "The Weight of the Nation" (theweightofthenation.hbo.com/) was aired in May of this year. Two years in the making, this timely documentary was produced in conjunction with two of the most prestigious biomedical institutions in the US – the Institute of Medicine and the National Institutes of Health (NIH) – and top US health officials were featured in the series and enlisted to promote it in media appearances. The documentary appropriately focuses on the health implications of obesity for current and future generations and explains how it results from complex interactions between inherited and environmental factors. It also highlights the important contributions to obesity risk made by unhealthy dietary and exercise habits and concludes with an impassioned plea for lifestyle change at the national level.

The show's call for healthier diet and exercise habits is well justified, given alarming recent increases of both obesity prevalence and per capita energy intake [1]. Growing evidence indicates that such "lifestyle intervention" has important potential to reduce the risk of developing not only obesity itself, but obesity-related complications, based on data from the Diabetes Prevention Program (DPP) [2]. This NIH-sponsored clinical trial was appropriately praised in the HBO documentary because it demonstrates that weight loss induced by lifestyle intervention substantially reduces the risk of type 2 diabetes. Given its many benefits and the lack of any real downside (unless you are in the fast food business), efforts to educate the public about healthier dietary choices and how to implement them would seem to make perfect sense. But what if there were a downside?

At issue here is that the HBO documentary also implies that healthier diet and exercise habits are effective for the treatment of obesity. While there is little question that this type of intervention can reduce disease risk and limit weight gain, the claim that obesity itself can be effectively managed with these tools is much harder to justify. This is because weight lost through caloric restriction or lifestyle intervention tends to be regained over time [2–4]. This phenomenon can be traced to a biological process termed "energy homeostasis", which employs humoral signals and the neurocircuits upon which they act to achieve highly accurate matching of energy intake to energy expenditure over extended time intervals [5–7]. Activation of this system is easily detected when body fat mass deviates from its defended level, as occurs following weight loss induced by voluntary calorie restriction. The homeostatic response to this challenge includes both an increase in the drive to eat and a decreased rate of energy expenditure [8,9]. This combination persists until lost weight is regained, at which point food intake and energy expenditure also return to baseline values. Since these responses occur in obese as well as lean individuals, obesity can be viewed as a regulatory disorder characterized by an increase in the defended level of body fat stores [7], and it is for this reason that voluntary weight loss is so difficult to maintain.

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Should we therefore conclude that we have no say over our weight and that obesity is inevitable among susceptible individuals? Certainly not. Obesity risk is determined by interactions involving many extrinsic (diet, activity level and socioeconomic) as well as intrinsic (e.g., genetic, epigenetic, and developmental) factors, and a compelling case can be made for lifestyle intervention as a strategy for reducing obesity risk; i.e., as the linchpin of efforts aimed at obesity prevention. Once obesity is established, however, lifestyle modification is of limited benefit for those seeking to achieve a sustained reduction of body weight, because in most instances weight lost through this approach will eventually be regained [2–4].

The precision with which energy balance is maintained over time in normal individuals is nothing short of remarkable. Consider that a healthy adult weighing 75 kg typically consumes ~1 million kilo-calories each year, and that a mismatch of just 1% (e.g., expending 10,000 fewer kilocalories per year, or 27 kcal fewer per day, than are consumed) will yield a body fat increase of 1.1 kg after 1 yr. For individuals displaying smaller changes of weight on an annual basis, therefore, energy intake and expenditure must by definition be balanced with >99% accuracy. That this type of accuracy is the rule rather than the exception among non-obese individuals is supported by a recent 10-year observational study of 15,624 healthy Swedish women [10]. In this cohort, the average annual weight gain was only 0.33 kg/yr, indicating not only that the participants were on average >99.5% accurate in their annual matching of energy intake to expenditure, but that this held true over 10 consecutive years of observation.

This degree of body weight stability is all the more impressive when one considers what each of us knows from our own, day-to-day experience: we eat more on some days than others, and are also more active on some days than others. Unlike what is observed over long time intervals, therefore, energy balance mismatch is the rule when measured on a day-to-day basis. Consistent with this conclusion is a study [11] showing that in military cadets, energy intake and energy expenditure were completely unrelated to one another when measured on a day-to-day basis, but became highly interrelated when assessed over longer time intervals. These and other observations [12] collectively suggest that the energy homeostasis system functions over long time intervals to correct for energy mismatch in the short-term.

A key mediator of this long-term matching of energy intake and expenditure is the hormone leptin, which is secreted by adipocytes in proportion to body fat mass [5,13,14], and acts in the brain as a negative feedback regulator of adiposity [5]. In conditions of weight loss, decreased leptin signaling promotes increase of food intake, positive energy balance and fat accumulation [5,13,14]. These responses to reduced plasma leptin levels are mediated by leptin-responsive neurons in the arcuate nucleus (ARC) and other hypothalamic nuclei [5], as well as in extra-hypothalamic regions involved in satiety processing and food reward [15]. The ARC is a major site for sensing and integrating input from leptin along with other peripheral energy balance signals (e.g., hormones such insulin and ghrelin, and nutrients such as fatty acids, amino acids and glucose) [5]. Among leptin-sensitive neuron subpopulations in the ARC are those that express pro-opiomelanocortin (POMC) and release melanocortin peptides such as α-MSH that inhibit food intake, and these neurons are stimulated by leptin [5]. Melanocortin signaling appears to play a key physiological role to defend against excess fat gain, particularly during exposure to energy-dense, highly palatable foods [16,17]. Located adjacent to POMC cells are neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP, an endogenous antagonist of the melanocortin-4 receptor) that are inhibited by leptin [5] and stimulate feeding behavior [18]. NPY/AgRP neurons are also GABAergic, and GABA is implicated as an important regulator of feeding released by these neurons [19,20].

In response to weight lost by dieting, therefore, reduced input from leptin and related negative feedback signals trigger activation of NPY/AgRP neurons, whereas POMC cells are inhibited, and this combination potently increases food intake, reduces energy expenditure and hence favors weight gain [5]. These responses persist until lost fat has been recovered and appear to be operative in obese as well as lean individuals.

As noted earlier, the HBO series appropriately praises the DPP for its definitive demonstration that lifestyle intervention lowers diabetes risk among obese individuals. During the first year of the study, the lifestyle intervention group (n=910) achieved an average weight loss of ~7% through diet and exercise, and this effect was associated with a dramatic reduction of diabetes risk (−58% and −34% relative to controls after 3 yr and 10 yr of observation, respectively). The success of the DPP, now recognized as a landmark study, gave rise to a follow-up study known as “Look AHEAD” [21] that investigates whether weight loss induced by lifestyle intervention can reduce morbidity and mortality in patients with established type 2 diabetes.

An unheralded but very robust finding from both the DPP and Look AHEAD trials is the tendency to regain weight lost through lifestyle intervention. Specifically, the mean body weight of subjects in the lifestyle intervention group of the DPP began to rise more or less immediately following their initial 7% weight loss. This trend continued, slowly but steadily, until body weights finally converged with control values by Year 10 [2], and a similar trend is playing out in 4-year data from the Look AHEAD trial [21]. Given the large sample sizes and meticulous long-term monitoring, DPP data stand as perhaps the most clear and compelling demonstration that weight lost through lifestyle intervention is eventually regained. Unlike the considerable emphasis placed on the benefits of lifestyle intervention, this outcome was not mentioned in either “The Weight of the Nation” or the associated media appearances by public health officials.

Why would both the show’s producers and leading health officials choose not to address what amounts to the single largest obstacle to obesity treatment? Perhaps they reasoned that acknowledging the inexorable recovery of lost weight would send a “defeatist” message in conflict with their advocacy of healthier lifestyle choices. As understandable as this decision may seem, it has several very negative consequences. First, the very public assertion that a healthier lifestyle is the solution to the obesity problem places blame for obesity treatment failure squarely on the shoulders of the obese, thereby sparing from any accountability the scientific community and health care providers, who have accomplished so little where nonsurgical obesity treatment options are concerned. Second, it turns a blind eye to the disorder of energy homeostasis that lies at the heart of why obesity is so resistant to treatment. Efforts to identify more effective treatment strategies have long been hindered by our limited understanding of how the defended level of body weight becomes elevated in the first place. Treatment breakthroughs will continue to prove elusive if the scientific community, health care providers and public health officials choose not to acknowledge the underlying problem.

Of perhaps greatest concern is that the scientific community and public health officials are entrusted by society to communicate relevant health information without bias. Of course, we can all endorse the call for a healthier lifestyle, but we must be realistic about what it can and cannot accomplish – including that it is not by itself an effective approach to long-term obesity treatment. If we withhold specific information because it conflicts with some other message that we are trying to send, this scientific “cherry-picking” will ultimately be uncovered, to the detriment of the public trust that the scientific establishment currently enjoys.

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