Title
Childhood obesity: Adrift in the "Limbic Triangle"

Journal
Annual Review of Medicine, 59

ISSN
0066-4219

Authors
Mietus-Snyder, Michele L.
Lustig, Robert H.

Publication Date
2008

Peer reviewed

Childhood obesity: caught (or lost) in the "limbic triangle"

Michele L. Mietus-Snyder, M.D.

Robert H. Lustig, M.D.

From the Department of Pediatrics, University of California San Francisco, San Francisco, CA 94143

Key words: obesity,

Address correspondence to:

Michele Mietus-Snyder, M.D.

The usual (and newer) suspects: causes or markers of the obesity epidemic?

The steady increase in both the prevalence and severity of childhood obesity over the past three decades{Flegal, 2000 #13} has continued unabated despite the parallel increased attention science and society have devoted to this problem.{Ogden, 2006 #944} It currently seems unlikely that America will reach the ambitious goal set forth in Healthy People 2010 to reduce the prevalence of obese children to 5 percent.{, #947} This is not for lack of knowledge of the First Law of Thermodynamics, normally interpreted to implicate behaviors of increased caloric intake and/or decreased energy expenditure. Nor is it for lack of appreciation of the severity of either the personal health burden{Schwimmer, 2003 #432} or societal cost of this burgeoning epidemic.{Wang, 2002 #22}

A wealth of evidence supports a role for decreased physical activity,{Strong, 2005 #773} increased television time,{Robinson, 2001 #576; , 2001 #957} and increased consumption of sugar-sweetened beverages{Ludwig, 2001 #960; James, 2004 #961; Berkey, 2004 #958} in the current rise in childhood obesity. Less compelling data suggest that lack of breastfeeding,{Arenz, 2004 #963; Owen, 2005 #964} skipping breakfast,{Barton, 2005 #968; Dubois, 2006 #966; Fiore, 2006 #967} reduced intake of fruits, vegetables,{Epstein, 2001 #972; Jen, 2007 #973} and other sources of dietary fiber,{Murakami, 2007 #975; Lairon, 2007 #976} fewer family meals,{Veugelers, 2005 #965} and more fast food restaurant dining{Ebbeling, 2004 #977} also contribute to current obesity trends. Although legislation and health policy are attempting to tackle some of these putative root causes,{Schwartz, 2007 #954; Hill, 2007 #986} numerous formidable individual, community, industrial, and societal barriers impede progress. A recent review made a compelling case for ten additional factors that favor persistent weight gain despite our best medical-social efforts to reverse this epidemic: sleep debt; endocrine disruptors

in the food chain; decreased variability in ambient temperature due to heating and air conditioning; decreased smoking; increased use of pharmacotherapies (notably steroids and antipsychotics that alter energy balance); demographic changes towards ethnicities with higher prevalence of obesity; and towards older age brackets more likely to accumulate extra adiposity; a parallel increase in gravida age; greater reproductive fitness at moderate degrees of overweight {Kelly-Weeder, 2006 #1006}); and assortative mating selection for obesigenic genes.{Keith, 2006 #985} Others posit that the obesity epidemic may be exacerbated by the preponderance of chronic stress in modern life, coupled with frequent dieting or self-imposed food restriction, with synergistic effects that increase the reward value of palatable foods.{Adams, in press #1040} The increasing prevalence of micronutrient deficiencies in energy-dense diets can be linked to numerous chronic conditions including obesity.{Molnar, 2004 #624}{Ames, 2006 #893} A link between modern changes in our ancient gut microbial flora and the increasing prevalence of metabolic syndrome, type 2 diabetes, and obesity has also been postulated.{Blaser, 2006 #1039}

While the contribution of any one of these risk factors may be small, their combined impact is likely considerable, and possibly synergistic.{Swinburn, 2004 #983} Indeed, the combination of risk factors coupled with our modern environment seems to make weight gain the default mechanism for the majority of the human species, as exemplified by the increasing prevalence of childhood obesity worldwide.{Ebbeling, 2002 #1038} People seem to be as likely to know what to do to maintain a healthful lifestyle as to not do it. Health awareness and attitude improved with a public health media campaign over time, but without parallel changes in health behavior.{Thorson, 2004 #1052} Even more concerning is the lack of efficacy with almost every lifestyle intervention attempted in children (Montori,

Center for Weight and Health. 2001 Pediatric overweight: a review of the

literature.http://www.cnr.berkeley.edu/cwh/news/announcements.shtml#lit_review

Summerbell, C.D., Ashton, V., Campbell, K.J., Edmunds, L., Kelly, S, Waters, E. 2003 Interventions for treating obesity in children. Cochrane Database Syst. Rev. CD001872) . Obese children who fail lifestyle interventions are often deemed "non-compliant", but it is increasingly clear that individual effort is a poor match for "genetics" coupled with a "toxic environment".

We will attempt here to link the complex network of genetic, behavioral, and environmental barriers that thwart our best attempts to restore or even maintain a healthy body weight. We propose that three human physiologic mechanisms underpinning energy homeostasis contribute to our current mismatch between health knowledge and behavior, favoring weight gain.

How much of our ingestive behavior do we really control?

Genetics

The identification of several exceedingly rare Mendelian monogenic syndromes affecting powerful hunger and satiety pathways{Farooqi, 2006 #945} has deepened our understanding of genetics in the elaboration of common obesity. Mutations in genes for leptin, leptin receptor, proopiomelanocortin, prohormone convertase 1, melanocortin 4 and 3 receptors, and SIM1 all disrupt the physiological crosstalk between peripheral signals and the hypothalamic receptors for satiety and hunger. Mutations of the melanocortin-4 receptor gene represent the most common monogenic mutation, accounting for approximately 5% children with morbid obesity.{Vaisse, 2000 #367} The other monogenic conditions together have been identified in fewer than two dozen individuals worldwide.{Farooqi, 2004 #988} Defects in these genes and their regulatory pathways lead to a phenotype of abnormal eating behavior and/or energy expenditure that results

in positive energy balance from birth. Although these mutations are sporadic, they have changed the common perception that weight gain is purely volitional.

Epigenetics

Heritability for obesity has been suggested at approximately 50% by twin and other genetic studies;{Maes, 1997 #952} yet the sheer magnitude and the rapidity of the obesity epidemic outpaces the timeline required for genetic change. The more recent application of covariance structure analysis of body mass index (BMI) using monozygotic, dizygotic, and virtual twin pairs (same-age unrelated siblings) has found a significant non-genetic influence on BMI.{Segal, 2002 #953} This suggests that obesity is rarely genetic destiny, but more often a tendency towards increased energy efficiency that can be sealed as 'epigenetic fate' when the genome is coupled with a "toxic" environment.{Gallou-Kabani, 2005 #1008; Lustig, 2006 #955}

These nature-nurture epigenetic interactions that lock physiologic pathways into predictable phenotypes are thought to occur after conception but before birth. The "*fetal origins hypothesis*" {Barker, 2004, 1248} states that some aspect of the *in utero* environment contributes to the development of obesity and diabetes in later life. This is seen in babies born small or large for gestational age (SGA, LGA) or premature, who later develop obesity, insulin resistance, and Type 2 diabetes. This phenomenon of prenatal programming can be replicated in animal models of caloric restriction during pregnancy leading to SGA status at birth,{Petry, 2000, 1297; Simmons, 2001, 1300} and the development of obesity and diabetes in adulthood {Vickers, 2000, 1296}. Similarly, gestational diabetes mellitus, as well as simple maternal obesity or excessive weight gain during pregnancy, are significant risk factors for fetal hyperinsulinemia and LGA status,{Catalano, 2001 #1016} which also confers lifelong predisposition to obesity

and the metabolic syndrome.{Carrapato, 2003 #1018; Silverman, 1998 #1017} Thus, in addition to the "thrifty genotype", converging data support the hypothesis that individuals may experience energy conserving epigenetic programming during perinatal development that may even be transmitted to the next generation.{Gallou-Kabani, 2005 #1008}

The energy überfuhrer; brain regions that control redundant mechanisms favoring weight gain

The control centers for appetite regulatory signals and energy expenditure at the root of the energy mismatch lie deep within three areas of the primitive limbic system of the brain. Each of these centers perceives a separate but complementary sensation which drives ingestive behavior.

The ventromedial hypothalamus and starvation

A few morphologically well-defined regions within the ventromedial hypothalamus (VMH), composed of the ventromedial nucleus (VMN) and arcuate nucleus (ARC), mediate complex afferent and efferent neuroendocrine signals necessary for energy homeostatsis. VMH neurons contain receptors for and receive afferent signals related to: adiposity (leptin), nutrient metabolism (insulin), hunger (ghrelin), and satiety (peptide YY_{3-36}).{Lustig, 2006 #703} The VMH in turn transduces these afferent hormonal signals via the paraventricular nucleus (PVN) and lateral hypothalamic area (LHA), through neurons containing the melanocortin-4 receptor, to either stimulate or suppress appetite, and to adjust energy expenditure accordingly {Balthasar, 2005 #1009}. Efferent signals are then transmitted which activate either of the two components of the autonomic nervous system; sympathetic activation promotes energy expenditure via gluconeogenesis and lipolysis, while parasympathetic activation promotes energy storage through lipogenesis. Decline in leptin signal transduction is interpreted by the VMH as

"starvation", which promotes sympathetic reduction to conserve energy, and parasympathetic activation to store energy {Lustig, in press #1011}. This phenomenon is at work in animal models with VMH lesions {Rohner-Jeanrenaud, 1980 #996} and in children with brain tumors{Lustig, 2002 #1041} which manifest neurally-mediated pancreatic insulin hypersecretion, sympathetic reduction, and intractable weight gain,{Rohner-Jeanrenaud, 1980 #996} even upon food restriction.(Bray,G.A., Gallagher,T.F. 1975 Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. Medicine 54:301-333.) {Tokunaga, 1989 #997}

The ventral tegmental area, nucleus accumbens, and reward

Positron emission tomography suggest that these hunger and satiety neuronal circuits in the VMH connect several regions of the brain.{Tataranni, 1999 #994} VMH neurons are tightly linked to the rest of the limbic system, where primal emotions, reproductive activity, and survival instinct are housed; such that complex orexigenic and anorexigenic peptides trigger a "mindless" ingestive response. In order to maintain eating as one of the most powerful urges of animal and human behavior, evolution has also made it a rich source of hedonic pleasure and reward. It has been argued that much of the impasse in the efforts to both treat and prevent obesity stem from the intrinsic difficulty of overriding instinct with reason.{Peters, 2002 #987}

The limbic structures of the hedonic pathway that motivate the "reward" of food intake are the ventral tegmental area (VTA) and nucleus accumbens (NA). The NA is also referred to as the "pleasure center" of the brain; this is the brain area responsive to morphine, nicotine, and ethanol. Compulsive food intake is a reflexive reaction to stimulation of this reward pathway, as evidenced by morphine microinjection into the NA.{Bakshi, 1994 #1042; Yeomans, 2002 #1045} Dopamine neurotransmission from the VTA to the NA mediate the reward properties of

food, {Kelley, 2002 #1007} especially under stress.{Dallman, 2005 #884} The palatability of available food further undermines normal satiety signals and motivates energy intake independent of energy need.{Pelchat, 2002 #1012; Erlanson-Albertsson, 2005 #995} Sweet and high fat foods mobilize both opioids and dopamine within the NA and establish hard-wired pathways for craving in these areas that can be identified by functional magnetic resonance imaging.{Pelchat, 2004 #1015} {Kelley, 2002 #1007} In obese subjects, dopamine D_2 receptor abundance is inversely related to BMI, fueling a perceived need for compulsive food intake to provide excess stimulation of depressed circuits. This is consistent with the observation that drugs that block D_2 receptors (e.g. antipsychotics) are associated with a higher risk of obesity.{Volkow, 2005 #1044} Under normal circumstances, leptin and insulin signal adipose and nutrient sufficiency to the VTA, suppressing dopamine neurotransmission to the NA and the reward of food (Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ. 2006 Leptin receptor signaling in midbrain dopamine neurons regulates feeding.Neuron 51:801-10). However, these negative feedback loops are blocked by the states of insulin and leptin resistance that characterize obesity.{Figlewicz, 2006 #1056}

The amygdala and stress

Functional hedonic pathways, with input from the hypothalamus, help mediate satiety when energy stores are replete, but appear to be easily overridden by amygdala activation and resultant stress,{Epel, 2001 #348} a state of physiologic insulin resistance.{Black, 2006 #1057} Numerous lines of evidence suggest that the stress glucocorticoid corticosterone (in the rat) or cortisol (in the human) is essential for the full expression of obesity,{Tokunaga, 1989 #997} and helps to explain the disruptive role that stress plays in weight regulation.{Dallman, 2005 #884}

There is clear animal evidence for the role of stress and glucocorticoids in promoting adiposity and the Metabolic Syndrome. Adrenalectomized (ADX) rats maintained pharmacologically with high levels of corticosterone demonstrate that exogenous fat intake is directly proportional to circulating corticosterone concentrations {La Fleur, 2004 #956; Dallman, 2003 #954}, while amygdala activation by stress is dampened by the ingeston of energy-dense food (Dallman, M.F., Pecoraro, N., Akana, S.F., La Fleur, S.E., Gomez, F., Houshyar, H., Bell, M.E., Bhatnagar, S., Laugero, K.D., Manalo, S. 2003 Chronic stress and obesity: a new view of "comfort food". PNAS 100:11696-11701). In intact rats, corticosterone stimulates eating, particularly of high fat food, and in humans, cortisol administration also increases food intake {Tataranni, 1996, 1105}. Human research shows increased caloric intake of “comfort foods” (i.e. those with high energy density) after acute stress {Epel, 2000, 961; Epel, 2004, 1018; Epel, 2001, 1002}. Lastly, people identifying themselves as “stress-eaters” exhibited significant increases in insulin, weight, and nocturnal cortisol during a stressful period, compared to people who identified themselves as “stress non-eaters” {Epel, 2005, 1017}. Several studies in children have observed relationships between stress and unhealthy dietary practices, including increased snacking,{Oliver, 1999, 1122} and elevated risk for problems with weight during adolescence and adulthood.{Johnson, 2002 #1046} In a controlled study of 9 year olds, children who were both high on dietary restraint and felt more stressed by lab challenges tended to eat more comfort food {Roemmich, 2002, 1121}.

Adipose-Gut-Brain signals that favor weight gain

For all of their overlapping central circuits, food ingestion remains much more complex than drug consumption (don’t understand, do you mean abuse of street drugs?) because it is modulated by both peripheral and central signals.{Volkow, 2005 #1044} Peripheral afferent

hormonal signals continually inform the CNS about the status of hunger vs. satiety. For instance, the stomach peptide ghrelin is a hormone that increases food intake and body weight by stimulating VMH orexigenic neurons.{Cummings, 2007 #1020} Contrary to satiation peptides, ghrelin also increases GI motility and decreases insulin secretion. Levels normally rise during fasting, and fall upon eating, suggesting a role in meal initiation and termination. Increasing evidence indicates that ghrelin also acts on midbrain pathways governing reward through neural circuits that process the hedonic properties of food.{Abizaid, 2006 #1028} Consistent with this notion, a primary effect of ghrelin is to stimulate appetitive aspects of eating behavior and the motivation to obtain food, as indicated, for example, by increased foraging in an animal model.{Keen-Rhinehart, 2005 #1026}. Postprandial ghrelin suppression is independent of luminal nutrient exposure in either the stomach or the duodenum, where 80%–90% of this gut peptide is produced, but results instead from neurally transmitted, nonvagal intestinal signals, augmented by insulin, and muted by insulin resistance.{Zwirska-Korczala, 2007 #1051} Fasting ghrelin levels are lower in obesity and states of insulin resistance and fail to decline further with food intake, which may contribute to overeating.{English, 2002 #1053} Other intestinal peptides in the afferent system include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY3-36 (PYY), all of which promote satiety by binding to receptors in the VMH and medulla.{Chaudhri, 2006 #993} As with ghrelin, both fasting and postprandial responses of GLP-1, PYY, and CCK levels are diminished in obese as compared with normal controls, potentially further contributing to dysfunctional appetite regulation.{Zwirska-Korczala, 2007 #1051} Furthermore, while these hunger and satiety signals confer protection against obesity in normal-weight individuals, differential postprandial brain signaling with gut peptides in obese vs. lean individuals suggests neural underpinnings of hyperphagia that would be expected to

favor weight gain.{DelParigi, 2005 #1055} (Michele, is this paragraph on GI hormones really necessary to our thesis? We may want to cut it.)

Insulin is an endogenous leptin antagonist

In addition, the hormones insulin and leptin convey information to the CNS regarding long-term peripheral energy homeostasis. Both hormones are secreted during periods of energy sufficiency, their receptors co-localize to the same VMH and VTA neurons, and both have similarly anorexigenic effects when administered acutely into the cerebrospinal fluid.{Lustig, 2006 #703}. However, obesity is a state of chronic hyperinsulinemia and hyperleptinemia in the face of leptin resistance (and often insulin resistance), and the negative feedback on food intake that should result from VMH exposure to insulin and leptin is ineffective. In obesity, this system paradoxically becomes a positive feedback loop or "vicious cycle."{Niswender, 2003 #1025} Appetite remains uncurbed and weight accrues despite excess energy stores.

Although insulin and leptin bind to separate receptors in the VMH, they share the same signaling cascade, called insulin receptor substrate 2 (IRS2)/phosphatidyl inositol-3-kinase (PI3K) {Niswender, 2003, 878} (**Fig. 2**). It is thought that when insulin levels at the VMH are high, leptin cannot turn on its signaling cascade. Thus, hyperinsulinemia blocks leptin signaling, and is one cause of leptin resistance. Furthermore, leptin transport across the blood brain barrier is impaired by hypertriglyceridemia, which occurs in both starvation and with the insulin resistance of obesity.{Banks, 2006 #1060} In that leptin communicates the level of adipose stores to the brain, leptin resistance in the VMH invokes the "starvation pathway" and promotes increased caloric intake. Leptin resistance in the VTA simultaneously invokes the "hedonic pathway" and promotes increased reward of food.

The constitutional symptoms of obese and starved individuals are very similar; both are associated with fatigue, malaise, lack of activity, inability to motivate, and depression. Both obesity and starvation are states of free fatty acid mobilization and insulin resistance.{Boden, 1998 #1061} In both states, the VMH transduces a deficient leptin signal; in starvation because there is inadequacy of leptin, and in obesity because there is resistance to leptin.{Lustig, 2006 #955} Furthermore, serum leptin concentrations drop precipitously during periods of short-term fasting (within 12 hours), declining faster than body fat stores {Keim, 1998, 876}, which helps explain the recidivism of obesity; the hypothalamus reads a declining leptin signal as starvation and promotes increased energy intake and decreased energy expenditure.

Teleologically, what could be the biological advantage of insulin-leptin hormonal antagonism? Leptin is a necessary signal to the VMH for the initiation of high-energy processes, such as puberty and pregnancy {Flier, 1998, 774}. If leptin signaling were not modulable, the weight accrual required for reproductive competency during puberty and pregnancy would be compromised. The reversible antagonism of peripheral leptin action by insulin is in the best interest of our survival; since insulin causes energy deposition into fat, it makes sense that it should also be the central blocker of leptin. Indeed, both puberty and pregnancy are insulin resistant states with requisite increases in insulin levels.{Li, 2005, 1224} In both, leptin levels increase acutely, and then when adulthood is reached or post-partum, insulin levels fall, weight stabilizes or is lost, and leptin returns back toward baseline {McLachlan, 2006, 1226}.

An ancient "limbic triangle" adapted to starvation, reward, and acute stress promotes persistent weight gain in our modern world of palatable foods and chronic stress

Any process which results in hyperinsulinemia (either due to increased secretion or resistance) is likely to interfere with leptin signal transduction, and promote further weight gain. Each of the members of this “limbic triangle” are capable of promoting hyperinsulinemia in maladaptive circumstances. Chronic insulin action at the VMH, by inhibiting leptin signaling, is interpreted as starvation, which in turns decreases sympathetic activity (reducing energy expenditure) and increases vagal activity (promoting energy storage). Chronic insulin action at the VTA, by inhibiting leptin signaling, dysregulates hedonic reward pathways, which in turn increase food-seeking behavior, especially for high fat and high sugar foods resulting in excessive energy intake. Chronic activation of the amygdala under conditions of stress, depression, or anxiety increases cortisol secretion, itself an orexigen and accumulator of visceral fat, and which promotes insulin resistance to further inhibit leptin and perpetuate the vicious cycle of hyperinsulinemia and accelerated weight gain.

Key risk factors for the current obesity epidemic; i.e. physical inactivity, television viewing, and sugared beverages, are direct stimulators of the “limbic triangle”. The benefits of physical activity are numerous, but improved insulin sensitivity is central to the prevention of obesity,{Gill, 2007 #1076} with benefits in turn on leptin sensitivity and central energy regulation. In the European youth study, cardiorespiratory fitness was more strongly correlated to metabolic risk than total physical activity, but predictably total and vigorous physical activity were inversely associated with metabolic risk.{Rizzo, 2007 #1075} A systematic review of controlled physical activity interventions in children concluded that the main factor distinguishing effective from ineffective lifestyle trials was the provision of moderate to vigorous aerobic activity in the former on a relatively 'compulsory' rather than 'voluntary' basis.{Connelly, 2007 #1074} Exercise is also a proven stress reducer, critical to success of cardiovascular health

promotion efforts.{Tsatsoulis, 2006 #1077; Das, 2006 #830} Television viewing, one of the most modifiable causes of childhood obesity, displaces time for physical activity,{, 2001 #957} provides constant exposure to advertising for high fat, sugar-laden processed foods and the opportunity to mindlessly indulge in them.{Kotz, 1994 #1079} Insulin resistance is promoted by such "junk foods",{Isganaitis, 2005 #656} arguably due to both the abundance of fructose and lack of fiber. Average daily fructose consumption has increased by over 25% over the past 30 years.{Guthrie, 2002 #1062} Animal models demonstrate that high-fructose diets lead to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance.{Jurgens, 2005 #1063} Fructose ingestion has also been shown to suppress ghrelin secretion, perhaps because fructose fails to trigger a postprandial insulin rise.{Teff, 2004 #572} Cohort studies of adults demonstrate that increased fiber intake is inversely associated with weight gain, fasting insulin levels, and risk of T2DM.{Liese, 2005 #1065} An inverse association between fiber intake and the metabolic syndrome has also been described in children.{McKeown, 2004 #1064} Fiber may influence body weight regulation by several mechanisms involving intrinsic, hormonal, and colonic effects, which eventually decrease food intake by promoting satiation (lower meal energy content), satiety (longer duration between meals), or by increasing fat oxidation and decreasing fat storage. Fiber-containing foods engender slower glucose absorption, which lessens the post-prandial insulin surge and decreases lipogenesis.{Pereira, 2001 #1066} In addition, high-fiber meals allow for delivery of undigested triglyceride to the colon, favoring intestinal flora responsible for fermentation to short-chain fatty acids and their absorption improve lipids and insulin sensitivity.{Slavin, 2003 #1068} Archeologists surmise that our ancestors used to consume 100-300 grams of fiber/day; current dietary fiber intake is 12 g/day.{Leach, 2007 #1067} High fiber food choices are generally also lower in glycemic load, which can lower leptin yet raise resting energy expenditure (inferring

improved leptin sensitivity), suggesting that physiologic adaptations to energy metabolism can be modified by dietary composition.{Agus, 2000 #1080} Although little is known about the mechanism for the link between short sleep duration, stress, and obesity, especially among children,{Taheri, 2006 #1071} the disruption of tissue (???) timing that occurs when sleep, food intake, and activity are altered seems to be linked to central molecular clockwork that link circadian and metabolic systems.{Kohsaka, 2007 #1073} (Don't like this sentence, Michele). Sleep is one of the most powerful longitudinal predictors of childhood obesity in prepubertal children.{Reilly, 2005 #1072} and increasing numbers of children are chronically sleep-deprived. This is especially true of obese children, who have been found to get less sleep than those of normal weight.{Hasler, 2004 #1070}

What we're currently doing doesn't work, and why

The need for better approaches to childhood obesity prevention and treatment is clear, but the evidence for efficacy of most weight management strategies remains sparse and conflicted (Montori,

Center for Weight and Health. 2001 Pediatric overweight: a review of the literature.http://www.cnr.berkeley.edu/cwh/news/announcements.shtml#lit_review

Summerbell, C.D., Ashton, V., Campbell, K.J., Edmunds, L., Kelly, S, Waters, E. 2003 Interventions for treating obesity in children. Cochrane Database Syst. Rev. CD001872). This is certainly compounded by our tendency to seek simple reductionist etiologic mechanisms for a chronic, multifactorial, and arguably hard-wired condition.{Robinson, 2005 #950} Given the redundancy of these CNS pathways, the relative ease with which satiety signals are overridden, and the fact that leptin falls prior to insulin during caloric restriction,{Keim, 1998 #1084} it should not be surprising that dieting alone results in almost universal recidivism.

Each of these three CNS limbic paradigms needs to be addressed for lifestyle modification to be effective, which difficult and expensive to achieve. Although nutrition and exercise education is necessary to help individuals negotiate our current "toxic environment" {Peters, 2002 #987}, it is clearly insufficient to reverse the obesity epidemic, in the absence of intensive family-based psychological counseling and effective stress reduction.{Epstein, 1998 #488}

Taking back our health — a chronic care model

The "toxic environment", coupled with activation of the "limbic triangle", conspire to make the maintenance of a normal body weight practically unattainable. In the absence of a continuous and conscious effort to maintain a healthful lifestyle, weight gain seems to be the default mechanism for the majority. Furthermore, due to the starvation response, the reduced weight state is an energy efficient one, with a 20% reduction in expended calories (Leibel,R.L., Rosenbaum,M., Hirsch,J.1995 Changes in energy expenditure resulting from altered body weight. N Engl J Med 332:621-628). Thus, once overweight or obese, the effort required to lose weight and keep it off is considerable, as evidenced by the collective experience of individuals who belong to the National Weight Control Registry. In order to maintain an average weight loss of 30 kg for 5.5 yr, they report continuous effort to restrict food intake, eat a low fat diet, regular breakfast, and engage in high levels of physical activity, averaging 11,000 steps per day.{Wing, 2005 #1030} The majority (62.3%) also watch significantly less television (<10 h/wk) than the reported national average of 28 hr/wk.{Raynor, 2006 #1029} Clearly, this minority of subjects has made the conscious decision that their health is worth the exceptional and sustained effort.

American children watch an average of 3 hr of television daily{Vereecken, 2006 #1081} and most eat a calorie replete but nutritionally poor diet.{Moshfegh, 2005 #923} Most overweight children also fail to meet minimum fitness standards.{Malina, 2007 #1035} Fitness and muscular strength play a central role in whole-body metabolism. Even a relatively small difference of 10 kg in muscle mass could have a significant effect on energy balance, translating to a difference in energy expenditure of 100 kcal/d, assuming a constant rate of protein turnover.{Wolfe, 2006 #1036} If a net of 100 daily kcal could be taken off the daily ledger of energy balance, it has been suggested this could reverse the current steady weight gain responsible for much of the obesity epidemic.{Hill, 2003 #1082} It is reasonable to argue that maintaining muscle tissue in children improves insulin sensitivity, and converting adipose to muscle with exercise can help maintain weight loss. Adding to the challenge however is the harsh reality that achieving metabolic health will be harder for the same children who gain weight more easily.*(can this be referenced?)* (Don't know, and I'm not sure it's true; I would get rid of these two sentences). It is not fair, but it is arguably still worth the effort.

Because prevention of obesity in children is more easily achievable than treatment, the challenge for both physicians and society is to identify more up-front compelling arguments that both their and their childrens' health is worth the effort. It would help considerably if we were able to institutionalize environmental changes that support healthy behaviors.{Schwartz, 2007 #954} The competition that drives a 24/7 din of junk food advertising, and pours high fructose corn syrup, salt, saturated and trans-fats into our most vulnerable developing brains while seducing them to stay seated for the next show, is better funded and ruthlessly profit-oriented. However, health promotion advocates ultimately have the better product to market. A well nourished,

efficient metabolism simply generates a higher quality of life than the churning low level of inflammation associated with obesity and insulin and leptin resistance.{Lustig, 2006 #703}

If you examine our society's response to other stimulators of the "limbic triangle", i.e. tobacco, street drugs, and ethanol, each challenge has been met with governmental policies of education, regulation, and interdiction. But for obesity, only education is currently on the table. The health care industry, health care providers, and the U.S. Government must each acknowledge its unique and critical role in addressing childhood obesity, and act to support implementation of health policies based upon the best available evidence,{Homer, 2007 #948} including increased physical activity, decreased television time, and decreased consumption of sugar-sweetened beverages, including juice. Banning junk food advertising, instituting a penny tax on each teaspoon of fructose, and reinsitutionalizing physical activity as part of every child's afternoon either in school or as an afterschool intramural program, are all ideas that have been floated but currently have enormous political opposition. The school is a natural forum in which to introduce and continually reinforce lifelong nutrition and activity skills as well as provide the built environment in which to practice healthy eating and active living. Children at higher risk need to be identified early, and parental education started immediately. This effort will need additional resources to support a comprehensive multidisciplinary intervention that includes behavioral modification therapy with family participation, and both evaluation and counseling from nutrition, exercise, and medical specialists.

Further research into the application of a chronic care model may begin to close the gap between knowledge and behavior for obese children. Like other addictions, obesity is a chronic condition with periods of abstinence (dieting) and periods of relapse (compulsive eating). Like other

disorders of the “limbic triangle”, treatment will in most cases require continuous care, the use of more effective motivational counseling techniques, and sustainable links of health care provider recommendations to community programs to enhance the sustainability of clinical interventions. Group visits may be more cost effective and have added motivational therapeutic benefit (like Alcoholics Anonymous).{Goldfield, 2001 #1083} However. we must not forget that “an ounce of prevention is worth a pound of cure”. Nowhere is this truer than for childhood obesity. Government and financial incentives and support up front that formally acknowledge the value and necessity of lifestyle change are necessary to save both human and financial resources in the future.

Acknowledgments

The authors would like to thank Drs. Elissa Epel and Mary Dallman, and Ms. Laurel Mellin for their perspective and collegiality.

REFERENCES

1. Gross LS, Li S, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. *Am. J. Clin. Nutr.* 2004;79:774-779.

2. Jurgens H, Haass W, Castaneda TR, et al. Consuming fructose-sweetened beverages increases body adiposity in mice. *Obes. Res.* 2005;13(7):1146-1156.

3. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr. Rev.* 2005;63(5):133-157.

4. Roden M. Mechanisms of disease: hepatic steatosis in type 2 diabetes-pathogenesis and clinical relevance. *Nat. Clin. Pract. Endo. Metab.* 2006;2:335-348.

5. Ludwig DS, Pereira MA, Kroenke CH, et al. Dietary fiber, weight gain, and cardiovascular disease risk factors in young adults. *JAMA.* 1999;282(16):1539-1546.

6. Liese AD, Schulz M, Fang F, et al. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. *Diab. Care.* 2005;28(12):2832-2838.

7. Pereira MA, Ludwig DS. Dietary fiber and body weight regulation. Observations and mechanisms. *Pediatric Clinics of North America.* 2001;48:969-980.

8. Rigaud D, Paycha F, Meulemans A, Merrouche M, Mignon M. Effect of psyllium on gastric emptying, hunger feeling and food intake in normal volunteers: a double blind study. *Eur. J. Clin. Nutr.* 1998;52:239-245.

9. Slavin J. Why whole grains are protective: biological mechanisms. *Proc. Nutr. Soc.* 2003;62(1):129-134.

10. Leach JD. Evolutionary perspective on dietary intake of fibre and colorectal cancer. *Eur. J. Clin. Nutr.* 2007;61(1):140-142.

11. Martlett JA, McBurney MI, Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *Journal of the American Dietetic Association.* 2002;102:993-1000.

12. Taheri S. The link between short sleep duration and obesity: we should recommend more sleep to prevent obesity. *Arch. Dis. Child.* 2006;91:881-884.

13. Sekine M, Yamagami T, Hamanishi S, et al. Parental obesity, lifestyle factors and obesity in preschool children: results of the Toyama birth cohort study. *Journal of Epidemiology.* 2002;12:33-39.

14. Reilly JJ, Armstrong J, Dorosty AR, et al. Early life risk factors for obesity in childhood: cohort study. *BMJ.* 2005;330:1357.