Obesity is rising steadily around the world. Convincing evidence suggests that diet and activity level are not the only factors in this trend—chemical “obesogens” may alter human metabolism and predispose some people to gain weight. Fetal and early-life exposures to certain obesogens may alter some individuals’ metabolism and fat-cell makeup for life. Other obesogenic effects are linked to adulthood exposures.
Focus | Obesogens

The role of environmental chemicals in obesity has garnered increased attention in academic and policy spheres, and was recently acknowledged by the Presidential Task Force on Childhood Obesity and the National Institutes of Health (NIH) Strategic Plan for Obesity Research. “Over the past ten years, and especially the past five years, there’s been a flurry of new data,” says Kristina Thayer, director of the Office of Health Assessment and Translation at the National Toxicology Program (NTP). “There are many studies in both humans and animals. The NTP found real biological plausibility.” In 2011 the NIH launched a 3-year effort to fund research exploring the role of environmental chemical exposures in obesity, type 2 diabetes mellitus, and metabolic syndrome.

Multiple Modes of Action

The main role of fat cells is to store energy and release it when needed. Scientists also now know that fat tissue acts as an endocrine organ, releasing hormones related to appetite and metabolism. Research to date suggests different obesogenic compounds may have different mechanisms of action, some affecting the number of fat cells, others the size of fat cells, and still others the hormones that affect appetite, satiety, food preferences, and energy metabolism. Some obesogenic effects may pass on to later generations through epigenetic changes, heritable modifications to DNA and histone proteins that affect when and how genes are expressed in cells, without altering the actual genetic code.

Bruce Blumberg, a biology professor at the University of California, Irvine, coined the term “obesogen” in 2006 when he discovered that tin-based compounds known as organotins predisposed laboratory mice to gain weight. “If you give tributyltin [TBT] to pregnant mice, their offspring are heavier than those not exposed,” he says. “We’ve altered the physiology of these offspring, so even if they eat normal food, they get slightly fatter.”

Human exposure and health-effect data are relatively rare for organotins, but studies have documented the presence of these compounds in human blood, milk, and...
Obesogens are endocrine disruptors. Many are widespread, and exposures are suspected or confirmed to be quite common. In one 2010 study, Kurunthachalam Kannan, a developmental biologist now retired from the NTP. This pattern of catch-up growth is often observed with developmental exposure to chemicals now thought to be obesogens, including diethylstilbestrol (DES), which Newbold spent the last 30 years studying, using mice as an experimental model. Doctors prescribed DES, a synthetic estrogen, to millions of pregnant women from the late 1930s through the 1970s to prevent miscarriage. The drug caused adverse effects in these women's children, who often experienced reproductive tract abnormalities; “DES daughters” also had a higher risk of reproductive problems, vaginal cancer in adolescence, and breast cancer in adulthood.16 Newbold discovered that low doses of DES administered to mice pre- or neonatally also were associated with weight gain,37 altered expression of obesity-related genes,38,39 and modified hormone levels.18,39

“What we’re seeing is there’s not a difference in the number of fat cells, but the cell itself is larger after exposure to DES,” Newbold says. “There was also a difference in how [fat cells] were distributed—where the fat was more diffuse in utero to TBT, then never again, yet TBT caused a permanent effect.”

Even those at the lower end of the BMI curve are gaining weight. Whatever is happening is happening to everyone, suggesting an environmental trigger.

—Robert H. Lustig
University of California, San Francisco

A Growing List of Potential Obesogens

Obesity is strongly linked with exposure to risk factors during fetal and infant development.15 “There are between fifteen and twenty chemicals that have been shown to cause weight gain, mostly from developmental exposure,” says Jerry Heindel, who leads the extramural research program in obesity at the National Institute of Environmental Health Sciences (NIEHS). However, some obesogens have been hypothesized to affect adults, with epidemiologic studies linking levels of chemicals in human blood with obesity24 and studies showing that certain pharmaceuticals activate PPARγ receptors.15,25

Chemical pesticides in food and water, particularly atrazine and DDE (dichlorodiphenyldichloroethylene—a DDT breakdown product), have been linked to increased BMI in children and insulin resistance in rodents.26,27 Certain pharmaceuticals, such as the diabetes drug Avandia® (rosiglitazone), have been linked to weight gain in humans and animals,31 as have a handful of dietary obesogens, including the soy phytoestrogen genistein28 and monosodium glutamate.29

Most known or suspected obesogens are endocrine disruptors. Many are widespread, and exposures are suspected or confirmed to be quite common. In one 2010 study, Kurunthachalam Kannan, a developmental biologist now retired from the NTP, has a large ligand-binding pocket that can accommodate many chemical structures. When a molecule capable of activating the receptor enters the pocket, it turns on the adipogenic program.9,7

“If you activate PPARγ in a preadipocyte, it becomes a fat cell. If it already is a fat cell, it puts more fat in the cell,” Blumberg says. “TBT is changing the metabolism of exposed animals, predisposing them to make more and bigger fat cells.” PPARγ selectively causes multipotent stromal cells to differentiate into bone or fat, and Blumberg found TBT exposure caused these stem cells to show an increased commitment to becoming adipocytes at the expense of the bone lineage. “The insidious thing is that our animals are exposed in utero to TBT, then never again, yet TBT caused a permanent effect.”

A 65
of fat cells but programs them to incorporate more fat, so there are fewer but very large fat cells,” explains University of Missouri biology professor Frederick vom Saal, who has studied BPA for the past 15 years. “In animals, BPA exposure is producing in animals the kind of outcomes that we see in humans born light at birth: an increase in abdominal fat and glucose intolerance.”

Many endocrine disruptors exhibit an inverted U-shaped dose–response curve, where the most toxic response occurs at intermediate doses. However, in a recent unpublished study, vom Saal found that TBT is changing the metabolism of exposed animals, predisposing them to make more and bigger fat cells.

If you activate PPARγ in a preadipocyte, it becomes a fat cell. If it already is a fat cell, it puts more fat in the cell. TBT is changing the metabolism of exposed animals, predisposing them to make more and bigger fat cells.

—Bruce Blumberg
University of California, Irvine

BPA affected rodent fat cells at very low doses, 1,000 times below the dose that regulatory agencies presume causes no effect in humans, whereas at higher doses he saw no effect. Receptors typically respond to very low levels of hormone, so it makes sense that they may be activated by low levels of an endocrine mimic, whereas high levels of a chemical may actually cause receptors to shut down altogether, preventing any further response. This is known as “receptor downregulation.” As a result, some endocrine disruptors have greater effects at low than at high doses; different mechanisms may be operating.

Still another widespread obesogen is perfluorooctanoic acid (PFOA), a potential endocrine disruptor and known PPARγ agonist. “Pretty much everyone in the U.S. has it in their blood, kids having higher levels than adults, probably because of their habits. They crawl on carpets, on furniture, and put things in their mouth more often,” explains NIEHS biologist Suzanne Fenton. PFOA is a surfactant used for reduction of friction, and it is also used in nonstick cookware, Gore-Tex™ waterproof clothing, Scotchgard™ stain repellant on carpeting, mattresses, and microwavable food items. In 2005 DuPont settled a class-action lawsuit for $107.6 million after its factory outside Parkersburg, West Virginia, tainted nearby drinking water supplies with PFOA. In December 2011 an independent science panel found the first “probable link” between PFOA and a human health outcome, pregnancy-induced hypertension (for more information, see “Pregnancy-Induced Hypertension ‘Probably Linked’ to PFOA Contamination,” p. A59 this issue).

Fenton studied how PFOA levels similar to those in the tainted drinking water affected the hormone levels and weight of rodent offspring exposed in utero. “We gave pregnant mice PFOA only during pregnancy. It has a long half-life, so it hangs around during lactation and gets delivered in milk to babies,” Fenton says. “Once the offspring reached adulthood, they became obese, reaching significantly higher weight levels than controls.”

Exposed offspring also had elevated levels of leptin, a hormone secreted by adipose tissue that affects appetite and metabolism. Leptin normally suppresses appetite, but obese people and animals have elevated leptin levels, leading researchers to suspect the brain can become resistant to its effects. Fenton did not observe weight gain when mice were exposed to PFOA as adults, although her team did find abnormalities in the uterus and mammary gland in exposed adults.

Eye on Prevention
If exposure during pregnancy predisposes people to gain weight, can diet and exercise ultimately make any difference? Blumberg does not consider the situation hopeless. “I would not want to say that obesogen exposure takes away free will or dooms you to be fat,” he says. “However, it will change your metabolic set points for gaining weight. If you have more fat cells and propensity to make more fat cells, and if you eat the typical high-carbohydrate, high-fat diet we eat [in the United States], you probably will get fat.”

Blumberg postulates that the effects of early-life exposure are irreversible, and those people will fight a life-long battle of the bulge. However, if such people reduce their exposure to obesogens, they will also reduce health effects that may arise from ongoing adulthood exposures. Blumberg believes it’s good to reduce exposure to all kinds of endocrine-disrupting chemicals. “Eat organic, filter water, minimize plastic in your life,” he says. “If there’s no benefit and some degree of risk, why expose yourself and your family?”

Heindel hopes the NIH’s new grant-making effort will yield important discoveries. “It’s a very new field, and people are always skeptical of new fields,” he says. “It’s up to us to get more data to show that chemicals are actually interfering with the endocrine system that controls weight gain and metabolism. And there’s still the question of how important is this to humans. We’re never going to know until we get more data.”

“What if this was really true and chemicals are having a significant effect on obesity?” muses Heindel. “If we could show environmental chemicals play a major role, then we could work on reducing exposure during sensitive windows, and that could have a huge effect [on obesity prevalence].” It would change the focus from treating adults who are already obese to preventing obesity before it starts—a fundamental shift in thinking about obesity.

The NIEHS is crafting priorities for research on potential obesogens. Thayer was the primary force behind the workshop “The Role of Environmental Chemicals in the Development of Diabetes and Obesity,” held in January 2011 and cosponsored by the NTP, the Environmental Protection
Known and Suspected Obesogens

Diet
• Fructose
• Genistein
• Monosodium Glutamate

Smoking*
• Nicotine

Pharmaceuticals
• Diethylstilbestrol
• Estradiol

Industrial Chemicals
• Bisphenol A (BPA)
• Organotins
• Perfluorooctanoic Acid (PFOA)
• Phthalates
• Polybrominated Diphenyl Ethers (PBDEs)
• Polychlorinated Biphenyl Ethers (PCBs)

Organophosphate Pesticides
• Chlorpyrifos
• Diazinon
• Parathion

Other Environmental Pollutants
• Benz[a]pyrene
• Fine Particulate Matter (PM_{2.5})
• Lead

* Cigarette smoke is also a source of exposure to benz[a]pyrene and PM_{2.5}.

REFERENCES
1. Costa DL, Steckel RH. Long-term trends in health, welfare, and economic growth in the United States. In: Health and Welfare During Industrialization (Steckel RH, Roud R, eds.). Chicago, IL: The University of Chicago Press (1997).
2. Flegal KM, et al. Prevalence and trends in obesity among US adults, 1999–2008. JAMA 300(5):235–241 (2008); http://dx.doi.org/10.1001/jama.2009.17 (online 17 Jan 2012).
3. Flegal KM, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA; http://dx.doi.org/10.1001/jama.2012.39 (online 17 Jan 2012).
4. Ogden CL, et al. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA; http://dx.doi.org/10.1001/jama.2012.40 (online 17 Jan 2012).
5. WHO. Obesity and overweight. Fact Sheet No. 311 [website]. Geneva, Switzerland: World Health Organization (updated Mar 2011). Available: http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 29 Dec 2011).
6. Klimendik YC, et al. Carcinies in the coal mine: a cross-species analysis of the plurality of obesity epidemics. Proc R Soc Biol Sci 278(1712):1626–1632 (2011); http://dx.doi.org/10.1098/rspb.2010.1890.
7. Lustig RH. Childhood obesity: behavioral aberration or biochemical drive? Reinterpreting the first law of thermodynamics. Nature Clin Pract Endocrinol Metab 2(6):447–458 (2006); http://dx.doi.org/10.1038/sj.npen.12222.
8. Newbold RR, et al. Environmental estrogens and obesity. Mol Cell Endocrinol 304(1-2):84–89 (2009); http://dx.doi.org/10.1016/j.mce.2009.02.024.
9. Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. Birth Defects Res Part C Embryo Today Rev 90(1):34–50 (2011); http://dx.doi.org/10.1002/bdrc.20197.
10. Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. Altern Complement Med 8(2):185–192 (2002); http://dx.doi.org/10.1089/107555302121737479.
11. White House Task Force on Childhood Obesity. Solving the Problem of Childhood Obesity within a Generation (May 2010). Washington, DC: White House Task Force on Childhood Obesity, Executive Office of the President of the United States. Available: http://www.letsmove.gov/sites/letsmove.gov/files/TaskForce_on_Childhood_Obesity_May2010_FinalReport.pdf (accessed 29 Dec 2011).
12. NIH. Strategic Plan for NIH Obesity Research: A Report of the NIH Obesity Task Force. NIH Publication No. 11-5493. Bethesda, MD: National Institutes of Health, U.S. Department of Health and Human Services (2011). Available: http://www.obesityresearch.nih.gov/about/strategic-plan.aspx (accessed 29 Dec 2011).
13. NIH. Role of Environmental Chemical Exposures in the Development of Obesity, Type 2 Diabetes and Metabolic Syndrome (ROI). National Institutes of Health Grants [website]. Bethesda, MD: National Institutes of Health, Department of Health and Human Services (2011). Available: http://grants.nih.gov/grants/guide/pa-files/PA-11-170.html (accessed 29 Dec 2011).
14. Cone M, et al. Diseases and Chemicals: Are Environmental Exposures Fueling Our Worst Epidemics? [panel session]. Presented at: Society of Environmental Journalists 21st Annual Conference, Miami, FL, 21 Oct 2011. Available: http://www.sej.org/initiatives/sej-annual-conferences/AC2011-agenda-friday [accessed 29 Dec 2011].
15. Lustig RH, ed. Obesity before Birth: Maternal and Prenatal Influences on the Offspring. New York, NY: Springer (2010).
16. Janesick A, Blumberg B. Monosodium Glutamate: as the target of obesogens. J Steroid Biochem Mol Biol 12(1-2):1-3 (2011); http://dx.doi.org/10.1016/j.jsbmb.2011.01.005.
17. Li X, et al. The environmental obesogen tributyltin chloride acts via peroxisome proliferator activated receptor gamma to induce adipogenesis in murine 3T3-L1 preadipocytes. J Steroid Biochem Mol Biol 12(1-2):9–15 (2011); http://dx.doi.org/10.1016/j.jsbmb.2011.03.012.
18. Grun Y, Blumberg B. Environmental obesogens: organotins and...
endocrine disruption via nuclear receptor signaling. Endocrinol 147(6):550–555 (2006); http://dx.doi.org/10.1210/en.2005-1129.

19. Kannan K, et al. Occurrence of butyltins in human blood. Environ Sci Technol 33(10):1776–1779 (1999); http://dx.doi.org/10.1021/es990917w.

20. Mino Y, et al. Determination of organotins in human breast milk by gas chromatography with flame photometric detection. J Health Sci 54(2):224–228 (2008); http://dx.doi.org/10.1248/jslfs.54.224.

21. Nielsen JB, Strand J. Butyltin compounds in human liver. Environ Res 88(2):129–133 (2002); http://dx.doi.org/10.1006/eres.2001.4321.

22. Cardwell KD, et al. Tri-butyltin in U.S. market-bought seafood and assessment of human health risks. Hum Ecol Risk Assess 5(2):317–335 (1999); http://dx.doi.org/10.1080/108070399284646.

23. Evins RM, et al. PFRs and the complex journey to obesity. Nat Med 10(4):355–361 (2004); http://dx.doi.org/10.1038/nm1025.

24. Tang-Péronnard JL, et al. Endocrine-disrupting chemicals and obesity development in humans: a review. Obes Res 12(8):622–636 (2004); http://dx.doi.org/10.1111/j.1467-789X.2004.00871.x.

25. Lustig RH. Fructose: metabolic, hedonic, and societal parallels with ethanol. J Am Diet Assoc 110(9):1307–1321 (2010); http://dx.doi.org/10.1016/j.jada.2010.06.038.

26. Vals G, et al. Prenatal concentrations of PCBs, ODE, DDT and overweight in children: a prospective birth cohort study. Environ Health Perspect; http://dx.doi.org/10.1289/ehp.1103862 [online 25 Oct 2011].

27. Lim S, et al. Chronic exposure to the herbicide, atrazine, causes mitochondrial dysfunction and insulin resistance. PLoS ONE 7(3):e35517 (2012); http://dx.doi.org/10.1371/journal.pone.0035517.

28. Penga M, et al. Germline affects adipose tissue deposition in a dose-dependent and gender-specific manner. Endocrinol 147(2):5740–5751 (2006); http://dx.doi.org/10.1210/en.2006-3065.

29. The Endocrine Disruption Exchange (TEDX) List of Potential Endocrine Disruptors (v2.2). Paonia, CO: The Endocrine Disruption Exchange (2011). Available: http://www.endocrine-disruption.com/TEDXListOverview.php [accessed 29 Dec 2011].

30. Kannan K, et al. Organotin compounds, including butyltins and acetylcholines, in house dust from Albany, New York, USA. Arch Environ Contam Toxicol 58:901–907 (2010); http://dx.doi.org/10.1007/s00244-010-9513-6.

31. Stahlhut R, et al. Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ Health Perspect 115(6):876–882 (2007); http://dx.doi.org/10.1289/ehp.9882.

32. von Kries R, et al. Maternal smoking during pregnancy and childhood obesity. Am J Epidemiol 156(10):954–961 (2002); http://dx.doi.org/10.1093/aje/kvf128.

33. Bergmann KE, et al. Early determinants of childhood overweight and adiposity in a birth cohort study: role of birth-feeding. Int J Obes 27(2):162–172 (2003); http://dx.doi.org/10.1038/sj.ijo.0802200.

34. CDC. Smoking & Tobacco Use: Secondhand Smoke (SHS) Facts. (website) Atlanta, GA: Centers for Disease Control and Prevention (updated 21 Mar 2011). Available: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/secondhand_smoke/general_facts/index.htm#disparities [accessed 29 Dec 2011].

35. Gas VJ, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perinatal adipose tissue function. Obes Res 13(6):687–692 (2005); http://dx.doi.org/10.1038/obesity.2005.77.

36. Newbold RR. Diethylstilbestrol (DES) and environmental estrogens influence the developing female reproductive system. In: Endocrine Disruption: Effects on Male and Female Reproductive Systems (Nazi KK, ed.). Boca Raton, FL: CRC Press (1999).

37. Newbold RR. Diethylstilbestrol (DES) and environmental estrogens influence the developing female reproductive system. In: Endocrine Disruption: Effects on Male and Female Reproductive Systems (Nazi KK, ed.). Boca Raton, FL: CRC Press (1999).

38. Newbold RR. Diethylstilbestrol (DES) and environmental estrogens influence the developing female reproductive system. In: Endocrine Disruption: Effects on Male and Female Reproductive Systems (Nazi KK, ed.). Boca Raton, FL: CRC Press (1999).

39. Newbold RR. Diethylstilbestrol (DES) and environmental estrogens influence the developing female reproductive system. In: Endocrine Disruption: Effects on Male and Female Reproductive Systems (Nazi KK, ed.). Boca Raton, FL: CRC Press (1999).

40. Newbold RR. Diethylstilbestrol (DES) and environmental estrogens influence the developing female reproductive system. In: Endocrine Disruption: Effects on Male and Female Reproductive Systems (Nazi KK, ed.). Boca Raton, FL: CRC Press (1999).

41. Welshons WV, et al. Large effects from small exposures. PLoS ONE 5(6):e11243 (2010); http://dx.doi.org/10.1371/journal.pone.0011243.

In one study by NIEHS biologist Suzanne Fenton, mice exposed prenatally to PFOA were more likely than controls to become obese when they reached adulthood.44