Obesity's Weighty Model

Kari Walsh

Writer's Comment: *I took Dr. Warden's class on how genetics is being used to understand obesity out of simple curiosity. I had recently begun a job at the Canine Genetics Lab at the vet school, and I wanted to understand more of what they did. While the class proved to be very valuable because it was both current and unafraid to challenge widely accepted beliefs, I realized that the techniques used to study obesity were quite different from the ones utilized by my boss, Dr. Mark Neff. So I decided to try and find research that used the dog as a model for obesity. The results were few and disappointing: I had my topic for this essay. I would particularly like to thank Dr. Neff who was unknowingly my main resource. His strong, and more importantly, possible vision for the future of dog genetics sparked my interest and I have never enjoyed researching or writing a paper more.*

—Kari Walsh

Instructor's Comment: *Students in NPB131 are asked to write a persuasive essay on a controversial topic in obesity by extracting information from studies published in the peer-reviewed scientific literature. For example, students might consider such questions as (1) Does exercise reduce everyone's weight? (2) Should models in fashion shows be required to exceed a minimum weight? (3) Why has the incidence of obesity increased in recent years? Kari Walsh chose to evaluate the advantages and disadvantages of studying obesity using animal models. Kari's paper smoothly integrates information from diverse publications into a persuasive argument favoring use of dogs as models for human obesity. She effectively points out that human selection may have made dog breeds better models than any mammal except humans. I recommended Kari's paper for the* Prized Writing *award both because it is a pleasure to read and because the arguments presented are scientifically sound.*

—Craig Warden, Neurology, Physiology, and Behavior

As humans shifted from hunters to consumers, only the dog moved with us: from pointer to companion. Indeed, when our traditional mainstay of fat and protein changed to today's diet of convenient carbohydrates, our dogs' diet of lean meat switched to one of processed kibble. And now the effects of these changes are similarly expressed—obesity and many of its health consequences are problems common to both human and hound. Despite the striking resemblance between us, the dog has been little utilized as a model for human obesity. With the recent sequencing of the dog genome, it is time to examine the potential role of man's best friend as man's best model.

As long as 500,000 years ago, humans and the gray wolf competed in the same environment, and for as long as 100,000 years we have mutualistically shared the same society (Wayne et al., 1999). An excellent example of this reciprocal relationship is the Inuit culture, where the dog was critical to the society's resiliency. Dogs enabled the Inuits to move efficiently by pulling sleds of supplies and, in exchange for this service, the dogs were cared for. When they hunted, the Inuits divided the meat between themselves and their dogs and were careful to provide each with the parts of the kill that were the easiest for them to digest (Phinney, 2004). Humans ate mainly fat, while the dogs primarily ate lean meat (Phinney, 2004). This division of food and labor worked well for their society, as can be seen in its long, successful history in one of the world's harshest climates. Similar relationships existed in many other areas, with man and dog sharing work and the benefits reaped from it (Lindblad-Toh et al., 2005).

When people began domesticating the wolf, they selected for dogs that could assist them in their line of work (Lindblad-Toh et al., 2005). Our ancestors' choices are still seen in today's breeds: pointers, herders, and retrievers. The artificial selection used to shape these breeds was often a response to the selection their owners labored under. For instance, a hunter and pointer had to travel for hours without tiring and be observant enough to identify prey. If they couldn't, neither one ate. Herding dogs had to gather and protect vast numbers of prey animals. Like their owners, these dogs had to interpret the other animals' behavior and respond appropriately to it. If either owner or dog failed to react, the herd would scatter and become vulnerable. In the above examples, the dogs had different requirements for temperament and conformation because of their owners' disparate duties. These requirements were often

similar to the attributes their owners needed to possess to be successful. This makes the dog a simplistic yet unique reflection of some of the phenotypic variability existing within people today.

Yet the phenotypic differences between dog breeds are more easily categorized than the phenotypic differences seen in people, because the dog is a product of artificial selection. As M. W. Neff describes in an article in *Cell*: "artificial selection leaves an indelible mark on the genetic architecture of the organism—traits selected by man stem from macromutations of observable effect" (2006). When dogs were selected in the past, they had to be suitable for the job they were bred to do; but another trait that was often selected for was the ability of the dog to thrive on limited resources. Feed efficiency is readily measurable, which means that it is possibly one of the macromutations Neff describes. For obesity researchers, finding the mutations that enable animals to maximize food resources would be of great interest, because they may be a major contributor to today's high rate of obesity.

In human populations, almost 66% of people are overweight, and in dogs, the incidence is as high as 40% (German, 2006). As in people, being obese in dogs is associated with a higher mortality rate (German, 2006). It is generally agreed that obesity is a risk factor for many health problems, such as orthopedic disorders, cardiorespiratory disease, reproductive disorders, neoplasia, and hypertension (German, 2006). However, the differences expressed between obese patients in their presentation of these diseases is still an area of active research.

One of the most significant obesity-related diseases in people is diabetes mellitus, and the incidence of it is increasing (Rand et al., 2004). Although no published research links obesity to increased risk of diabetes in dogs, dogs show equivalent forms of human type one and gestational diabetes (Rand et al., 2004). There is growing evidence of a genetic as well as an environmental component to these diseases with the discovery of a haplotype that makes dogs three times as likely to develop type one diabetes (Rand et al., 2004). This haplotype is comparable to a genetic sequence found in humans that may also result in an increased risk of diabetes (Rand et al., 2004). While the similarities between human and dog diabetes makes the dog a worthwhile model to study, it may be our differences that are even more revealing. To date, no studies have shown an equivalent form of human type two diabetes in dogs, even though dogs develop absolute insulin deficiency (Rand et al., 2004). What

prevents the dog from developing the marked signs of type two diabetes, while the human must suffer from its complications? The answer is in our genomes.

Another obesity-related disease for both humans and dogs is hypertension. The correlation between weight and blood pressure has been well established in humans and has recently been shown in dogs (Montoya et al., 2006). The human and dog closely model each other in the detrimental consequences high blood pressure has on the eyes, brain, and kidneys (Montoya et al., 2006). However, the incidence of stroke and heart disease in dogs is low, which is another significant difference between us (Montoya et al., 2006). This difference can be explained in one of two ways: first, that there is not enough data to accurately represent the incidence of heart disease in dogs, or second, that the molecular variability between us changes the expression of the same disease. Unfortunately, Montoya's paper referenced studies that induced obesity in dogs, which is different from naturally occurring obesity. Such an experimental design could have confounded the results and demonstrates the need to look at the variation that already exists in dog populations for weight.

Even though people and dogs show a few peculiar differences in the symptoms of obesity-related diseases, the traditionally proposed treatment for obesity in both is the same: diet and exercise. In humans, these treatments have been extensively researched, and no diet or exercise program has shown long term results for losing weight and then maintaining the loss. Some may say that weight loss is more achievable in dogs because the dog generally does not feed itself. This is true; yet, for many owners, when their dog begs or follows a command, they are usually persuaded to feed them an extra treat—even if their dog is obese. They identify so closely with their canine companion that they feel guilty withholding food from it. This can be seen in the steadily increasing rate of obesity amongst companion animals (German, 2006). But with this increase in obesity has come a greater awareness of its consequent health issues. No one wants their dog to suffer unnecessarily, leading to a new market for diet formula feeds that closely resemble their human counterparts.

But how effective are these diets? A high protein and low carbohydrate diet was tested in dogs because the same diet showed success, however debatable, in people. The principle behind this choice was simple: in humans and dogs, a diet with higher levels of protein conserved lean body mass (Diez et al., 2002). Diez's experimental design was basic:

eight obese dogs were split into groups based on body weight and sex, and these groups were given either a high protein or control diet (2002). Weight loss was shown to have no significant difference between the two groups, but the dogs with high protein diets lost about 80% of their excess body weight from fat, while the dogs on the control diet lost about 70% from fat (Diez et al., 2002). The p-value is not statistically significant at the 95% level for a difference between the control and high protein groups for weight loss from fat.

This lack of statistical significance could be from the flaws in the experimental protocol. Only eight dogs were used, a low n value. The dogs were from the same breed and housed in the same colony, but there was no mention of the familial relationship between the animals. As obesity is proving to have a critical genetic component, the pedigrees of the animals is essential information. The high protein diet had a high vegetable component (ingredients two through six), and both diets used were high in fiber (Diez et al., 2002). Diets high in fiber have been proposed in human obesity studies as having a greater effect on satiety. Diez used that assumption when composing the experimental diet in her study, with only the word "tradition" to support her reasoning (2002). If this experiment had used a meat-based, high protein diet, the results might have shown statistical significance.

This prediction is suggested by Phinney's research, which showed that people who returned to eating a native diet, like the Inuit diet of high fat with moderate protein, showed weight loss with almost 100% coming from fat stores (2004). Dogs would not be able to tolerate the high fat diet that the Inuits ate, as the Inuits well knew, because they fed their dogs only the lean parts of the kill (Phinney, 2004). But perhaps researchers studying dogs could also utilize the lessons learned from the Inuit culture and design a study with a lean, high protein diet. This would be the dog equivalent of a "native" diet, and it may prove to be more healthful to them.

As in humans, obesity studies in dogs have not shown a significant correlation between energy requirements and activity level, even within a distinct activity category (Butterwick et al., 1998). Studies investigating the effect of exercise on obesity have similar conflicting results for both humans and dogs (Butterwick et al., 1998). But the majority of researchers are still unwilling to look for alternative treatments and cling to the notion that diet and exercise must cure obesity—there just hasn't been

an experiment that is well designed or sensitive enough to prove the correlation (Butterwick et al., 1998). These unremarkable results may have a simple interpretation. Obesity likely has a strong genetic component, and the varied responses to exercise and diet help to show that. It is a condition that will not be successfully treated until genetic mutations are found and treatments are designed for each.

However, obesity is a disease that needs to be controlled right now, and researchers must continue to try to find treatments that work for a majority of people. One of the main problems confronting researchers in human obesity is that it is extremely difficult to replicate the home environment in a laboratory. Even well designed, effective treatments in a metabolic ward may fail when implemented by people on their own. Once again, our genetic makeup drives our varied responses to the current obesity-promoting environment, and the signaling differences that affect our behavior must be elucidated. It is in this respect that the dog's potential as a model for humans is most apparent.

A common joke about dog owners is how closely their dogs resemble them in both physical appearance and disposition. While this joke is only a joke, there is a perceptible resemblance between dog and human personalities: "Fear, aggression, loyalty, anxiety, and playfulness are but a few canine temperaments that resonate with us, and their genetic roots are likely to echo in our genome" (Neff et al., 2006). As Neff proposes, these temperaments may have a genetic basis (2006). And they are likely the result of the long history we share. In order for us to have lived mutualistically for perhaps thousands of years, we had to understand the needs of the other without the benefit of verbal communication. This ability may now prove to be exceedingly valuable to obesity researchers, because behavior is a critical component to the treatment of obesity. And no other animal so closely models basic human personalities as the dog.

There are many other reasons to consider the dog model as opposed to the mouse or human model more typically used in obesity research. Rigorous experiments that a person would not agree to could be performed with the dog. For instance, humans will not eat processed pellets for years, but dogs are routinely fed kibble of known nutritional value. Humans tend to lie about their diet, exercise program, and weight because these are sensitive and emotional issues. But people tend to be less emotional when speaking about their dog's weight, and so researchers could obtain more precise data using surveys. Dogs' reproductive

patterns are also more useful to researchers than humans: dogs produce multiple litters with large sibships, and dogs from similar lines are bred together. Inbreeding, because of the genetic uniformity it produces, has proven to be a valuable tool to researchers. Obviously, people cannot be forced to inbreed or produce litters of offspring, making these tools unavailable to human geneticists.

Using the mouse model instead of the dog or human model gives a researcher even greater access to inbred lines of offspring and a much shorter generation time between litters. But mice cannot model the natural phenotypic differences between people as accurately as the dog can, because they are so highly inbred and have induced mutations. As Neff explains, "Studying adaptive traits in a natural context stands in sharp relief to investigating induced, defective phenotypes in the laboratory" (2006). Mice have very practical, useful applications when studying major gene effects on human obesity. But the dog may have a much more useful genome for studying the effects of multiple genes on naturally occurring obesity, which is the direction that obesity research must soon head.

Numerous topics might be explored using the dog model, and each could provide exciting, new information on obesity and obesity-related pathologies. Elucidating the mechanisms that contribute to absolute insulin deficiency in dogs could clarify the difference between it and human type two diabetes. If dogs are somehow protected from developing overt type two diabetes, the pharmacological ramifications would be enormous. Another study could examine the percentage of obese dogs that develop heart disease, and if the correlation proved to be low, could lead to a more precise understanding of how adiposity affects the heart. As heart disease and obesity are such prevalent disorders in humans, a more precise understanding of their interactions would be valuable.

Researchers could also perform experiments with dogs to clarify the genetic and environmental components to obesity. One possible design is to take different families of siblings and separate the sibs into groups for different diets. Changes in adiposity could be measured and the sibs compared to each other and to unrelated families. While the sibs would not have the homogenous genetic background that identical twins or inbred mice have, the limited differences in their backgrounds could prove useful for finding obesity genes, particularly if sibs developed different levels of adiposity in the same environment.

Studying dogs as models for human obesity shows such promise. The artificial selection used with dogs has made genetic differences phenotypically visible. Obesity-related diseases have similar pathologies and our differences may lead to the discovery of better drug therapies. Dogs' personalities are highly discernable and closely reflect basic human temperaments and behaviors. And there are millions of dogs: millions with extensive pedigrees, millions with weight issues, and millions that are suffering from obesity-related diseases. This vast resource has become even easier to utilize with the sequencing of the dog genome, and the dog is merely waiting for the right person to realize just how weighty of a model it is.

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