

Pesticide Exposure and the Obesity Pandemic

Exposures to endocrine disrupting pesticides echo down the generations

BRUCE BLUMBERG, PHD

Ed. Note: This piece is taken from a talk that Bruce Blumberg, PhD, professor of Developmental and Cell Biology, University of California, Irvine, gave to the 36th National Pesticide Forum, "Organic Neighborhoods: For healthy children, families, and ecology," April 13-14, 2018 in Irvine, California. The full talk, Effects of Prenatal Obesogens: Exposure Echo Down the Generations, in the session Cutting Edge Science, is available on Beyond Pesticides YouTube channel. This talk summarizes the science in Dr. Blumberg's book The Obesogen Effect—Why we eat less and exercise more but still struggle to lose weight. The book includes a section on "what you can do," which is not included in his talk to the Forum. The book also includes more details on the science behind the obesity problem in the U.S. and its link to exposure to endocrine disrupting chemicals, including pesticides.

Thank you for introducing the general topic of how pesticides and chemicals in the environment are bad for our health. Today, I want to talk about a specific example of something that you may or may not have heard about. I want to tell you that the environment influences health and disease.

There are such things as obesogens and we believe they contribute to the current obesity pandemic. It is worldwide.

It is not limited to any one location. I want to show you that the effects of these exposures are heritable. So, the results I am going to briefly summarize actually go to this generation and the next generation. In human terms, if a woman was exposed while she was pregnant, her children, her grandchildren, her great grandchildren and her great, great grandchildren will show an effect. That is something we have never really thought about before.

BOX 1

Main Points

- Environment greatly influences health and disease.
- Obesogens exist and contribute to obesity epidemic.
- Effects of obesogen exposure are heritable.
- Obesogen exposure modifies response to diet and fasting.
- Prenatal tributyltin exposure leads to heritable epigenetic changes that alter susceptibility to obesity.



BOX 2

Non-Communicable Diseases on the Rise



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Non-communicable diseases

Now #1 cause of death in the world (WHO).

Leukemia, brain cancer

Over 20% increase since 1975.

Asthma

Doubled between 1980 and 1995, stays elevated.

Difficulty in conceiving and maintaining pregnancy

40% more women in 2002 than in 1982 (doubled in women aged 18–25).

Autism diagnosis

Increased 1,000% over the past three decades.

Obesity

Increased three-fold in U.S. over past 40 years, doubled worldwide in last 20 years.

The exposure that a woman had affects the response of the descendants to diet and exercise. We think that is because this exposure has led to heritable changes in the epigenome that permanently alter susceptibility to obesity.

Noncommunicable diseases are on the rise; that is, diseases that are not caused by bacteria, viruses, and fungi. (See Box 2.) They are now the number one cause of death in the world. That is pretty amazing to contemplate. We really do not know why that is, but we have some clues.

THE OBESITY PANDEMIC

I want to talk to you about the obesity epidemic, or the obesity pandemic. The latest statistics, just out, say that 39.6% of the U.S. population are clinically obese; that is, have a body mass index (BMI) greater than 30 ($BMI > 30$). It is disproportionately higher in females, which surprises my eyes, to be honest. It is even more prevalent in the minority population. In African American and Hispanic females, more than 50% are obese.

We care a lot about this because obesity adds a great amount of cost both in human misery and also to the health care system. The last number was around \$200 billion a year. These costs are associated with increases in metabolic syndrome—Type 2 diabetes, cardiovascular disease, heart attacks, stroke, and hypertension. Forty percent of all cancers occur in obese people. There are lots of ways that these costs are passed on to society.

DIET AND EXERCISE

Of course, we all know how we get obese. We eat too much and we exercise too little.

Here is how doctors view the population [pointing to a cartoon of a doctor examining an obese patient]: “Any history of diet or exercise in your family?” That is true to some extent. You cannot get fat by breathing the air. You have to actually consume calories if you want to put on weight. But, there is a lot of data that says it is a lot more complicated.

In the study *Canaries in the coal mine: a cross-species analysis of the plurality of obesity epidemics* (2010), David Allison, PhD and his colleagues looked at animal populations around the world. They looked at a large number of 200,000 animals from 24 different populations. These were, yes, our cats and dogs, but also wild rats, feral rats living in cities, and animals living in research colonies: monkeys, rats, mice. They found that they all became obese over the last 30 years, as well. So, of course you can say I probably feed my cat too much, and I probably do. But, how about the feral rats? How about the rats and mice and monkeys that live in our research colonies that get every speck of food from us? Their diets are strictly controlled. How are they possibly becoming obese? So, something about living with people is making animals fat as well.

Another great study, *Secular differences in the association between caloric intake, micronutrient intake, and physical activity with obesity* (Brown et al., 2016), came from an examination of data from the National Health and Nutrition Examination Study (NHANES). To summarize, the authors looked over time and they could show that, between 1988 and 2006, the frequency of leisure time activity increased 47% in men and 120% in women. Alright, so we are not just sitting on our butts not doing anything. We are trying hard not to become obese. And for a given amount of caloric intake

and exercise, for the same calorie intake and exercise expenditure, the BMI was 2.3 higher in 2006 than it was in 1988.

THAT SAYS TWO THINGS:

1. It is not true that we are lazy and not trying hard to not become obese. Physical activity is increasing, and
2. The energy balance model—diet and exercise, calories in/calories out—cannot explain the rise in BMI.

Something else is going on, in addition to eating.

MULTIPLE FACTORS

We know there are other factors. We know that, for example, stress is associated with obesity. We know that disrupted circadian rhythms—from not sleeping enough—is a factor. There are genes that have some role in obesity. You have probably heard that the microbiome, the bacteria that live in your intestines, has some role in obesity.

But, what about prenatal experience? There are great studies from David Barker, M.D. and his colleagues at the University of South Hampton, UK. Dr. Barker proposed what he called the Barker hypothesis, or the “thrifty phenotype hypothesis”—that prenatal under-nutrition predisposed babies to get fat later in life. There is a lot of data to support that idea. Dutch studies of the “Hunger Winter” support that conclusion. We know that, if Mom smokes while she is pregnant, her baby will be born small for gestational age and will be predisposed to become obese later in life. More than 35 epidemiological studies from different countries around the world all show the same thing.

IS THERE A ROLE FOR CHEMICALS?

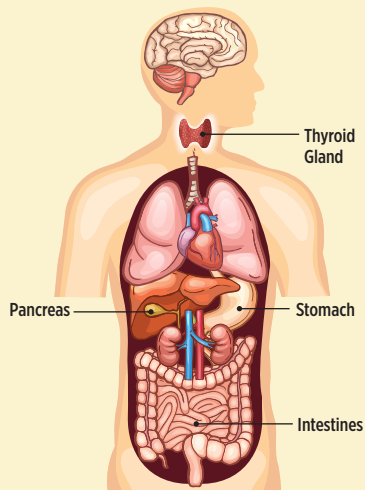
Paula Baillie-Hamilton, M.B. [UK equivalent of an M.D. in the U.S.], PhD, in a paper [*Chemical Toxins: A Hypothesis to Explain the Global Obesity Epidemic* (2002)] and subsequent book [*The Detox Diet: Eliminate Chemical Calories and Restore Your Natural Slimming System* (Penguin Books, 2002) after having children and experiencing weight gain, and reading about hormonal effects in animals of chemicals in the environment] writes that you will lose weight by following her detox diet. While that is not correct, it led Jerry Heindel, PhD, at the National Institute of Environmental Health Sciences (NIEHS) to write a paper about endocrine disrupting chemicals and the obesity epidemic, *Endocrine Disruptors and the Obesity Epidemic* (2003). This was in 2003—way before we even worked on this problem. Dr. Heindel had the insight that many of these chemicals that are in the environment have effects on the endocrine system. Yes, there are lots of toxic pesticides that damage various things, but these endocrine disrupting chemicals work at much lower levels than the so-called toxic levels and modify how our hormonal systems function.

FIGURE 1

Hormonal Control of Weight

Hormonal control of appetite and metabolism

- Leptin (fat), adiponectin, ghrelin are key players
- Leptin (fat), adiponectin—adipocytes
- Ghrelin—(stomach)
- Thyroid hormone/receptor
 - Sets basal metabolic rate



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Hormonal control of fat cell developmental and lipid balance

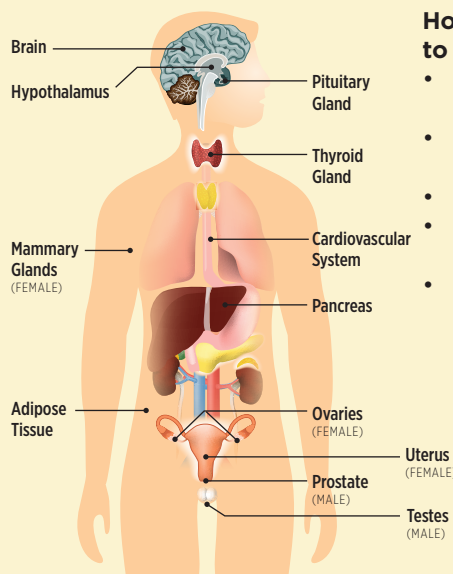
- Regulated through nuclear hormone receptors RXR, PPAR γ
- PPAR γ —master regulator of fat cell development
 - Increased fat cell differentiation
 - Increased storage in existing cells
 - Increased insulin sensitivity

FIGURE 2

Endocrine Disrupting Chemicals (EDCs) Affect Many Organ Systems

“**Endocrine disruptor**—an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.” — THE ENDOCRINE SOCIETY, 2012

- Wrong signal, loss of signal, wrong place at wrong time
- Hormones work at low concentrations and so do EDCs



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How are we exposed to EDCs?

- Persistent pollutants (food, water)
- Dietary components (pesticides)
- Food packaging
- Personal care products
- Cleaning materials

BOX 3

Endocrine Disrupting Chemicals (EDCs)

HERBICIDES

2,4,-D
2,4,5,-T
Alachlor
Amitro
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

INSECTICIDES

Aldicarb
Beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and Metabolites
Endosulfan
Heptachlor/H-epoxide
Lindane (gamma-HCH)
Malathion
Methomyl
Methoxychlor
Oxychlordane
Parathion
Synthetic pyrethroids
Transnonachlor
Toxaphene

FUNGICIDES

Benomyl
Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram-complex
Tributyltin
Vinclozolin
Zineb

INDUSTRIAL CHEMICALS

Bisphenol-A
Polycarbonates
Butylhydroxyanisole
Cadmium
Chloro- & Bromo-diphenyl
Dioxins
Furans
Lead
Manganese
Methyl mercury
Monylphenol
Octylphenol
PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
Perchlorate
PFOA
p-tert-Pentylphenol
Phthalates
Styrene

KEY

- Testosterone synthesis inhibitor
- Estrogen receptor agonist
- Thyroid hormone disruptor
- Androgen receptor antagonist

THE ROLE OF HORMONES

You probably know that weight in your body is under the control of hormones. There are key ones (see Figure 1), for example, leptin, which is the satiety hormone that tells your body you have enough energy. The thyroid hormone/receptor (which is a member of the family of receptors that I work on) sets the basal metabolic rate—how many calories your body needs to sustain itself. Basically, it is how many calories your body burns while you are sleeping. The biggest expenditure that your body makes in calories is that resting metabolic rate. If you change that, you totally change the amount of calories that you use.

FALL CELL DEVELOPMENT

It is also true that the development of fat cells themselves is under the control of hormones, and three receptors, which have the terrible name “peroxisome proliferator-activated receptors” (PPAR) are the key players here. That name is an artifact of history. These are actually fatty acid receptors. I discovered this when I was a post-doctoral student at UCLA almost 30 years ago.

This receptor, PPAR-gama, is called the master regulator of fat cell development. If you express this receptor in a stem cell, that stem cell is now a pre-fat cell, and if you activate it, that pre-fat cell now becomes a fat cell. And if you activate it in a fat cell, it accumulates triglycerides from the blood. So, it is a very important player in the whole process.

ENDOCRINE DISRUPTING CHEMICALS

You have heard the term endocrine disrupting chemicals. Endocrine disruptors, according to the Endocrine Society, are exogenous chemicals or mixtures of chemicals that interfere with every aspect of hormone action. And we have a little bit of a war with the toxicology community because they would say, “and causes adverse effects.” For an endocrinologist, disrupting how hormones work is adverse *per se*, adverse in and of itself. This could be the wrong signal, or the absence of the signal, or the right signal at the wrong place at the wrong time. The key point is that hormones work at very tiny concentrations. For all the women in the room, the estrogen receptor in your body is fully saturated at one part per billion of estradiol. That is an incredibly tiny amount—and it does not take much of an environmental chemical to disrupt that balance.

EXPOSURE TO ENDOCRINE DISRUPTORS WIDESPREAD

How are we exposed? We’re exposed from pollutants, the diet, food packaging, and personal care products. We live in a sea of endocrine disruptors.

Box 3 is just a partial list from of endocrine disruptors from NIEHS. You have heard of many of these chemicals. Here is our friend, the weed killer 2,4-D. DDT is on the list. There are quite a lot. For some of them, we know the mechanisms of action. For some of them, we do not.

An important point to note here is that there are probably about 1,000 endocrine disruptors known, but that must be an understatement because there has been no systematic attempt to identify endocrine disruptors. We have learned about these by accident.

Endocrine disruptors are everywhere. Box 4 identifies the kinds of categories: agrichemicals, pesticides, solvents, industrial flame retardants, industrial byproducts, surface protectors, sunscreens, plastics, plasticizers, cosmetics, etc.

There are quite a few of them. We willingly expose ourselves to endocrine disruptors all the time. Most personal care products are full of endocrine disruptors, like parabens and benzophenones—all kinds of chemicals like that.

One argument would be that we are not really exposed—you put the cream on your skin, but it does not really get inside. Well, if you believe that, I recommend this book with a very silly name, *Slow Death by Rubber Duck: How the Toxic Chemistry of Everyday Life Affects our Health* (2009). It is actually a very serious book. The authors, Rick Smith and Bruce Lourie, used themselves as guinea pigs. They had their blood levels of a whole bunch of chemicals—phthalates, perfluorinated compounds, etc.—measured and then they sat in a room. They sprayed scotch guard on the couch and they sat there and watched television. And they had the levels measured again. Sure enough, as you might expect, the chemicals were taken up into their body. Using the products as intended, in just the way you should experience them, causes the chemicals to be in your body.

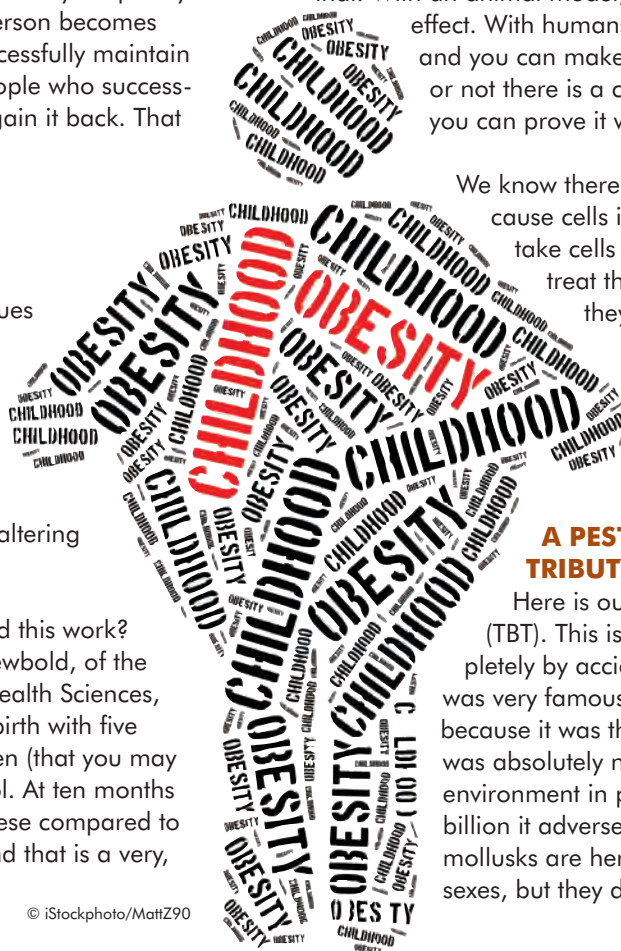
The data I want to talk to you about has to do with whether endocrine disrupting chemicals are disturbing how the body functions and leading our kids to become obese. If you travel the world, you will see that in the U.S. we have lots and lots of obese kids. You will not see that in many other countries. A really big problem is kids that are fat very frequently turn into adults that are obese. Once a person becomes obese, it is virtually impossible to successfully maintain weight loss. Data say that 83% of people who successfully lose a large amount of weight, gain it back. That is a very, very big problem.

How does this happen?

THE OBESOGEN HYPOTHESIS

About 15 years ago now, my colleagues and I developed what we called the *obesogen hypothesis*. I define obesogens as chemicals that inappropriately stimulate the development of fat cells or the storage of fat into those cells, either directly by fiddling with how the cells work, or indirectly altering appetites tied to metabolism.

Was there any evidence before we did this work? The answer: yes. My friend, Retha Newbold, of the National Institute of Environmental Health Sciences, exposed a mouse for five days after birth with five parts per billion of a synthetic estrogen (that you may have heard of) called diethylstilbestrol. At ten months old, the animal became morbidly obese compared to the animal that was not exposed—and that is a very, very tiny dose.



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BOX 4

Categories of Consumer Products in Endocrine Disrupting Chemicals (EDCs)

Pesticides	Surface Protectors
Herbicides	Sunscreens
Fungicides	Plastics
Solvents	Plasticizers
Flame Retardants	Cosmetics
Industrial Byproducts	Over 1,000 EDCs

We know that there are drugs that have the side effect of making people fat. There is a kind of drug with a terrible name, thiazolidinediones. You may have heard the brand name Avandia. These are diabetes drugs that make people fat. Yes, they make them insulin sensitive, but they also make them fat. These drugs act on our friend PPAR-gamma.

We know that there are quite a number of chemicals for which levels of the chemical can be linked to obesity in people. Of course, that does not prove that the chemical causes obesity. But it suggests that maybe somebody ought to study that. With an animal model, we can directly study cause and effect. With humans, you can make associations and you can make some inference about whether or not there is a causal effect, but in animals, you can prove it without a doubt.

We know there are bunches of chemicals that cause cells in culture to become fat cells. We take cells growing happily in a dish and treat them with these chemicals, and they become fat cells.

So, the existence of obesogenic chemicals was plausible even before we did the work that I'm going to tell you about.

A PESTICIDAL OBESOGEN, TRIBUTYLTIN

Here is our favorite obesogen, tributyltin (TBT). This is something we discovered completely by accident. Tributyltin, for a long time, was very famous as an endocrine disruptor because it was the only chemical for which there was absolutely no controversy. They exist in the environment in parts per billion, and in parts per billion it adversely affects mollusks. Gastropod mollusks are hermaphrodites, they have both sexes, but they do not mate with themselves.

They mate with other animals. In animals exposed to tributyltin, the penis grows to gigantic size, and, as you can imagine, parts do not fit anymore. So, these animals become sterile.

I confess, I am a vertebrate developmental biologist, I do not care so much about snails, except that they taste good when they are not contaminated.



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I was in a meeting in the south of Japan sleepily listening to presentation after presentation in Japanese, and one of them was in English. Professor Shinsuke Tanabe, PhD got up and said that tributyltin could sex reverse genetically female flounders, a population of fish that would become 100% female if he exposed them to tributyltin, and 30% became male. That got my attention. So, I called back to the lab and I said, "Guys, will you test which of the 48 hormone receptors that we know about and have in the lab are activated by organotins?" I was thinking that it would be a sex hormone receptor because, if you want to change sex, you should fiddle with an estrogen or a testosterone receptor. Instead, we found that tributyltin activated, again, our friend, PPAR-gamma and its partner, which is called RXR. These two receptors work together as a heterodimer [molecule with different subunits] and they control the development of fat cells.

There was only one way to go with these data. This was not something we were working on, and not something that I ever contemplated studying, but here we were with this observation: This chemical activated a receptor that regulates the development of fat.

TAKING IT TO THE LABORATORY

So, we asked the question: What happens in cell culture? We found that it made cells in culture become fat cells. We found that prenatal exposing pregnant mice made the mice

get fat, and we could show that this exposure reprogrammed stem cells in the body to become fat cells. That was very interesting to us, as you can imagine.

The next thing we asked: Were these exposures heritable? And, of course, we asked this question because Michael Skinner, PhD at Washington State University had shown that the effects of some kinds of chemical exposures were passed on many generations later. So we asked: Are these chemicals similar? Unlike Dr. Skinner, we decided to use levels that are relevant to all of us. The magic word in toxicology is NOAEL, no observed adverse effect level. It is magic because that is the number that you use to set allowable human exposure. So, some relationship between the NOAEL and human exposure is always inferred. We exposed these mice throughout pregnancy. We took the babies, assayed some, and bred them out to the F3 [third] generation.

If you see an effect in the first two generations, that is called a multigenerational effect. That is distinguished from a trans-generational effect because the first and second generations were exposed. If a pregnant mom is exposed to a chemical, the baby is exposed. But, inside the baby are the germ cells to make the next generation, and they are exposed also. So, the first two generations have been exposed. The third, F3, and beyond have never been exposed to the chemical.

We saw that the animals were not heavier, but they were fatter. They had more fat cells, bigger fat cells, the brown fat [brown adipose tissue] did not work normally, and they had fatty livers and lots of other problems.

Then we repeated the experiment because we wanted to know how this happened? What changes did we cause in these animals? And because we wanted to know more, we went to the F4 generation—the great-great-grandchildren of the exposed animal.

The first thing we did was to test all the same parameters we saw before—and we got the same results. Then we did a diet challenge to these animals, and that gave a very interesting result. The animals remained on a normal low fat diet up until 19 weeks of age. Then we switched it to a slightly higher fat diet, not even double—from 13% to 21%. That is still a low fat diet. We kept them on that diet for six weeks, then switched them back.

The first thing we asked was: What happens when we fast the animals? Did they respond to the fasting? Normally, fasting mice lose weight really quickly. If you fast them for four hours, they lose some. If you fast them overnight, they lose as much as 10% of their body weight. The animals that had been exposed four generations before to tributyltin lost a little less fat, but in the overnight fast, they lost a lot less fat. So, these animals did not metabolize the fat. Is not this every dieter's

FIGURE 3

Obesogens—Just the Tip of the Iceberg?

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lament? “I don’t eat and I still do not lose weight.” So, keep that one in mind.

Second, we tracked body weight and body composition over time. We monitored the females and the males, and those animals exposed four generations ago. No real difference in the weight between males and females was found. But, if you look at the fat in the males, you can see that at 19 weeks they are already a little bit fatter. Immediately, when you change the diet, these animals get obese in one week. They continue to gain that weight and, when you put them back on the normal diet, they keep the weight on.

These animals are predisposed to respond differently to the diet than the control animals. That also means that body weight is not an acceptable surrogate for obesity. A lot of times in the literature, you will read: “These animals did not gain any weight, so they must not be fat.” These animals did not gain any weight, but they gained fat. They gained fat and they lost something else—they lost lean muscle and bone mass.

Next, we asked the question: What genes are changing in expression? I will not bore you by going through biochemical pathways that you memorized in biology class. The key player is leptin—the satiety hormone, the energy-balance hormone. Leptin was elevated in the F4 males, so the messenger RNA that encodes leptin was elevated, and circulating levels of leptin in the blood were elevated. In the clinic—and the doctors in the room may agree with me, if you see obesity and elevated leptin levels, that means the individual is leptin-resistant. So, we created animals that four generations after their mom’s exposure had a leptin-resistant thrifty phenotype.

What we think happened is that we changed the way DNA is in the nucleus. In the nucleus of a cell, the DNA is like a bowl of spaghetti. But, that spaghetti has a structure. There are parts that always like to be next to other parts and separate from different parts.

In the obesogen-exposed animals, this structure is disturbed, and that leads to heritable changes in which genes are expressed. This altered structure is inherited, and that leads us to get this leptin-resistant thrifty phenotype four generations later, as published in *Ancestral perinatal obesogen exposure results in a transgenerational thrifty phenotype in mice* (Chamorro-Garcia, et al, 2017).

HOW MANY OBESOGENS ARE THERE?

We have studied just the tip of the iceberg. I have shown you data on tributyltins, there is good data for phthalates and perfluorinated chemicals. There is really strong data for estrogens. There is really strong data for nicotine and air pollution. Who has heard Robert Lustig, MD shouting from the rooftops about fructose? And sugar? There are quite a number of other chemicals. You have heard of organophosphates.

FUNGICIDES

We have found in a different study that many fungicides are obesogens. Here are six different classes of fungicides. Where are we exposed to fungicides? Ladies and gentlemen, in fruits and vegetables, in general. Tributyltin and triflumizole we know are obesogens in animals. Tributyltin, triflumizole, zoxamide, and quinoxifen activate PPAR-gamma, so they are for sure going to be obesogens. Flusilazole activates the PPAR-gamma partner, RXR. It is going to be an obesogen. And, fludioxonil, we have no idea what it activates.

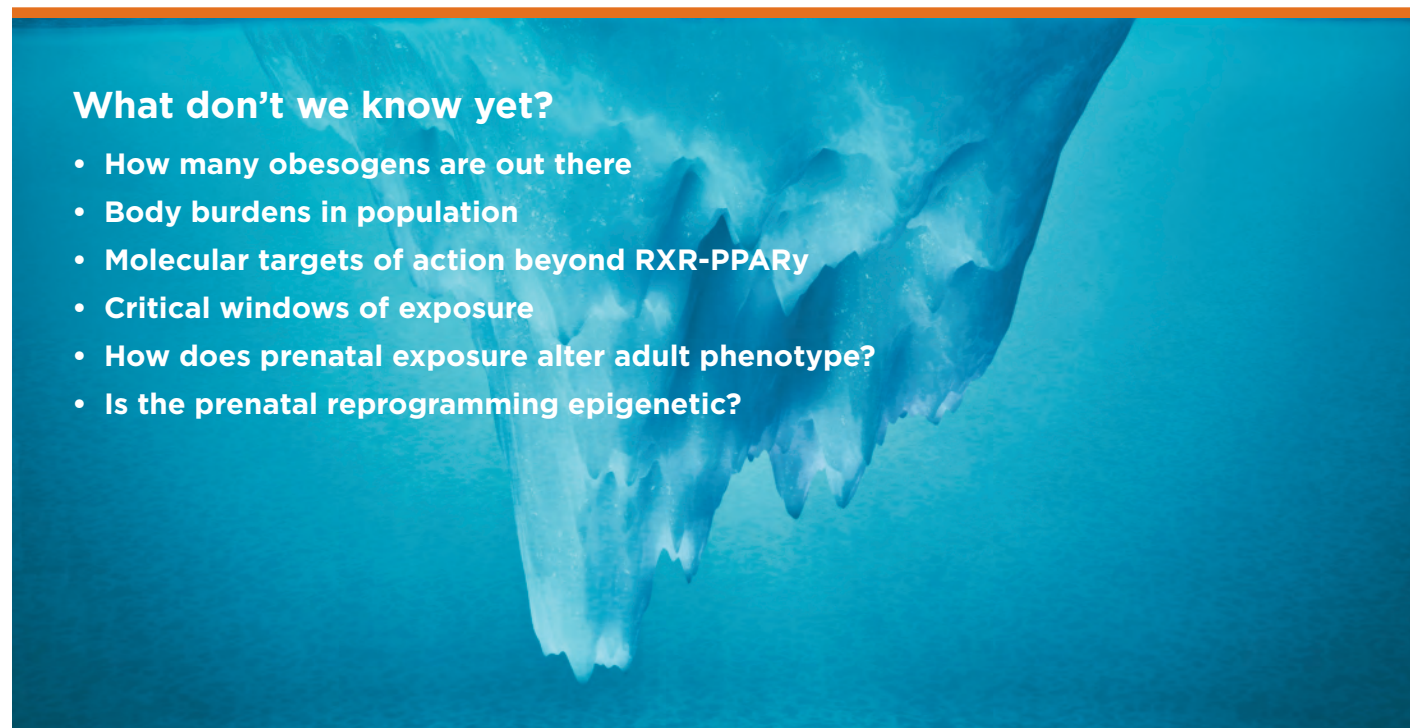
CONCLUSION

We do not know many things yet. We do not know how many are there? We know about 50 obesogens. Are there 500? 5,000? We simply do not know.

We do not know what the body burdens are in us for any of these chemicals. They are not on the monitoring list. We do not know what all the targets are. We know some of the targets in which they work, but certainly do not know all of them. We do not know much about how this prenatal

FIGURE 4

Obesogens—What Lies Beneath?



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What don't we know yet?

- How many obesogens are out there
- Body burdens in population
- Molecular targets of action beyond RXR-PPAR γ
- Critical windows of exposure
- How does prenatal exposure alter adult phenotype?
- Is the prenatal reprogramming epigenetic?

exposure heritably changes the phenotype. We have some ideas in our model. Does that apply to all the other ones?

So what are the implications for human health? What is the take-home message?

First is that diet and exercise by themselves do not explain the obesity pandemic. We know this because there are pharmaceutical obesogens. Even if you do not believe what I have told you about chemical obesogens, there are prescription drugs that we take that have the side effect of making people obese.

Thiazolidinediones, the anti-diabetes drugs and all kinds of atypical anti-psychotics, anti-depressants make people fat. **So, if drugs have the side effect of making people fat, why would not chemicals that target the same pathways have the same effect? That would be an unreasonable conclusion to draw.** And we know quite a few of those.

We know that this prenatal exposure reprograms the animals and their descendants that have been exposed to become fat. We know that there are some epigenetic changes and changes in the three-dimensional structure of how the DNA is packed in the nucleus that lead to this predisposition.

In one of my favorite cartoons, “Damn you, epigenome,” the obese character interacts with his butter pecan ice cream

to make him fat—just exactly like my mice. This is exactly the same thing.

Seriously, the existence of obesogens says we need to shift the paradigm. We need to prevent kids and adults from becoming obese rather than trying to cure people who have already become obese with an 83% failure rate.

And, we know how to do it. We need to reduce exposures, we need to optimize nutrition, we need to feed kids organic contaminant-free fresh food. I do not need to tell that to this audience, but somehow the public health community is not getting it.

Another favorite cartoon has a regulator—pick your favorite from FDA, EPA, USDA—saying to a child eating a meal, “We do test for the safety of pesticides in your food. It’s kind of long-term test.” And it is! We are the subjects and you see the results. The results are quite clear. Chronic diseases are on the rise, and people are not as healthy as they once were. I think that what to do next is quite clear.

Bruce Blumberg, PhD is professor of Developmental and Cell Biology, University of California, Irvine. Dr. Blumberg thanks his students, post-doctoral assistant Raquel Chamorro-Garcia, PhD, research assistant Carlos Diaz-Castillo, PhD, and researchers Riann Egusquiza, Victor Hung, Bassem Shoucri, Gin Wang, Sigal Willner, former lab members, other collaborators, and NIEHS.