

## OBESITY OF INFECTIOUS ORIGIN – A REVIEW

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### INTRODUCTION

Obesity has become the number one public health problem in America.<sup>1</sup> Obesity is a complex, multifactorial disease that involves the interaction of genetic, metabolic, social, behavioral and cultural factors. In the decade from 1980 to 1990, the number of people with obesity increased by 30% in the US; the number of obese adults further increased to 61% between 1991 and 2000.<sup>2</sup> The numerous health risks associated with obesity are well known to the medical community.

The epidemic increase in obesity, its medical consequences, and the rapidly escalating health care costs associated with it have prompted a multidisciplinary approach by health professionals, government, and non-governmental

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#### From The Editor's Desk

Obesity has reached epidemic proportions worldwide; the term "globesity" defines the current situation. If the prevalence of obesity remains unabated this will be the first generation of children who die before their parents! The disease is now attracting the attention of pediatric endocrinologists. At the LWPE/APS there were multiple presentations on the subject and a symposium on adiposity. Obesity is now recognized to be at the crossroads of insulin resistance, a condition implicated in the "deadly quartet" of western civilization: diabetes mellitus, hyperlipidemia, hypertension and cardiovascular disease, as well as other common pediatric endocrine conditions, ie, PCOS, acanthosis nigricans, glucose intolerance, etc. The obesity epidemic has its roots in a lifestyle which facilitates consumption of excess calories over and above energy expenditures.

Adipocytes function as an endocrine organ and play an important role in the pathogenesis of obesity and its complications. However the potential role of infectious agents triggering or being associated with obesity and/or its co-morbidities is rarely discussed, nor are the potential endocrine alterations that may be induced by infective processes. In this issue of *GGH* such an omission is addressed by Drs. Dhurandhar, Atkinson and Ahmed. Their review should shed light and attract attention to this poorly understood area and facilitate an understanding of obesity in its entirety. Filling the void of this often neglected aspect may also stimulate research by pediatric endocrinologists wishing to clarify the endocrine interactions with adipocytes and infective agents.

The editors have reviewed a variety of papers addressing subjects of great interest. Noteworthy in the growth field are the papers on the long-term mortality of recipients of pituitary derived growth hormone, the novel dysfunctional growth hormone variant, the growth hormone and IGF-I effects on longitudinal growth, and cancer risk. Also note the papers disproving the risk of type 1 diabetes mellitus with childhood vaccinations as well as those addressing new discoveries of leptin action and a novel treatment of osteogenesis imperfecta. I also want to highlight the 2 papers on intersex, intersexuality and sexual identity which denote the current state of treatment controversies.

I am also pleased to bring to your attention enhancements in the print and web-based journal with the addition of color figures and a more efficient search capability. Please keep us posted with your comments and suggestions so we may continue improving the journal.

Respectfully,  
Fima Lifshitz, MD

organizations to search for new methods to control it.<sup>3</sup> Such efforts are likely to be facilitated by a better understanding of the etiology of obesity. Sclafani<sup>4</sup> classified the etiology of animal obesity into 9 groups, including obesity of neural, endocrine, pharmacological, nutritional, environmental, seasonal, genetic, idiopathic, and viral origin. Of these factors, the viral etiology of obesity, a relatively recent discovery first noted in 1982,<sup>5</sup> has barely been studied. Over the past 20 years, 8 pathogens have been reported to cause obesity in animal models.<sup>5-11</sup> The relative contribution of these pathogens to human obesity is not yet clear. Considering the emerging reports addressing an infectious etiology of several other chronic diseases,<sup>12</sup> the contribution of certain infections to the etiology and pathogenesis of obesity need not be inconceivable. If shown to be relevant to humans, this relatively novel concept may be potentially important. An adequate understanding of such pathogens is needed for better management of obesity. A new perspective about the infectious etiology of this disease may initiate additional research in the field to assess the contribution of pathogens in human obesity and its co-morbidities and possibly to prevent or treat the obesity of infectious origin.

The known obesity-producing infective agents are listed in Table 1. There are 7 viral pathogens known to cause obesity in animal models, 4 are either known human pathogens or have been shown to be associated with human obesity. In addition *Chlamydia pneumoniae* has been associated with obesity in humans. In this paper we review the present knowledge in the field as this may be of importance to those who deal with patients and/or those who are interested in obesity.

**Table 1. Pathogens responsible for obesity**

Pathogen (Reference)	Animal model	Possible Mechanism(s)
Human adenovirus-36* (11,15,16)	Chickens, mice, non-human primates	Up-regulation of pre-adipocyte differentiation
Human adenovirus-37* (33)	Chickens	Unknown
SMAM-1 adenovirus* (8,9)	Chickens	Unknown
Borna-disease virus* (10,50,51)	Rats	Hypothalamic damage
<i>Chlamydia pneumoniae</i> * (68)	No animal model, associated with weight gain in humans	Unknown
Scrapie agent (76-79)	Mice	Hypothalamic-pituitary-adrenal axis damage
Canine Distemper virus (5)	Mice	Hypothalamic damage, reduced hypothalamic leptin receptor expression
Rous-Associated virus-7 (6,7)	Chickens	Reduced thyroid hormone levels

\* Human pathogens, and/or associated with human obesity.

## ADENOVIRUS AND OBESITY

### Human Adenovirus Type-36

In 2000 we reported that adenovirus type 36 (Ad-36) causes adiposity in animals.<sup>11</sup> Adenoviruses are naked

DNA viruses with icosahedral symmetry and a diameter of 65-80 nm. In humans, adenoviruses are frequently associated with acute upper respiratory tract infections, and may also cause enteritis and conjunctivitis. Adenoviral infections are transmitted via respiratory, fomite, droplet, venereal, and fecal-oral routes; these are easily isolated from nasal swabs or from feces. There are more than 50 types of human adenoviruses listed with the American Type Culture Collection. Ad-36 cross-reacts minimally, or not at all, with other human adenoviruses<sup>13,14</sup> and apparently is antigenically unique. Ad-36 was first isolated in 1978 in Germany in the feces of a 6-year-old girl suffering from diabetes mellitus and enteritis.<sup>14</sup>

In 4 separate experiments, chickens and mice were inoculated with human adenovirus Ad-36.<sup>11</sup> These animals developed a syndrome of increased adipose tissue and paradoxically low levels of serum cholesterol and triglycerides. This syndrome was not present in chickens inoculated with avian adenovirus chick embryo lethal orphan virus (CELO).<sup>11</sup> Sections of the brain and hypothalamus of Ad-36 inoculated animals did not show any overt histopathological changes. Ad-36 DNA was detected in the adipose tissue, but not in skeletal muscles for as long as 16 weeks after Ad-36 inoculation. Subsequently, to ascertain if blood transfusion from Ad-36 infected chickens could produce adiposity in uninfected animals, 4 age- and weight-matched groups of chickens were used: infected donors and recipients (I-D, I-R) and control donors and recipients (C-D, C-R).<sup>15</sup> Blood was taken from the I-D and C-D groups and injected into the recipient groups. The I-D and the I-R groups developed 2.5 and 1.8 times more visceral fat

as compared with the C-D group. Ad-36 DNA was detected in the adipose tissues of I-D and I-R groups, but not in the controls. The 2 infected groups showed significantly decreased serum cholesterol levels and the I-D group had a significant reduction in serum triglycerides. These data confirmed that Ad-36 produces adiposity and paradoxical reductions in serum lipids. In addition, the study fulfilled a Koch's postulate, namely that adiposity was transmitted from infected animals (I-D group) to a new set of animals (I-R group).

Furthermore, two studies were conducted in nonhuman primates to investigate the adiposity—promoting potential of Ad-36.<sup>16</sup>

In the first study, spontaneously occurring Ad-36 antibodies were detected in stored serum samples from adult male rhesus monkeys that were collected over a 7-year period at the Regional Primate Research Center located at the University of Wisconsin, Madison, WI. The monkeys gained approximately 0.1 kg of body

weight during the year preceding seroconversion, and gained 1.8 kg of weight during the following year. Serum cholesterol fell about 35 mg/dL after the appearance of Ad-36 antibodies. In the second experiment, male marmosets inoculated with Ad-36 had a 4-fold weight gain, with a 60% increase in body fat, and a 34mg/dL reduction in serum cholesterol levels as compared with controls over a 6-month period. These data demonstrate that Ad-36 is capable of increasing body fat in non-human primates.

### Mechanism of Action

The exact mechanism of action on adipocytes by Ad-36 is incompletely understood (Figure 1). Ad-36 was recently reported to up-regulate preadipocyte differentiation *in-vitro*.<sup>17,18</sup> Inoculation of 3T3-L1 preadipocytes with Ad-36, but not Ad-2, a non-adipogenic human adenovirus, resulted in increased adipocyte number, cellular lipid accumulation and glycerol 3-phosphate dehydrogenase levels (an adipocyte differentiation specific enzyme marker).<sup>17,18</sup> On the other hand, expression and secretion of leptin (an adipocytokine involved in body weight regulation) by Ad-36 inoculated fat cells was reduced compared to uninfected controls.<sup>19</sup> The phenomenon of increased lipid accumulation and decreased leptin secretion was observed in 3T3-L1 preadipocytes inoculated with Ad-36 or Ad-37, but not in Ad-2 inoculated cells.<sup>20</sup> Extrapolation of these findings to an *in-vivo* situation would suggest increased adipogenesis due to a relative absence of leptin. Thus, the mechanism may involve up-regulation of fat cell differentiation due to a local, direct effect of the virus, as well as a systemic effect of leptin.<sup>21</sup> The interaction of the viral and the cellular genes involved has not yet been elucidated.

### Adipose Tissue-Immune System Interaction

In light of well documented interactions of adipose tissue involvement with modulators and mediators of immune response, an adipogenic effect of certain pathogens should not be surprising. Cousin et al<sup>22</sup> reported that preadipocytes function like macrophages and possess phagocytic and microbicidal activity. Adipocytes too, participate in the immune response. Leptin, an adipocytokine, enhances proliferation and activation of human circulating T lymphocytes and stimulates cytokine production.<sup>23</sup> In addition to leptin-induced modulation of cytokine release, adipocytes themselves secrete various cytokines<sup>24,25</sup> and, in turn, preadipocytes and adipocytes are subject to cytokine directed modulations.<sup>26,27</sup> Certain cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ), down-regulate preadipocyte differentiation<sup>27,28</sup> and increase leptin secretion by adipocytes<sup>30</sup> and adenoviral proteins sensitize cells to TNF  $\alpha$ .<sup>31</sup> Although Ad-36 reduces leptin expression and secretion from fat cells,<sup>19</sup> its effect on TNF  $\alpha$  is unknown. It is hypothesized, but not tested that Ad-36 proteins decrease both TNF  $\alpha$  levels and leptin, thereby contributing to up-regulation of preadipocyte differentiation by their relative absence.

Considering the extensive interaction between the immune system and the adipose tissue, expansion of the latter in response to certain infections is conceivable. For instance, Macrophage colony-stimulating factor, which promotes the production of macrophages, is also secreted by adipocytes and, when overexpressed *in vivo*, induces significant adipose tissue hyperplasia.<sup>32</sup> It is unknown if any of the obesity promoting pathogens stimulates macrophage colony-stimulating factor production leading to the growth of adipose tissue.

### Human Adenovirus Type-37

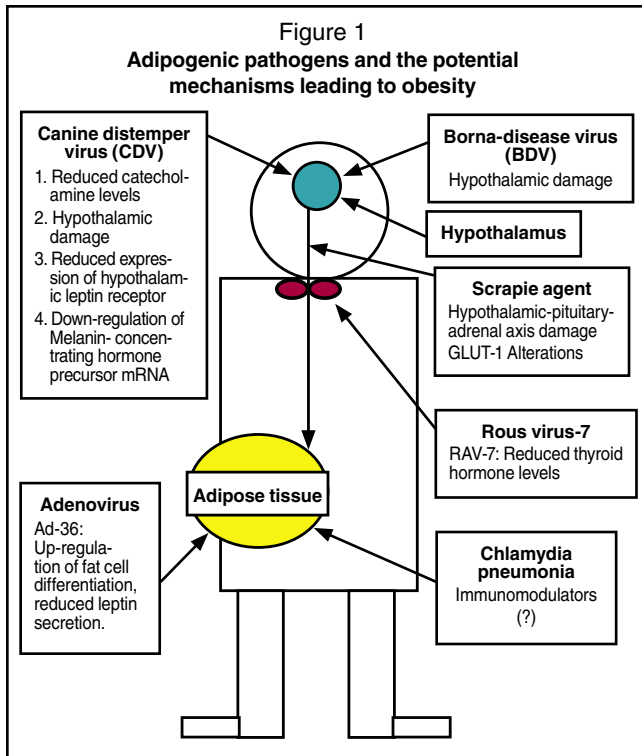
There are other adenoviruses with adipogenic potential properties. In preliminary studies it was demonstrated that Ad-37 increased adiposity in chickens, but that Ad-2 and Ad-31 did not.<sup>33</sup> Currently, minimal additional information is available on Ad-37, but the adipogenic mechanism of this virus may be similar to Ad-36 (Figure 1). However, these results demonstrate that more than one human adenovirus is capable of producing obesity in an animal model, but the adipogenic property is not necessarily shared by all human adenoviruses.

### Adenovirus and Human Obesity

In preliminary studies, human serum samples were obtained from over 500 obese (BMI  $\geq 30$  kg/M<sup>2</sup>) and non-obese volunteers from 3 different sites (Wisconsin, Florida, and New York). The sera were screened for the presence of Ad-36 antibodies using serum neutralization assays. A positive antibody status is suggestive of previous exposure of the individual to the virus. The prevalence of Ad-36 antibodies pooled across the 3 experimental sites was 11% for the non-obese and 30% for the obese subjects.<sup>34,35</sup> Antibody-positive subjects had a significantly higher BMI than antibody-negative individuals. Also, antibody-positive obese subjects had significantly lower serum cholesterol levels compared with the antibody-negative individuals.<sup>34,35</sup> Serum triglyceride measurements were only available at the Wisconsin site, the levels were significantly lower in the antibody-positive subjects versus the antibody-negative counterparts. These data demonstrated that antibody-positive humans were heavier and had lower serum cholesterol and triglycerides levels; these findings were similar to the data of experimentally infected animals with Ad-36. However, extensive research will be needed to establish the contribution of Ad-36 to the etiology of human obesity.

### Adenoviral Infections and Weight Gain in Children: Conjectures

It is well known that respiratory viral infections including adenoviral infections are very common among children.<sup>36,37</sup> Additionally, a very high prevalence of adenovirus is reported in lymphoid tissue obtained by tonsillectomy.<sup>38</sup> Although adipogenic properties of all adenoviruses have not been examined, it is interesting to note that excess weight gain occurs with or without



gain in height in children undergoing tonsillectomy.<sup>39-41</sup> It is not known if tonsillectomy provides the impetus for latent adenoviruses to promote the weight gain. In addition, obese and overweight children have higher levels of markers of inflammation.<sup>42</sup> It is now believed that excess body weight is associated with a state of chronic low-grade inflammation in children as measured by higher levels of C-reactive protein.<sup>43</sup> It is unknown if the inflammatory process is due to infections, or whether it is a causative factor for weight gain in children. Duncan and colleagues<sup>44</sup> showed that fibrinogen and other putative markers of inflammation can predict weight gain in middle-aged adults, which suggests a possible contribution of inflammation to weight gain and/or to co-morbidities associated with obesity. Longitudinal studies that track weight changes in children with and without adenovirus infections are needed to address these issues.

### SMAM-1 Avian Adenovirus

SMAM-1, an avian adenovirus identified in the early 1980s during a poultry epidemic,<sup>45</sup> was found to produce adiposity in chickens.<sup>8,9</sup> We inoculated 3-week-old chickens with SMAM-1 and noted development of excessive visceral fat and paradoxically lower levels of serum lipids compared to the uninfected controls.<sup>8,9</sup> Uninoculated chickens sharing the same room with inoculated chickens (in-contact group) developed the obesity syndrome, presumably due to infection with virus particles carried in the air.<sup>8,9</sup> There was no difference in food intake among the controls, inoculated, and the in-contact group. Visceral fat was greater by 53% and 33% in the inoculated and in-contact groups, respectively. SMAM-1 was reported to be associated with human

obesity. Antibodies to SMAM-1 were found in 11 of 52 subjects.<sup>46</sup> Antibody-positive subjects were heavier ( $95.1 \pm 2.1$  kg vs  $80.1 \pm 0.6$  kg,  $p < 0.02$ ) and had a higher BMI ( $35.3 \pm 1.5$  kg/m<sup>2</sup>, vs  $30.7 \pm 0.6$  kg/m<sup>2</sup>,  $p < 0.001$ ) vs the antibody-negative group. Serum cholesterol was 15% lower and triglycerides were 60% lower in SMAM-1 antibody-positive subjects. Since the prevailing thought was that avian adenoviruses do not infect humans and that human adenoviruses do not cross-react with avian adenoviruses,<sup>47</sup> the findings were surprising. It is possible that a human adenovirus antigenically similar to SMAM-1 produced antibodies that cross-reacted with SMAM-1. Further research is necessary to determine if SMAM-1 is capable of producing obesity and changes in serum lipids in humans. The potential mechanisms whereby infections with this virus lead to obesity remain to be proven (Figure 1).

### Borna Disease Virus

Borna disease virus (BDV) has also been implicated in obesity. This virus was first described in the early 1800s.<sup>48</sup> BDV, has been recently characterized as an enveloped, nonsegmented, negative-stranded RNA virus with a genomic size of approximately 9 kb and nuclear site for replication and transcription.<sup>49-51</sup> The genomic organization is similar to that of members of the Mononegavirales order; therefore, BDV is the prototype of the new family Bornaviridae within this order. BDV infects a broad range of warm-blooded animals from birds to primates. It replicates at lower levels than most known viruses,<sup>52,53</sup> is not lytic, and persists in the nervous system despite a vigorous immune response. Infected animals exhibit movement and behavior disorders.<sup>54,55</sup> BDV-specific antibodies were detected in asymptomatic horses in several countries.<sup>56-60</sup> suggesting that natural infections in animals remain subclinical in most cases.

Gosztanyi and Ludwig<sup>10</sup> reported that BDV infection produces a syndrome of obesity in rats, characterized by lympho-monocytic inflammation of the hypothalamus, hyperplasia of pancreatic islets, and elevated serum glucose and triglyceride levels. The expression of BDV-induced obesity syndrome varies with the age of the animals at the time of inoculation, the genetic background of the host and the viral strain used.<sup>10</sup> Rats infected as newborns with BDV show progressive neurological disease. On the other hand, weanling or adult rats similarly inoculated with BDV develop acute encephalitis and die within 1 to 4 months. Some of these rats survive the infection and develop marked obesity.<sup>61</sup> The obese phenotype has a characteristic distribution of inflammatory lesions and BDV-antigen in the rat brain. Infiltration with mononuclear immune cells and viral antigen expression are restricted to the septum, hippocampus, amygdala and ventromedian tuberal hypothalamus. Therefore, infection with obesity-inducing BDV most likely results in neuroendocrine dysregulations leading to development of obesity.<sup>62</sup> This might be due to the restriction of viral

antigen expression and inflammatory lesions to brain areas that are involved in the regulation of body weight and food intake (Figure 1).<sup>62</sup>

BDV may also be a human pathogen.<sup>48</sup> BDV-specific antigen and BDV-RNA were detected in 4 autopsied human brains with hippocampal sclerosis and astrocytosis. BDV-seropositive neurologic patients have been observed to become ill with lymphocytic meningoencephalitis.<sup>63</sup> In humans BDV is also associated with schizophrenia and mental depression<sup>64,65</sup> that are responsive to treatment by amantadine, an antiviral agent.<sup>66,67</sup> However, the contribution of BVD infections and the relationship to obesity in humans is unknown. Although it would be interesting to know if those with such infections gain more weight; such a relationship has not been reported.

### **Chlamydia pneumoniae**

The relationship between *Chlamydia (C) pneumoniae* infection and coronary heart disease (CHD) is of interest. There are studies that showed that *C. pneumoniae* was related to the development of CHD.<sup>68</sup> While others have found negative results,<sup>72-74</sup> in Australia newly identified cases of CHD compared with matched controls were tested for the presence of serum IgG and IgM against *C. pneumoniae*, *C. trachomatis* and *C. psittaci*. None of the subjects had IgM against chlamydia and only few were positive for *C. trachomatis* and/or *C. psittaci*.<sup>73</sup> The prevalence of seropositivity for *C. pneumoniae* was not significantly different for subjects with or without CHD. Similarly, a number of known CHD risk factors such as hypertension, serum lipids, and glucose levels lacked a significant difference between the antibody-positive and antibody-negative groups. However the antibody-positive group had significantly greater BMI and smaller LDL particle size. Antibody prevalence was significantly greater for subjects with insulin levels above the median and for those with LDL particle size below the median. However, after multivariate analysis, only BMI continued to be associated with seropositivity.

Although the association of *C. pneumoniae* antibodies with CHD may be questioned, the increased BMI with seropositivity to this infection is very intriguing. Approximately 10% of the subjects were obese. The greater prevalence of antibodies in patients in the highest BMI quartile as well as the relationship of BMI with the presence of positive *C. pneumoniae* antibodies may be the result of impaired immunity. Unlike *C. pneumoniae*, antibodies to *C. trachomatis* and *C. psittaci* did not show such a selective or high prevalence among those with higher BMI. A possible explanation offered by Dart et al,<sup>68</sup> which has neither been proved nor disproved, is that *C. pneumoniae* infection may be causally related to increased BMI, though the mechanism involved in this process is not completely known.

### **Scrapie Agent**

Scrapie is a neurodegenerative disease of prion proteins, with a long incubation period, known to occur in sheep and goats. Scrapie affects the brain and is transmissible from animal to animal. The key features of such infections include abnormal behavior and deficits in motor function. Certain scrapie strains induce obesity in experimental animals.<sup>70,71</sup> The obesity-promoting characteristic is a function of the scrapie strain, but not the mouse type. Regardless of the mouse strain tested, scrapie strain ME7 induced obesity. The effect was not observed with scrapie strains 139A or 22L in mice.<sup>78</sup> Vacuolation in the forebrain of the mouse was caused by ME7, whereas 22L and 139A caused vacuolation in the cerebellum and white matter, respectively.<sup>77</sup> The difference in the obesity-promoting potential of the agents may be linked to the differences in the brain lesions. Kim et al<sup>79</sup> demonstrated that ME7-induced weight gain in mice was associated with increased adrenal gland weight and adrenalectomy prevented ME7-induced obesity. Based on these findings, they suggested that scrapie-induced obesity depends on an effect of scrapie on the hypothalamic–pituitary–adrenal axis (Figure 1). Recently, Vorbrot et al<sup>80</sup> demonstrated differences in the distribution of glucose transporter (GLUT-1) in the microvascular endothelium of scrapie-infected SJL/L hyperglycemic mice. These animals showed clinical signs of scrapie, obesity, and reduced glucose tolerance. GLUT-1 receptor density was significantly lower in microvasculature supplying the thalamus, cerebellum and, to a lesser degree, the hippocampus, but was unaffected in microvessels supplying the cerebral cortex and olfactory bulb.<sup>80</sup> Glucose, the major energy source for the brain, is passed across the blood–brain barrier by facilitative diffusion catalyzed by GLUT-1. Reduced GLUT-1 density in the scrapie-infected mice impairs transvascular glucose transport in the above-mentioned brain regions and presumably disturbs their function, which may lead to obesity.<sup>79</sup>

### **Canine Distemper Virus**

Canine distemper virus (CDV) was reported to cause obesity in mice in 1982.<sup>5</sup> CDV is a member of the genus Morbillivirus of the family Paramyxoviridae that causes severe health problems including respiratory, gastrointestinal, and central nervous system disease in dogs and other wild mammals.<sup>81</sup> CDV-induced encephalomyelitis in dogs is the most common cause of death.<sup>82</sup> CDV invades the nervous system and replicates in neurons and glial cells of the white matter during a period of severe viral-induced immunosuppression.<sup>83</sup> An increase in body weight and fat cell size and number was reported in Swiss albino mice experimentally infected with canine distemper virus.<sup>5</sup> Six to 20 weeks after CDV infection obesity was observed in approximately 26% of the mice with intracerebral infection compared to 16% of mice with intraperitoneal infection. Catecholamine levels were reduced significantly in the infected obese mice. The phenomenon of CDV-induced obesity in mice is believed to be due to virus-induced

hypothalamic damage.<sup>84-86</sup> Bernard et al<sup>87</sup> reported down-regulation of expression of the leptin receptor in the hypothalamus of CDV infected obese mice, and suggested this as the cause of the weight gain. Recently Verlaeten et al<sup>88</sup> demonstrated that melanin-concentrating hormone precursor mRNA, an anorexigenic neuromodulator was down-regulated in the late stage of acute phase of CDV infection in mice. Bernard et al<sup>87</sup> speculated that the data demonstrated a “hit and run” type of relationship between CDV and the expression of obesity, ie, the initial viral impact in the hypothalamus may initiate changes that would continue to promote obesity in animals even after the acute infection subsided. CDV is not considered a human pathogen, and its contribution to human obesity is unknown. However, measles virus is a human virus closely related to the CDV, and both belong to the paramyxovirus family, though its relationship to human obesity is not known. Animal experiments showing the effect of measles virus on adiposity are also unavailable.

### Rous Associated virus 7

Carter et al<sup>6</sup> reported that Rous-associated virus 7 (RAV-7) induced obesity in chicken characterized by stunting, hyperlipidemia, and hypercholesterolemia. Inoculation of 10-day-old chick embryos with RAV-7 produced fat deposition around crop and abdominal fat pads in the adult birds.<sup>6</sup> Intravenous inoculation of 1-day-old chickens with RAV-7 did not produce stunting and obesity.

Chicken embryos infected with RAV-7 developed fatty, yellow colored livers, hepatomegaly, anemia, and immune suppression.<sup>6</sup> Livers of infected animals constituted 6.2% of the body weight vs 2.4% of the body weight in the uninfected controls. These signs and symptoms manifested within 3 to 4 weeks after hatching. Obesity, stunting of growth and hyperlipidemia were the most striking features observed in the RAV-7 infected chickens. The mean body weight of the 50-day-old RAV-7 infected chickens was 515 g compared to 194 g of the same age controls. Both the RAV-7 infected and control groups were offered the same amount of food. Although the usual triglycerides levels for chickens are around 100 mg/dL, chickens from the RAV-7 group had serum triglycerides levels over 2000 mg/dL. The authors suggested that the reduced thyroid hormone level in the RAV-7 infected chickens was the cause of the observed obesity and hyperlipidemia.<sup>6</sup> Although lymphoblastoid infiltration of the thyroid gland was noted in the RAV-7 infected chickens, antibodies to thyroglobulin indicative of autoimmune thyroiditis, were absent. Administration of exogenous thyroxine prevented the syndrome.

### CONCLUSIONS AND SPECULATION

Although obesity has multiple causes, an overlooked possibility is that in some instances obesity could be due to an infection. Seven viral pathogens are reported to

cause obesity in animals. Of which, at least 4 are human pathogens and are associated with human obesity. In addition *Chlamydia pneumoniae* has also been associated to human obesity; however more research is needed to further define the mechanisms and the role of these pathogens in its etiology and/or co-morbidities.

It is possible that viral infections exacerbate and facilitate the development of obesity, or its complications, by working in conjunction with other adipogenic factors. For example obese children have been shown to have a cluster of conditions that put them at a high risk for developing diabetes and heart disease.<sup>89</sup> Over one-third of obese children studied presented with dysmetabolic syndrome, defined as hypertension, low HDL cholesterol, high insulin levels, elevated blood glucose and triglyceride levels. In addition, they presented elevated levels of C-reactive protein (CRP); which reflect an inflammatory reaction associated with an increased risk of heart disease. Furthermore, there were decreased levels of adiponectine with increased adiposity. Adiponectine is an anti-inflammatory hormone produced in fat cells that helps regulate glucose and cholesterol metabolism and may help protect blood vessels.

The insidious onset of human obesity makes it difficult to retrospectively link obesity or any of its co-morbidities to a particular episode of infection. Thus, a causative role for infectious pathogens in human obesity is difficult to establish. Due to ethical considerations, humans cannot be experimentally infected with these pathogens; linking the infection to long term weight gain is often impossible. In order to determine the role for viral pathogens in human obesity it is necessary to collect overwhelming indirect evidence in the area, and that remains to be done.

Elucidating the role of obesity of infectious origin could have two goals, prevention and treatment. The prevention of obesity of infectious origin could be achieved by vaccination against individual adipogenic pathogens; whereas the treatment may be more difficult and will depend on the adipogenic mechanism of individual pathogens. Antiviral agents may be of help only if the body continues to harbor the pathogen. Antivirals may be useless if the virus operates in a “hit and run” fashion. In such cases, the offending pathogen will have been cleared from the body long before its resulting impact on weight gain is noticed. Such cases will have to be treated by responding to the metabolic consequences of the infection in a genetically susceptible individual.

Understanding the causes and the mechanisms of obesity of infectious origin will be of immense help in individualizing the management of obesity by permitting cause-specific treatments. Recognizing the role of the above-stated pathogens and identifying more such candidates contributing to human obesity is the first step.

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