Beyond Calories and Exercise:

The Influence of Gut Health and Environmental Chemicals on Obesity and Diabetes

The incidence of diabetes and obesity is a global health crisis. In the Unites States (U.S.) alone, 11.3% (25.6 million) of all people over the age of twenty have diagnosed or undiagnosed diabetes.(CDC 2011) Another 35% are estimated to have pre-diabetes and it is recognized that 11% of these will develop type 2 diabetes each year during the next three years.(CDC 2011; Thayer, Heindel et al. 2012) The total direct medical costs and indirect costs (disability, work loss, premature death) associated with diabetes in the U.S. during 2007 was $174 billion.(CDC 2011) Globally, the prevalence of obesity has doubled since 1980 and it is acknowledged that overweight and obesity contribute to the development of 70% of type 2 diabetes cases. (WHO 2011; Thayer, Heindel et al. 2012) Sadly, the incidence of obesity among U.S. children and adolescents 2-19 years old has tripled in the same timeframe with 16.9% (12.5 million) obese adolescents, providing a grim outlook for future incidence of diabetes.(Thayer, Heindel et al. 2012)

Clearly, excessive calories and a lack of exercise are recognized risk factors for obesity and type 2 diabetes and yet many experts have a growing interest in exploring additional contributing factors outside of these conventional two. In fact, a search of the literature uncovered a wide range of very recent journal articles reviewing knowledge from the last four decades and highlighting new, groundbreaking research in the field of gut health, environmental chemicals, obesity and diabetes. Research has clearly demonstrated that gut heath is uniquely individual, likely contributing to obesity and type 2 diabetes (Walker, Ince et al. 2011; Flint, Scott et al. 2012; Snedeker and Hay 2012) and that environmental chemicals stimulate obesity and diabetes.(Grun and Blumberg 2009; Casals-Casas and Desvergne 2011; Snedeker and Hay 2012; Thayer, Heindel et al. 2012) Cutting edge research is considering the intersection of gut health and environmental chemicals as they impact obesity and diabetes. (Grun and Blumberg 2009; Johnson, Patterson et al. 2012; Snedeker and Hay 2012)

Influence of Gut Health on Obesity and Diabetes

The human gut contains approximately 1000 different bacterial species. These bacteria outnumber the number of human cells by 10x and the gene set of the bacteria living in and on you is roughly 150x the human genome. (Musso, Gambino et al. 2010; Snedeker and Hay 2012) The bulk of these bacteria reside in the large intestine, although they are present throughout the digestive tract in increasing numbers as you progress from the stomach through the three sections of the small intestine and into the large intestine.(Musso, Gambino et al. 2010) This unique set of bacteria, known as the microbiome, is in you and on you, contributing about four pounds of weight to your body and is as metabolically active on a daily basis as your liver! (Jones 2005; Campbell-McBride 2010)

Beyond Calories and Exercise:

The Influence of Gut Health and Environmental Chemicals on Obesity and Diabetes

Your microbiome contributes to immune function, nutrient formation, detoxification, regulation of fat storage, appetite control and energy extraction from nutrients, mostly indigestible carbohydrates. (Musso, Gambino et al. 2010; Snedeker and Hay 2012) In a healthy state, the microbiome identifies dangerous bacteria and neutralizes them, forms vitamins B, K and more through fermentation, suppresses fat storage, increases satiety (the fullness factor) and minimizes energy extraction from indigestible carbohydrates. (Flint, Scott et al. 2012; Snedeker and Hay 2012) In an unhealthy gut, the balance of bacterial species is altered creating several mechanisms leading to obesity and type 2 diabetes risk. Inflammation becomes rampant, excess energy is extracted from foods, fat storage is no longer suppressed leading to weight gain and hormones signaling satiety are shut down creating a constant hunger. (Delzenne and Cani 2010; Musso, Gambino et al. 2010; Flint, Scott et al. 2012) This delicate balance is highlighted in figure 1. (Musso, Gambino et al. 2010)

The most telling studies that support this impact of the gut microbiome and development of disease involve germ free mice and sets of twins. Researchers know that the microbiome of obese mice is different than the microbiome of lean mice. The major difference is that the obese mice have a higher percentage of genes associated with energy extraction.(Turnbaugh, Ley et al. 2006) This has often been labeled an efficient digestive system, making use of every calorie eaten as if the body sensed a hibernation mode. This same phenomena has been shown in sets of twins where one is obese and one is lean. These studies have shown that obesity is associated with a greatly reduced bacterial diversity, demonstrating that the gut microbiota may play a more important role that the genetic makeup of the individuals. The study also suggested that the microbiome is largely inherited from the mothers, although lifestyle issues clearly influence the microbiome over time.(Musso, Gambino et al. 2010)

To test whether the obesity caused the gut change or the gut caused the obesity, researchers then utilized mice that are bred to be "germ free" meaning they have a sterile digestive tract with no healthy or unhealthy bacteria. Microbiota from lean mice were transferred to one group and microbiota from obese mice in to another and evaluated the results. Even though food consumption remained the same, the mice with the obese microbiota developed increased weight gain and body fat in comparison to the lean mice.(Turnbaugh, Ley et al. 2006)

Influence of Environmental Chemicals on Obesity and Diabetes

Xenobiotics include any foreign compound that the body does not produce itself or eat as part of a normal diet. Considering that this includes drugs, environmental pollutants, make-up, lotions and other personal care products, dietary supplements that are not whole food and food additives you can understand the estimate of exposure to 1-3 million xenobiotics over a lifetime. (Johnson, Patterson et al. 2012) These compounds can be harmless or toxic but all are foreign to the body

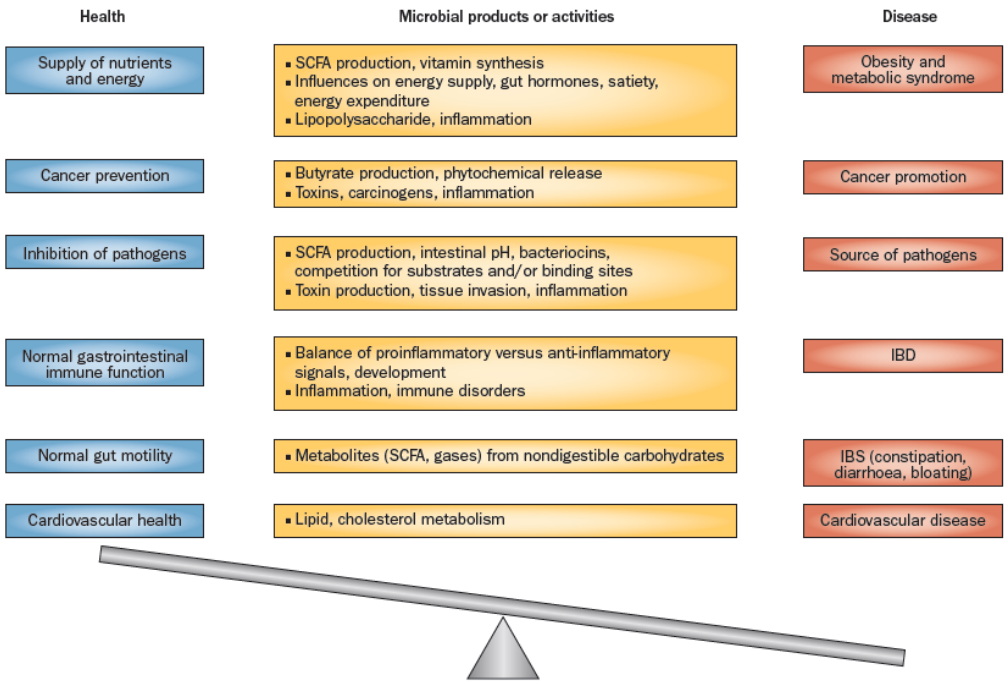

Figure 1 | Influence of gut microbial communities on health. Most of the microbial activities indicated in the centre column are functions of the whole community of gut microbiota rather than being attributable to a single species. The balance of the community and its output determines the net contribution to health or disease. Abbreviation: SCFA, short-chain fatty acid.

and must be processed through the digestive tract and/or the liver and ultimately eliminated through the urine, bile (gall bladder & liver) and feces. (Johnson, Patterson et al. 2012)

The role of environmental chemicals, specifically endocrine disruptors, has been studied for decades. A 1991 conference at Wingspread brought together expert scientists globally to study the impact of environmental chemicals on the endocrine system. It was concluded that "Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife and humans." (Hotchkiss, Rider et al. 2008) The focus at that point was developmental and reproductive disorders. However, the dramatic rise in obesity and type 2 diabetes over the last two decades have caused scientists to expand their focus to include metabolic disorders and subsequently add the subcategory to endocrine disruptors, metabolic disrupting chemicals. (Hotchkiss, Rider et al. 2008; Casals-Casas and Desvergne 2011; Snedeker and Hay 2012)

A 2012 review by Snedeker and Hay summarizes much of the research to date on the obesogenic and diabetogenic effect of exposure to environmental chemicals. (Snedeker and Hay 2012) Although associations seem clear, there is not always an understanding of mechanisms, the impact of developmental timing of exposures or the influence of bio-individuality on the development of obesity and diabetes. What is clear through epidemiological studies is that there

is an association with the incidence of type 2 diabetes and/or obesity to the exposure to PCB's, DDE, HCB, dioxin, chlordane and occupational insecticides, pesticides and herbicides.(Baillie-Hamilton 2002; Grun and Blumberg 2009; Newbold 2010; Casals-Casas and Desvergne 2011; Dirinck, Jorens et al. 2011; Lee, Lind et al. 2011; Snedeker and Hay 2012) In addition, there is a clearer understanding of the effects in human populations and often an understanding of the mechanism when looking at arsenic, cadmium, tributyltin, BPA, DES, genistein and PBDE flame retardants. (Grun and Blumberg 2009; Casals-Casas and Desvergne 2011; Snedeker and Hay 2012)

In 2011 a diverse group of scientists gathered as part of a National Institute of Environmental Health Sciences workshop to evaluate the current state of science on the links between environmental chemicals, obesity and diabetes. This was for the purpose of identifying linkages solidly proven in research and to highlight data gaps for future research. As the findings from this group likely impacts public policy, they were understandably conservative in their findings. However, they found supportive evidence for the role of environmental chemicals as obesogens and suggested further research regarding diabetogens. (Thayer, Heindel et al. 2012) In particular, the most evidence for obesogenic effects was found in maternal smoking (nicotine), plasticizers in PVC plastics and pesticides. Evidence for diabetogenic effect were found in POP's (persistent organic pollutants), pesticides, herbicides and insecticides. Some positive associations for each were found with arsenic, phthalates and BPA.(Thayer, Heindel et al. 2012) In summarizing this topic of environmental chemicals as metabolic disruptors, the following summary points taken from a 2011 review by Christina Casals-Casas, particularly points #1 and #5, are appropriate. (Casals-Casas and Desvergne 2011)

1. *Increasing human exposure to endocrine-disrupting chemicals (EDCs) has been associated with the development of some of the main ailments of the industrialized world, particularly metabolic disorders like obesity, diabetes, and metabolic syndrome.*
2. *Among different mechanisms of action, lipophilic EDCs compounds can bind specifically to nuclear receptors and can displace the corresponding endogenous ligands to modulate hormone-responsive pathways.*
3. *Persistent organic pollutants such as organochlorine pesticides, dioxins, and polyfluoroalkyl compounds and non-persistent pollutants such as bisphenol A and several phthalates are suspected of metabolic disruption activity.*
4. *A major mechanism of EDC-mediated metabolic disruption is through EDC interaction with nuclear receptors, including (a) sex steroid hormone receptors, (b) receptors acting as xenobiotic sensors, and (c) receptors specialized in metabolic regulations.*
5. *This field is littered by controversies, in part due to the difficulties in proving or disproving EDC activity. The major issues are the monitoring of exposure levels, the identification of the metabolic effective dose, and the establishment of a link between (a)*

> *either exposure during critical periods of development or chronic exposure at very low doses and (b) metabolic effects. Finally, this area of research would benefit tremendously if common methodologies of experimental EDC exposure were established. All these issues need further work to create a common and effective regulatory policy for environmental chemical pollutants.*

Intersection of Gut Health and Environmental Chemicals on Obesity and Diabetes

It is interesting to note that the majority of research published in the previous five years and presented thus far on the role of the microbiome and metabolic disruptors in obesity and diabetes has been conducted by scientists outside of the United States (U.S.). While the interpretation is unclear, it is surprising considering the social and economic impact of these metabolic diseases on the U.S. However, 2012 proves a turning point as three research papers from U.S. scientists have been published thus far that suggest an intersection between gut health and environmental chemicals acting as metabolic disruptors and the development of obesity and diabetes. (Grun and Blumberg 2009; Johnson, Patterson et al. 2012; Snedeker and Hay 2012) The intersection of the two can be summarized as:
The role of the microbiome in support of healthy metabolic processes, whatever else it might do to impact inflammation, regulation of fat storage, appetite control and energy harvesting, has a direct impact on the metabolism of metabolic disrupting chemicals (MDC) to which we are exposed that in turn increase or decrease their obesogenic and diabetogenic effects. At the same time, alteration of the microbiome by MDC's can further exacerbate the exposure to MDC's increasing their obesogenic and diabetogenic effects. (Johnson, Patterson et al. 2012; Snedeker and Hay 2012)

This complicated interconnectedness of gut microbiota and environmental chemicals as well as genetics and lifestyle is highlighted in Figure 2. (Johnson, Patterson et al. 2012) The authors coined the term "Metabotype" to incorporate a more holistic view of a human being as not simply pieces and parts but the intersection of all of these inputs coming together. As mentioned earlier, genetics are part of the human makeup but it is also evident that the microbiome can play a more important role, overruling the genetic tendencies. (Musso, Gambino et al. 2010) Diet and lifestyle impact our exposure to metabolic disrupting chemicals and the health or imbalance of our microbiome. This will be discussed further in the next section as we consider the impact of our personal choices on our health outcomes.

The Impact of the Microbiome on the Metabolism of Metabolic Disrupting Chemicals

Gut microbiota play a role in the metabolism of xenobiotics, contributing to potential toxicity. Once a xenobiotic is broken down in Phase I detoxification, it is often more toxic than when it started and most certainly needs to be bound and removed from the body via the urine, bile or

feces. This binding interaction is called Phase II detoxification. If the individual is genetically predisposed with poor Phase II detoxification capabilities and at the same time has an active microbiome conducting Phase I detoxification, the potential for toxicity is greatly increased.(Johnson, Patterson et al. 2012; Snedeker and Hay 2012) In addition, some microbiota can produce their own xenobiotics, requiring further metabolism and others can influence the effectiveness of liver detoxification function. (Johnson, Patterson et al. 2012; Snedeker and Hay 2012) There is hope that this information will prove valuable in understanding drug toxicity as

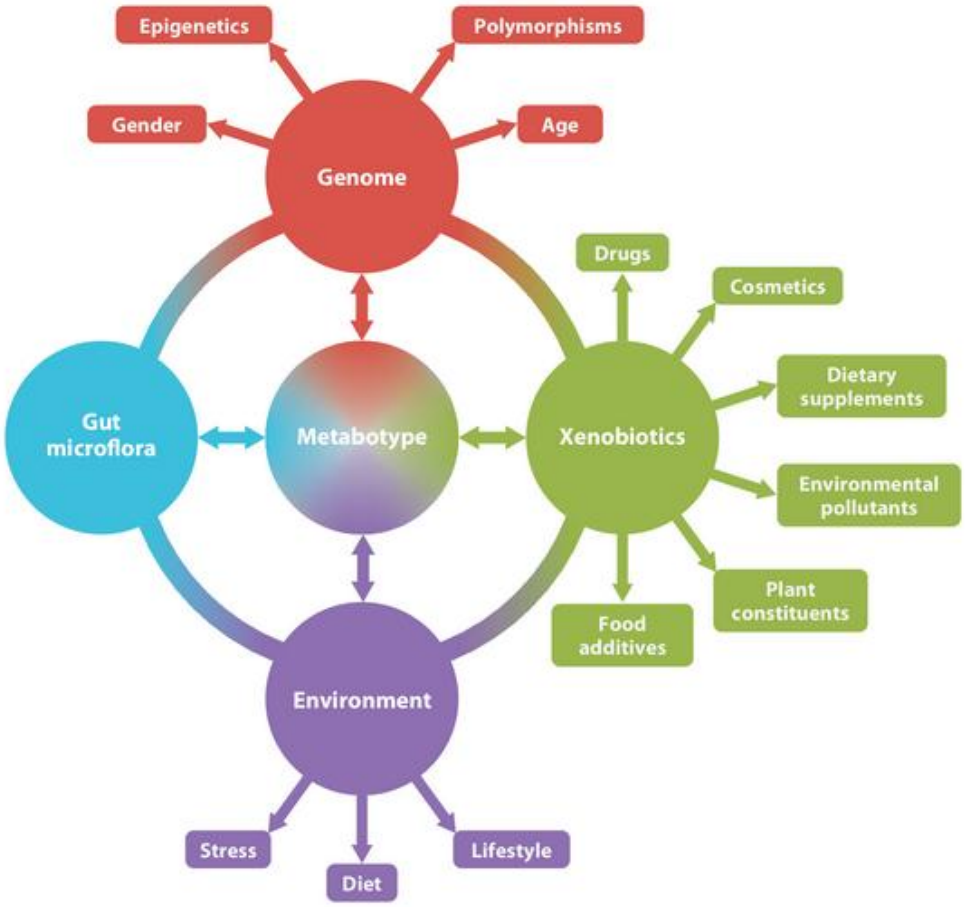

Figure 1

Interindividual genomic, environmental, and gut microflora variation can contribute to an individual-specific metabotype or metabolomic fingerprint. Each of these factors can influence the others and determine the outcome of the metabotype. Conversely, the individual's metabolome can affect each one of the factors.

variations in gut microbiota can affect the metabolism of commonly used over the counter medications. In fact, this has already proven true as researchers have found the markers for predicting acetaminophen toxicity. (Snedeker and Hay 2012)

The Impact of Metabolic Disrupting Chemicals on the Microbiome

Certain xenobiotics impact the gut microbiome balance leading to infections (digoxin) or alterations in digestive processes (antibiotics) such as bile creation by the liver or hormonal processes such as the breakdown and detoxification of hormones. (Johnson, Patterson et al. 2012) On a positive note, there are other xenobiotics that are typically thought of as food, although they might be called functional foods, such as dark chocolate, pomegranate, prebiotics and probiotics that are supportive of a healthy microbiome. (Johnson, Patterson et al. 2012) This will be discussed more fully in the section on diet and lifestyle.

Diet and Lifestyle Implications

If we step back and look at the big picture, we could say with some certainty that a microbiome with the right balance of good, bad and neutral bacteria is a healthy microbiome that supports healthy digestion and healthy metabolism of xenobiotics. With that in mind, the issue at hand is how to support a healthy microbiome. This involves understanding where our microbiome originates, the influence of our normal diet, the influence of medications and the influence of functional foods. (Musso, Gambino et al. 2010; Snedeker and Hay 2012)

The Origination of Your Microbiome

Your microbiome originates at your birth. In the uterus, the gut is sterile, lacking any bacteria. As the baby passes through the birth canal he/she is exposed to vaginal and fecal microbiota that seed their own colonization of their individual microbiome.(Jia, Li et al. 2008; Snedeker and Hay 2012) After birth, the baby receives bacteria through contact with skin, their mouth and breast milk. This contact continues and by a few months old the microbiome has largely stabilized and by 1-2 years old the toddler has a microbiome resembling an adult. As is evident by each of these pathways, babies receive the predominant influence on their microbiome from their mother. Current research indicates that the colonized microbiome you start life with is largely the one you keep for life. (Jia, Li et al. 2008; Campbell-McBride 2010) Given this impact, the mother and father would be wise to utilize the diet, lifestyle and functional food recommendations to support their individual microbiome before, during and after pregnancy.

The Influence of Your Normal Diet

Research shows that either restricting excessive fats or restricting excessive carbohydrates in the diet brings the microbiome back into balance. In fact, dietary changes impact the microbiome relatively quickly, often a matter of two weeks, for the positive or negative. (Jia, Li et al. 2008; Walker, Ince et al. 2011; Snedeker and Hay 2012) Dietary support for Phase II detoxification is also supportive of balancing the microbiome. These foods include cruciferous vegetables such

as cabbage, broccoli, kale, Brussels sprouts, mustard greens and turnips, turmeric and curry, green tea, and sulfur containing foods such as eggs, garlic and onions. (Hyman 2010)

The Influence of Medications

The frequent use of antibiotics can destroy healthy bacteria and leave physical space in the gut for the growth of pathogenic (bad) bacteria. The cautious and appropriate use of antibiotics is recommended to avoid these unintended consequences. (Delzenne and Cani 2010; Musso, Gambino et al. 2010)

The Influence of Functional Foods

Functional foods fall into two categories: probiotics and anything that supports the gut environment for healthy probiotic growth. Probiotics occur naturally in fermented foods such as sauerkraut, lacto fermented vegetables such as pickles, carrots, onions, beets and more as well as some traditionally made yogurts. Unfortunately, the pasteurization of foods kills the bacteria (good and bad) and therefore these foods are no longer commonly part of a normal diet.(Campbell-McBride 2010) In order to compensate for this, many people choose to prepare their own fermented foods and/or supplement with probiotics and prebiotics.

Prebiotics such as inulin and honey contain non-digestible oligosaccharides that are fermented by microbiota in the colon and create an environment that enhances the growth of healthy bacteria. These prebiotics have been shown to improve satiety, weight loss, glucose metabolism, inflammation and barrier function in the gut. (Jia, Li et al. 2008; Campbell-McBride 2010; Delzenne and Cani 2010; Musso, Gambino et al. 2010; Erejuwa, Sulaiman et al. 2011; Snedeker and Hay 2012)

Recommendations:

- Learn to prepare fermented foods and make them a part of your regular diet.
- Consider the regular use of probiotic & prebiotic supplements, especially if you do not add the fermented foods to your diet.
- Eat a diet that supports a healthy gut. A lower carbohydrate, Mediterranean diet rich in foods that encourage Phase II detoxification is effective for many people.

Conclusion

This new understanding of the intersection of the microbiome and environmental chemicals highlights our unique bio-individuality, we are not all the same, and the role of epigenetics, inputs above the genes that effect gene function, in our health outcomes. For anyone who has

unsuccessfully attempted to lose weight or maintain control over their blood sugar, these studies provide hope. However, they also highlight the challenge of adaptive change, individually and for researchers. Unlike the infectious disease model where researchers searched for a technical solution to destroy a pathogenic microbe, these adaptive, lifestyle challenges involve infinite inputs and unique, changing environments.(Flint, Scott et al. 2012) There are still many questions and additional research for years to come, but the glimpse that we are understanding more and more about our influence over our health outcomes and that of our children is empowering. (DiBaise, Zhang et al. 2008; Flint, Scott et al. 2012)

References

Baillie-Hamilton, P. F. (2002). "Chemical toxins: a hypothesis to explain the global obesity epidemic." Journal of alternative and complementary medicine **8**(2): 185-192.

Campbell-McBride, N. (2010). Gut and Psychology Syndrome. Cambridge, Medinform Publishing.

Casals-Casas, C. and B. Desvergne (2011). "Endocrine disruptors: from endocrine to metabolic disruption." Annual review of physiology **73**: 135-162.

CDC. (2011). "National Diabetes Data & Trends." Retrieved October 22, 2012, from http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

Delzenne, N. M. and P. D. Cani (2010). "Nutritional modulation of gut microbiota in the context of obesity and insulin resistance: Potential interest of prebiotics." International Dairy Journal **20**: 277-280.

DiBaise, J. K., H. Zhang, et al. (2008). "Gut microbiota and its possible relationship with obesity." Mayo Clinic proceedings. Mayo Clinic **83**(4): 460-469.

Dirinck, E., P. G. Jorens, et al. (2011). "Obesity and persistent organic pollutants: possible obesogenic effect of organochlorine pesticides and polychlorinated biphenyls." Obesity **19**(4): 709-714.

Erejuwa, O. O., S. A. Sulaiman, et al. (2011). "Oligosaccharides might contribute to the antidiabetic effect of honey: a review of the literature." Molecules **17**(1): 248-266.

Flint, H. J., K. P. Scott, et al. (2012). "The role of the gut microbiota in nutrition and health." Nature reviews. Gastroenterology & hepatology **9**(10): 577-589.

Grun, F. and B. Blumberg (2009). "Minireview: the case for obesogens." Molecular endocrinology **23**(8): 1127-1134.

Hotchkiss, A. K., C. V. Rider, et al. (2008). "Fifteen years after "Wingspread"--environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go." Toxicological sciences : an official journal of the Society of Toxicology **105**(2): 235-259.

Hyman, M. A. (2010). "Environmental toxins, obesity, and diabetes: an emerging risk factor." Altern Ther Health Med **16**(2): 56-58.

Jia, W., H. Li, et al. (2008). "Gut microbiota: a potential new territory for drug targeting." Nature reviews. Drug discovery **7**(2): 123-129.

Johnson, C. H., A. D. Patterson, et al. (2012). "Xenobiotic metabolomics: major impact on the metabolome." Annual review of pharmacology and toxicology **52**: 37-56.

Jones, D. S. (2005). Textbook of Functional Medicine. Gig Harbor, The Institute for Functional Medicine.

Lee, D. H., P. M. Lind, et al. (2011). "Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study." Diabetes care **34**(8): 1778-1784.

Musso, G., R. Gambino, et al. (2010). "Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded?" Diabetes care **33**(10): 2277-2284.

Newbold, R. R. (2010). "Impact of environmental endocrine disrupting chemicals on the development of obesity." Hormones **9**(3): 206-217.

Snedeker, S. M. and A. G. Hay (2012). "Do interactions between gut ecology and environmental chemicals contribute to obesity and diabetes?" Environmental health perspectives **120**(3): 332-339.

Thayer, K. A., J. J. Heindel, et al. (2012). "Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review." Environmental health perspectives **120**(6): 779-789.

Turnbaugh, P. J., R. E. Ley, et al. (2006). "An obesity-associated gut microbiome with increased capacity for energy harvest." Nature **444**(7122): 1027-1031.

Walker, A. W., J. Ince, et al. (2011). "Dominant and diet-responsive groups of bacteria within the human colonic microbiota." The ISME journal **5**(2): 220-230.

WHO. (2011). "Obesity and Overweight." Retrieved October 22, 2012, from http://www.who.int/mediacentre/factsheets/fs311/en/.