INFECTOBESITY: OBESITY OF INFECTIOUS ORIGIN

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ADVANCES IN FOOD AND NUTRITION RESEARCH VOL 52 ISSN: 1043-4526

DOI: 10.1016/S1043-4526(06)52002-9

The rapid increase in obesity and the associated health care costs have prompted a search for better approaches for its prevention and management. Such efforts may be facilitated by better understanding the etiology of obesity. Of the several etiological factors, infection, an unusual causative factor, has recently started receiving greater attention. In the last two decades, 10 adipogenic pathogens were reported, including human and nonhuman viruses, scrapie agents, bacteria, and gut microflora. Some of these pathogens are associated with human obesity, but their causative role in human obesity has not been established. This chapter presents information about the natural hosts, signs and symptoms, and pathogenesis of the adipogenic microorganisms. If relevant to humans, ''Infectobesity'' would be a relatively novel, yet extremely significant concept. A new perspective about the infectious etiology of obesity may stimulate additional research to assess the contribution of hitherto unknown pathogens to human obesity and possibly to prevent or treat obesity of infectious origins.

I. INTRODUCTION

The World Health Organization recently declared that we are experiencing an epidemic of obesity. In the past 20 years, the prevalence of obesity has increased by 30% in the United States and several developed as well as developing countries have reported increased prevalence (Astrup *et al.*, 1998; Powledge, 2004; Rossner, 2005). In the best of hands, obesity treatment usually yields marginal and transient weight loss. More effective and longer lasting strategies for prevention and treatment of obesity are urgently needed. Understanding contribution of various etiologic factors of obesity may lead to treatments directed specifically toward the cause, and consequently, its successful management.

In addition to genetic, behavioral, endocrinal, and other causative factors of obesity, infectious etiology has been known for over two decades

(Sclafani, 1984) but largely ignored for the purpose of obesity prevention and treatment strategies. To date, adipogenic effects of 10 pathogens have been described, which include human and nonhuman viruses, scrapie agents, bacteria, and gut microflora. A comprehensive understanding of their adipogenic role may facilitate further investigation in determining certain infections as an etiologic factor in human obesity. This chapter describes various adipogenic pathogens reported since the first report about obesity-promoting effects of *Canine distemper virus* (CDV) in 1982 (Lyons *et al.*, 1982). A summary of the effects of these adipogenic pathogens on the host and the potential mechanism involved is provided in Tables I and II.

II. *CANINE DISTEMPER VIRUS*

A. CDV GENERAL INFORMATION

The first obesity-promoting pathogen reported (Lyons *et al.*, 1982), CDV of the genus *Morbillivirus*, subgroup of paramyxoviruses, is a lymphotropic and neurotropic negative-stranded RNA virus (Rozenblatt *et al.*, 1985; Vandevelde and Zurbriggen, 1995; Yamanouchi, 1980). CDV causes a frequently fatal disease that affects dogs and a wide range of mammals (Leisewitz *et al.*, 2001; Lyons *et al.*, 1982; Raine, 1976; Summers and Appel, 1994; Vandevelde and Kristensen, 1977). CDV and *Measles virus* (MV) produce similar systemic disorders and are antigenically related (Hall *et al.*, 1980). Although an association of CVD with other human diseases was suggested (Summers and Appel, 1994), CDV is not considered a human pathogen. CDV invades the nervous system and replicates in neurons and glial cells of the white mater subgroup (Vandevelde and Zurbriggen, 1995). Mice or dogs experimentally infected with CDV showed viral inclusions, giant cell formation, reactive gliosis, and myelin degradation (Lyons *et al.*, 1982; Raine, 1976; Vandevelde and Kristensen, 1977). Bernard *et al.* (1993) suggest that CDV infection spreads by humoral and intracellular space pathways or by axonal transport. CDV infection results in acute encephalitis and death of 40–50% of the animals, followed by either motor impairment or obesity syndrome in a late phase in the survivors (Bernard *et al.*, 1988, 1993).

B. CDV-INDUCED OBESITY

Lyons *et al.* (1982) first reported that CDV induces obesity in Swiss albino mice. Results were confirmed later by Bernard *et al.* (1988, 1991, 1993). CDV produced significant increase in body weight and fat cell number as well as

TABLE I
ADIPOGENIC PATHOGENS—AN OVERVIEW

	Year first reported	Animal model used, age, and sex	Duration of onset of obesity	Effect of infection on body weight	Effect of infection on biochemical parameters	Association with human obesity
CDV	1982 (Lyons *et al.*, 1982)	Swiss albino mice, male and female, 4–5 weeks old (Lyons *et al.*, 1982)	Developed 6–10 weeks postinfection and reaches a plateau after 16–20 weeks (Lyons *et al.*, 1982)	Mean weight of infected obese animals was 63.7 g versus 33.1 g in the uninfected group (Lyons *et al.*, 1982)	↑ Insulin (Bernard *et al.*, 1988, 1999) No significant change in glucose (Bernard *et al.*, 1988) ↓ Leptin levels (Bernard *et al.*, 1999) ↓ MCH, NPY (Griffond *et al.*, 2004) ↓ Catecholamine (Lyons *et al.*, 1982) ↓ Neuropeptides (Griffond *et al.*, 2004)	Association with human multiple sclerosis (Summers and Appel, 1994)
RAV-7	1983 (Carter *et al.*, 1983a)	10-day-old embryos—SC white leghorn chicken line (Carter *et al.*, 1983a,b, 1984; Carter and Smith, 1983)	Stunting—14 days posthatching (Carter *et al.*, 1983a) Obesity—3 weeks of age (Carter *et al.*, 1983b)	Stunting ↑ Visceral fat (Carter *et al.*, 1983a,b)	Anemia Hyperlipidemia Immune suppression ↑ Amylase ↑ Insulin ↓ Glucose ↓ Thyroxine (Carter *et al.*, 1983a,b, 1984)	No
BDV	1991 (Gosztonyi and Ludwig, 1995)	Weaning/adult Lewis rats (Gosztonyi and Ludwig, 1995; Herden *et al.*, 2000)	2-month postinoculation (Gosztonyi and Ludwig, 1995)	Obesity with ↑ visceral fat (Gosztonyi and Ludwig, 1995)	↑ Tryglyceride Moderate ↑ blood glucose (Gosztonyi and Ludwig, 1995)	Transmission of BDV from animals to humans is possible (Ludwig and Bode, 2000)

Scrapie	1968 (Pattison and Jones, 1968)	6- to 9-week-old female mice SJL, C57NL, A2G, SAMP8, SAMR1, AKR, 22L (Kim *et al.*, 1987, p. 91; Carp *et al.*, 1998)	12 weeks postinfection (Carp *et al.*, 1984)	↑ Body weight due to fat accumulation (Carp *et al.*, 1984, 1989)	↑ Blood glucose (Vorbrodt *et al.*, 2001) ↓ GLUT-4 density in certain brain areas (Vorbrodt *et al.*, 2001)	Not reported
SMAM-1	1990 (Dhurandhar *et al.*, 1990)	3-week-old white leghorn broilers (Dhurandhar *et al.*, 1990, 1992)	3 weeks postinoculation (Dhurandhar *et al.*, 1990, 1992)	Stunting ↑ Visceral fat (Dhurandhar *et al.*, 1990, 1992)	↓ Cholesterol ↓ Triglyceride (Dhurandhar *et al.*, 1990, 1992)	Yes. Seropositive obese subjects were heavier versus seronegative obese counterparts (Dhurandhar *et al.*, 1997b)
Ad-36	2000 (Dhurandhar *et al.*, 2000)	Chickens Mice Male rhesus and marmoset monkeys Rats (Dhurandhar *et al.*, 2000, 2001, 2002; Pasarica *et al.*, 2006)	4 weeks (Dhurandhar *et al.*, 2000, 2001), 6- to 7-month postinoculation (Dhurandhar *et al.*, 2002; Pasarica *et al.*, 2006)	↑ Body weight ↑ Visceral, epididymal-inguinal, retroperitoneal fat (Dhurandhar *et al.*, 2001; Pasarica *et al.*, 2006)	↓ Cholesterol (Dhurandhar *et al.*, 2000, 2001; Pasarica *et al.*, 2006) ↓ Triglyceride (Dhurandhar *et al.*, 2000, 2001; Pasarica *et al.*, 2006) ↓ HOMA (↑ insulin sensitivity) (Pasarica *et al.*, 2006) ↑ Leptin (Pasarica *et al.*, 2006) ↓ Corticosterone and norepinephrine (Pasarica *et al.*, 2006)	Yes. Greater prevalence of seropositivity in obese versus nonobese subjects. Seropositive subjects were heavier than seronegative counterparts (Atkinson *et al.*, 2005)
Ad-37	2002 (Atkinson *et al.*, 2002)	3-week-old white leghorn chickens (Atkinson *et al.*, 2002)	4-week-postinoculation (Atkinson *et al.*, 2002)	No difference in body weight ↑ Visceral fat (Atkinson *et al.*, 2002)	↓ Triglycerides (Atkinson *et al.*, 2002)	Keratoconjunctivitis and genitourinary tract infections in humans (de Jong *et al.*, 1981)

(*continued*)

TABLE I (*continued*)

	Year first reported	Animal model used, age, and sex	Duration of onset of obesity	Effect of infection on body weight	Effect of infection on biochemical parameters	Association with human obesity
Ad-5	2005 (So *et al.*, 2005)	3-week-old female outbread CD1 mice (So *et al.*, 2005)	22- to 13-week postinoculation (So *et al.*, 2005)	↑ Body weight ↑ Whole body adiposity (So *et al.*, 2005)	–	Respiratory tract infection in humans (Limbourg *et al.*, 1996)
Chlamydia pneumoniae	2000 (Ekesbo *et al.*, 2000)	Humans (Dart *et al.*, 2002; Ekesbo *et al.*, 2000)	Association with increased BMI (Dart *et al.*, 2002; Ekesbo *et al.*, 2000)	Significantly higher BMI (Dart *et al.*, 2002; Ekesbo *et al.*, 2000)	Association with CHD (Danesh *et al.*, 1997; Kuo *et al.*, 1993; Saikku *et al.*, 1988)	Association with increased BMI 27.3 versus 25.8 kg/m^2 (Ekesbo *et al.*, 2000) 26.6 versus 25.5 kg/m^2 (Dart *et al.*, 2002)
Gut microbiota	2004 (Backhed *et al.*, 2004)	8- to 10-week-old germfree male B6/NMRI mice (Backhed *et al.*, 2004)	After 14 days colonization (Backhed *et al.*, 2004)	No difference in body weight ↑ Whole body fat ↑ Epididymal fat ↓ Lean mass (Backhed *et al.*, 2004)	Insulin resistance ↓ Metabolic rate ↑ Hepatic triglyceride content ↑ Expression of *de novo* fatty acid synthesis pathway ↓ Expression Fiaf (Backhed *et al.*, 2004)	–

TABLE II
MECHANISM OF ACTION OF ADIPOGENIC PATHOGENS

	Natural host	Organs/systems affected	Mechanism of action
CDV	Dogs (Leisewitz *et al.*, 2001; Summers and Appel, 1994)	Brain Pancreas Reproductive organs Kidneys Liver (Lyons *et al.*, 1982)	Alters hypothalamic integrity (Bernard *et al.*, 1993, 1999; Nagashima *et al.*, 1992; Verlaeten *et al.*, 2001) ↓ Leptin long receptor and ↑ leptin (Bernard *et al.*, 1999) ↓ MCH (Verlaeten *et al.*, 2001) ↓ Neuropeptides (Griffond *et al.*, 2004) ↓ Catecholamine (Lyons *et al.*, 1982) ↑ Cytokines production (Bencsik *et al.*, 1996) Changes in lipid metabolism (Anderton *et al.*, 1982, 1983a,b; Wild *et al.*, 1986)
RAV-7	Avian	↓ Thymus weight ↓ Bursa weight Fatty, yellow, enlarged livers Lymphoblastic infiltration of thyroid and pancreas (Carter *et al.*, 1983a,b; Carter and Smith, 1983)	↓ Thyroxine (Carter and Smith, 1983)
BDV	Horses and sheep (Gosztonyi and Ludwig, 1995)	Brain Hyperplasia islet of Langerhans (Gosztonyi and Ludwig, 1995)	Inflammatory lesions and viral replication in hypothalamus (Herden *et al.*, 2000)
Scrapie	Sheep and goats (Hunter, 1972)	↓ Size—spleen, liver, kidney, brain, uterus ↑ Adrenal weight (Carp *et al.*, 1984; Kim *et al.*, 1988)	Brain function alteration (Kim *et al.*, 1987; Vorbrodt *et al.*, 2001) ↓ GLUT-1 density, ↓ glucose tolerance (Vorbrodt *et al.*, 2001) ↑ Adrenal weight disturbs hypothalamic-pituitary-adrenal axis (Kim *et al.*, 1988)

(*continued*)

TABLE II (*continued*)

	Natural host	Organs/systems affected	Mechanism of action
SMAM-1	Avian (Ajinkya, 1985)	Liver—↑ size, congested, fatty, infiltrated with intranuclear inclusion bodies Kidney—↑ size ↓ Size of bursae, thymus, spleen (Dhurandhar *et al.*, 1990, 1992)	Impaired liver function (Dhurandhar *et al.*, 1992) Impaired lipogenesis (Dhurandhar *et al.*, 1992) Glucagons deficiency (Dhurandhar *et al.*, 1992)
Ad-36	Human (Wigand *et al.*, 1980)	–	Increased replication, differentiation, and lipid accumulation in preadipocytes (Pasarica *et al.*, 2005; Vangipuram *et al.*, 2004) ↑ Insulin sensitivity (Yu and Dhurandhar, 2005) ↓ Leptin secretion (Vangipuram *et al.*, 2007) and expression (Yu and Dhurandhar, 2005) in fat cells
Ad-37	Human (de Jong *et al.*, 1981)	–	Increased
Ad-5	Human (Limbourg *et al.*, 1996)	–	Increased preadipocyte differentiation (So *et al.*, 2005) Anti-inflammatory response determined by infection (So *et al.*, 2005)
Chlamydia pneumoniae	Humans (Hogan *et al.*, 2004)	Respiratory tract (Kuo *et al.*, 1995)	Mechanism unknown. Preponderance of seropositivity in obese subjects is not an effect of obesity (Dart *et al.*, 2002)
Gut microbiota	Human gut (Xu and Gordon, 2003)	–	Increased processing of polysaccharides Increased calories Increased inefficient metabolism (Backhed *et al.*, 2004)

moderate increase in fat cell size in mice surviving the infection (Lyons *et al.*, 1982). Food intake was slightly but not significantly increased for the obese group (Bernard *et al.*, 1988). Obese and lean animals had comparable titers of anti-CDV-neutralizing antibodies (Lyons *et al.*, 1982).

Obesity was observed in 26% of the animals after an intracerebral inoculation of CDV, while only 16% of animals become obese following an intraperitoneal inoculation. Body weights of the obese animals were comparable to those seen in genetic or hypothalamic models of obesity. When the body weight plateaued at 16–20 weeks postinoculation, mean weight of infected obese animals was 63.7 g versus 33.1 g in the uninfected group (Lyons *et al.*, 1982).

Obese animals had three times more lipid per cell and twice as many fat cells in the inguinal fat pads compared with the lean counterparts. A comparable change was observed in the gonadal and retroperitoneal fat pads (Lyons *et al.*, 1982).

Brains and reproductive organs were lighter and livers, kidneys, and pancreas were heavier in the obese animals, and this difference was statistically significant only for the females. There was no difference in the adrenal and pituitary gland weights. The increase in liver weight was mainly due to accumulation of triglyceride, while no change was detected in phospholipid composition.

Obese mice had decreased lipogenesis in white adipose tissue with unaffected glycogenesis (Bernard *et al.*, 1988). Prior to developing obesity, the CVD-infected group of mice showed increased insulin levels that attained statistical significance of 4–6 months postinfection, when they were six times greater than those in lean animal (Bernard *et al.*, 1988, 1999). However, no significant difference in glucose levels was observed (Bernard *et al.*, 1988).

There was an initial increase, followed by a decrease in leptin long receptor and a dramatic increase in leptin levels accompanied by low levels of viral RNA in targeted CDV brain regions of infected animals (Bernard *et al.*, 1999). Melanin-concentrating hormone precursor mRNA (ppMCH) was downregulated in the late stage of the acute phase CDV infection in mice (Verlaeten *et al.*, 2001). In addition, Griffond *et al.* (2004) reported decreased expression of neuropeptide Y (NPY), melanin-concentrating hormone (MCH), and other neuropeptides in the obese animals.

Catecholamine levels in the obese-infected mice were reduced significantly in forebrain, but not in the brain stem (Lyons *et al.*, 1982). In substantia nigra, CDV infection downregulates tyrosine hydroxylase (TH), the rate-limiting enzyme of dopamine synthesis, which leads to motor impairment of infected animals (Bencsik *et al.*, 1996).

C. MECHANISMS OF CDV-INDUCED OBESITY

As described below, several possible pathways have been proposed to explain the mechanism involved in CDV-induced obesity.

1. CDV replication in the rain

The occurrence of obesity was correlated with the neurovirulence of the virus strain (Bernard *et al*., 1999). Prior vaccination with a vaccinia recombinant coding for CDV surface antigens partially protected against acute encephalitis and obesity (Sixt *et al*., 1998; Wild *et al*., 1993). Neuroadapted CDV strain inoculation by other routes (intranasal, footpad, and subcutaneous) does not produce obesity, suggesting that viral replication in the brain is a prerequisite for development of obesity, as suggested by Bernard *et al*. (1999).

2. Hit-and-run effect

Oldstone *et al*. (1982) reported a novel way by which viruses may cause disease, ''a hit-and-run'' model. Virus replicates in the cells that make growth hormone, thereby disrupting homeostasis and decreasing growth hormone synthesis but surprisingly without producing any cell death or inflammation. Bernard *et al*. (1999) speculated that the initial impact of CDV on hypothalamus may initiate changes that would continue to promote obesity in animals even months after the acute infection, suggesting a ''hit-and-run'' effect.

Viral products are expressed in high levels in the acute stage of infection and at lower levels in the late stage (1 year after infection). Survivors of acute encephalitis complete the elimination of virus-producing cells or suppress expression of viral antigens within a few weeks postinfection (Nagashima *et al*., 1992).

CDV nucleoprotein transcripts and F gene mRNA levels decrease with time, reaching low levels in the hypothalami of the infected rats 1 year postinoculation (Bernard *et al*., 1999). F surface protein of CDV has an essential role in infectivity, allowing viral spread. Defective expression of F gene, along with viral proteins M and HA, may produce viral persistence in brain cells, probably by escaping the host immune system (Liebert *et al*., 1986). There are no signs of inflammation in the hypothalamus (Bernard *et al*., 1999). Infected cells appear intact, despite vital presence (Bernard *et al*., 1993). Bernard *et al*. (1999) suggested that the hypothalamus acts as a reservoir for CDV, and this noncytolytic infection impedes specific hypothalamic functions like weight maintenance (Bray and York, 1971; Olney, 1969; Weingarten *et al*., 1985).

3. *CDV alters hypothalamic integrity*

Hypothalamic nuclei, neuropeptides, and neurotransmitters integrate central and peripheral signals in order to regulate energy balance of the organism (Elmquist *et al*., 1999; Kalra *et al*., 1999; Sawchenko, 1998). Verlaeten *et al*. (2001) suggested that CDV alters hypothalamic integrity and subsequently modifies the homeostasis of the brain, which leads to obesity.

Although CDV targets specific brain structures such as hypothalamic nuclei, thalamus, limbic system, substantia nigra, pars compacta, locus ceruleus, and raphe nuclei (Bernard *et al*., 1993), viral transcripts are only present in few structures, including hypothalamus (Bernard *et al*., 1999).

Nagashima *et al*. (1992) reported that CDV produces a disorganization or destruction of hypothalamic nuclei, including the paraventricular nucleus. Furthermore, obese-infected animals lost pro-opiomelanocortin (POMC) and TH cell bodies (Nagashima *et al*., 1992). Loss of POMC bodies is shown to be associated with development of obesity (Scallet and Olney, 1986). These findings suggest a role for food intake disregulation in the CDV-infected animals. In agreement with these findings, Lyons *et al*. (1982) had reported that food intake of the infected group was greater, but did not attain statistical significance. Perhaps, the small additional energy intake over several weeks eventually contributed to biologically significant gain in body energy stores.

4. *CDV downregulates long leptin receptor and increases leptin*

In the acute phase of infection, the expression of long leptin receptor was upregulated in all tissues targeted by CDV. With the exception of the hypothalamus, the same change was present in the late phase of the infection (Bernard *et al*., 1999). Long form of leptin receptor expression in the hypothalami was downregulated 70% and blood leptin levels were dramatically increased (53.4 μg/l vs 7.1 μg/l) in the late phase of infection when obesity occurred. Leptin, a protein mainly secreted by adipocytes, modulates food intake and energy metabolism (Paracchini *et al*., 2005). Downregulation of leptin receptor produces a state of leptin resistance. Consequentially, an increase in food intake and body weight may follow.

5. *CDV downregulates melanin-concentrating hormone*

Melanin concentration hormone, synthesized in lateral hypothalamus and zona incerta (Bittencourt *et al*., 1992), is recognized to be a potent anorectic peptide that is involved in hypothalamic regulation of feeding behavior (Presse *et al*., 1996; Qu *et al*., 1996; Shimada *et al*., 1998). CDV causes an

initial downregulation of ppMCH in infected mice and this change is maintained in the late stages of infection only in the mice that become obese (Verlaeten *et al.*, 2001). Verlaeten *et al.* (2001) speculated that either a disturbance in cAMP second messenger pathway or a strong induction in TNF-α is responsible for ppMCH downregulation. Expression of ppMCH mRNA is reduced in obese-infected mice by about 70% when compared to lean infected or uninfected mice. MCH protein expression is also decreased even in the absence of neuronal damage or reduction in cell number in hypothalamus, which suggests the "hit-and-run" effect described by Oldstone *et al.* (1982). Verlaeten *et al.* (2001) suggested that this downregulation is related to CDV-induced obesity, rather than CDV infection itself.

6. *CDV decreases expression of neuropeptides*

In the acute phase of infection, CDV decreases the expression of neuropeptides, in particular NPY, MCH, hypocretin, vasopressin, and tachykinins, disturbing homeostatic equilibrium. In the late stage of infection, the lean animals recover, while some of the obese animals surprisingly still have disturbed equilibrium. Interestingly, POMC, the precursors of anorexigenic α-MSH, is not modified, whereas orexigenic peptides like NPY, MCH, and hypocretin are downregulated (Griffond *et al.*, 2004). NPY is involved in the control of hunger, satiation, and satiety (Ramos *et al.*, 2005); MCH participates in food intake and energy expenditure modulation (Collins and Kym, 2003; Kawano *et al.*, 2002); and hypocretins contribute to appetite and satiety regulation, energy equilibrium, arousal and sleep wakefulness, and vigilance and defense behaviors (Burdakov, 2004; Mazza *et al.*, 2005; Sakurai, 2003). Implications of these findings are still unclear (Griffond *et al.*, 2004).

7. *CDV decreases catecholamine levels*

Changes in adrenergic system play a key role in regulating energy balance, and are associated with obesity (Clement *et al.*, 1997; Fisher *et al.*, 1998; Lipworth, 1996). Catecholamine levels were two to three times lower in CDV-infected mice (Lyons *et al.*, 1982). Lyons *et al.* (1982) did not find significant lesions in the brain. Therefore, at the time, they considered reduced catecholamine levels as the cause of the obesity observed in CDV mice.

8. *Increase cytokine production*

Cytokines produced in the brain play an important role in virus–host interaction that may influence viral spread and gene expression and consequently the functioning of neural cells (D'Arcangelo *et al.*, 1991; Merrill and Chen, 1991;

Patterson and Nawa, 1993; Zalcman *et al*., 1994). TNF-α, IL-β, and IL-6 transcripts are selectively expressed in CDV-targeted brain structures, suggesting a possible participation of cytokine in CDV-induced changes. Cytokines are only expressed in brain regions permissive to CDV, suggesting that viral replication is necessary for cytokine expression (Bencsik *et al*., 1996). Upregulation of cytokine expression may alter neural cell function, which the author speculates could trigger the ensuing neurological disorders (Bencsik *et al*., 1996).

III. ROUS-ASSOCIATED VIRUS-7

Rous-associated virus-7 (RAV-7) was the second pathogen reported to cause obesity. In addition, it causes stunting and hyperlipidemia in chickens (Carter *et al*., 1983a). The following is a description of the adipogenic effects of RAV-7.

A. RAV-7 GENERAL INFORMATION

RAV-7, an avian leukosis virus (Carter and Smith, 1984), has an 8.2-kb RNA (Carter *et al*., 1983a). It is the most common naturally occurring avian retrovirus associated with neoplastic disease condition in domesticated poultry (Fadly, 1997).

Avian leukosis viruses are RNA tumor viruses, a subfamily of the retroviridae (Vogt and Hu, 1977). All RNA tumor viruses carry three genes: gag (group-specific antigen), pol (directs the synthesis of the RNA-dependent DNA polymerase of the virion), and env (the gene for the envelope glycoprotein). The envelope glycoprotein of oncoviruses determines type-specific properties of the virion: host range, interaction with neutralizing antibodies, and viral interference. In the avian leukosis viruses, these specific properties are markers for virus classification into five subgroups: A, B, C, D, and F (Vogt and Hu, 1977). RAV-7 shares the least antigenic cross-reactivity within the subgroup C (Duff and Vogt, 1969).

Avian retroviruses have also been classified into two groups based on the time required to produce tumors (Graf and Beug, 1978). However between these groups, there is another group that produces tumors like osteopetrosis after an intermediate latency time (Smith and Moscovici, 1969), immunosuppression (Smith and Van Eldik, 1978), stunting (Banes and Smith, 1977), and anemia (Paterson and Smith, 1978; Smith and Schmidt, 1982). Carter

showed that RAV-7 is classified as an avian retrovirus that causes disease at an intermediate time.

B. RAV-7-INDUCED OBESITY

Carter *et al*. (1983a) showed that RAV-7 induces obesity in chickens, which is characterized by stunting and hyperlipidemia. Birds, when infected as 10-day-old embryos, developed fat deposition around crop and abdominal fat pads. Whereas inoculation of 1-day-old hatched chickens did not produce stunting or obesity (Carter *et al*., 1983a). Difference in food intake was observed only after 3 weeks, when stunting and obesity developed (Carter *et al*., 1983b).

Stunting of growth was the most striking effect of RAV-7. Failure to grow became apparent 14 days posthatching, and the infected animals had grown four times slower than the uninfected controls (3.9 g/day vs 16.3 g/day). Fifty days posthatching, mean weight of RAV-7-infected chickens was 194 g compared to 515 g of the control group. RAV-7 infection caused a marked reduction in thymus weight, whereas the spleen size remained unchanged (Carter *et al*., 1983a). Fifty days after hatching, bursa weight was 0.2 g versus 3.1 g in the uninfected controls.

Three weeks after hatching, infected chickens developed fatty, yellow colored livers, hepatomegaly, anemia, and immune suppression. Infected livers represented 6.2% of the body weight versus 2.4% in the uninfected controls. The liver cells from the 30-day-old RAV-7-infected chickens showed marked histological changes, with disorganization and swollen mitochondria with less cristae. RAV-7-infected chickens showed hyperlipidemia. The most striking effect was observed in several 30-day-old infected chickens that had serum triglyceride levels greater than 2000 mg/dl and interestingly one greater than 14,000 mg/dl.

There was no evidence of neoplastic transformation in the infected chickens, but lymphoblastoid infiltration of the thyroid and pancreas was present as early as 7 days posthatching, and the infiltration involved more tissue with time. Hypoglycemia was present in the infected animals 20 and 40 days after hatching. Serum amylase levels were increased for the infected animals, and this difference was significant 40 days posthatching. Carter *et al*. (1983a) suggested that increased amylase levels and decreased serum glucose values accompanied by histological alteration of the pancreas indicated pancreatic damage. Insulin levels in RAV-7-infected chickens were above normal all through 43 days posthatching and ranged from 114% to 352% of normal, with the exception of 3 days. Twenty and 30 days posthatching, glucagon

levels dropped to 34% and 44% of normal. This period also coincided with high mortality in RAV-7-infected chickens (Carter *et al*., 1983a).

C. SPECIFICITY OF RAV-7-INDUCED OBESITY

Carter *et al*. (1983a,b) reported that the obesity-promoting effects of RAV-7 are common for the subgroup C of avian leucosis viruses, but not for the other subgroups (A, B, D, or F). Chickens infected with subgroups A, B, D, E, and F showed osteopetrosis (predominant for MAV-1 and MAV-2), anemia, liver lesions, blood cysts, fibrosarcoma, or nephroblastoma (predominant for MAV-2), but did not develop adiposity (Carter and Smith, 1984).

Subgroup C viruses tested (RAV-7, transformation-defective B77, transformation-defective Prague strain of *Rous sarcoma virus*, RAV-49) caused stunting, lymphoblastoid infiltration of the thyroid and pancreas, decreased thyroxine, and increased insulin and liver weight, with RAV-7 showing the greatest change. These results were obtained from 10-day-old embryos intravenously inoculated with different types of viruses belonging to avian leukosis class. Subgroup C virus-infected chickens were significantly stunted 20, 30, or 40 days posthatching.

The possibility that the envelope of avian leukosis virus is involved in the pathogenesis of disease was examined by comparing the changes induced by RAV-7, and other viruses in subgroups A, B, D, and F. Subgroup C viruses produced similar changes, which were not common to those from other subgroups. This suggested that the envelope may be involved in pathogenicity (Carter and Smith, 1984). RAV-7 shares the least antigenic cross-reactivity within the subgroup C viruses (Duff and Vogt, 1969), which may explain its greater pathogenicity compared to other viruses in the same subgroup.

At 10 days posthatching, 25–75% of thyroid tissue from all subgroup C virus-infected chickens appeared to be lymphoblastoid and at 30 days posthatching, the effect was more prominent, showing the presence of plasma cells. T4 levels in the serum were significantly lower for RAV-7- and tdB77-infected chickens at 10 days posthatching, while those for RAV-49-infected chickens attained significantly lower levels after 20 days. T4 levels continued to decrease until 45 days posthatching, when all the viruses in subgroup C had significantly lower T4 levels.

Infiltration of the pancreas varied at 10 days posthatching among the viruses, being the most severe for RAV-7 and RAV-49. However by 20–30 days posthatching, all the subgroup C viruses tested showed germinal center formation. Insulin levels were increased 10 days after hatching compared with the control group and by 45 days after hatching the difference was significant for all subgroup C viruses.

Livers from all infected chickens showed mild lymphocytic infiltration 10 days posthatching with slight enlargement of hepatocytes after 30 days, which the authors attribute to fat accumulation. Chickens infected with all subgroup C viruses had significantly increased relative liver weights at all times compared with the controls.

Serum triglyceride levels in chickens infected with all subgroup C viruses were increased. The greatest change was induced by RAV-7 with a mean of 1500 mg/dl after 45 days compared with a range of 68.2–90.5 mg/dl in uninfected chickens. Cholesterol levels decreased initially followed by a significant increase, 45 days posthatching. Marked hyperlipidemia was present only in RAV-7-infected chickens.

Histological examination of thyroid, pancreas, and liver showed no similarity between subgroup C-induced changes and those by Rous-associated viruses of other subgroups (A, B, D, and F). Fat accumulation as adipose tissue and fatty liver was apparent only for RAV-7-infected chickens. Relative liver weights were higher for all infected animals. MAV-1- and RAV-1-infected chickens showed significant increase in insulin levels, but the increases were smaller compared to those induced by RAV-7. All avian leucosis virus-infected chickens showed decreased T4 levels, with a significant difference in RPV and RAV-61 (subgroup F). Changes in T4 levels in these chickens were smaller compared to the changes induced by RAV-7, which also showed thyroiditis.

D. MECHANISM OF RAV-7-INDUCED CHANGES

A decrease in thyroid hormone levels is the major metabolic change that may explain adiposity and other changes induced in RAV-7-infected chickens (Duff and Vogt, 1969). Chicken embryos infected with RAV-7 showed alteration in thyroid tissue 2 days posthatching, lymphoblastoid infiltration 7 days posthatching, and extensive infiltration, loss of normal thyroid structure, and significantly lower levels of T3 and T4 16 days posthatching. Chickens with hypothyroidism induced by Tapazole have near normal growth characteristics after daily administration of T4 (Singh *et al.*, 1968). When RAV-7-infected chickens received supplementation with Synthroid, the disease symptoms alleviated showing a decrease in body weight, relative liver weight, and insulin levels. Although an increased mortality in the group fed low-fat diet was noted, fat content of the diet did not influence stunting or obesity (Carter *et al.*, 1983b).

Levels of T4 were decreased for all avian leukosis virus-infected chickens and correlated with stunting of animals (Carter and Smith, 1984). The possibility of autoimmune thyroiditis was considered due to the similarity in thyroid infiltration and change of T4 levels (Carter and Smith, 1984) present in an obese chicken line and RAV-7-infected chickens. The obese chicken

line is a phenotypic expression of the genetically determined autoimmune thyroiditis (Wick *et al*., 1981). However, the possibility of autoimmune thyroiditis was excluded since no precipitating antithyroglobulin in the sera of RAV-7-infected chickens was observed.

RAV-7-induced hyperlipidemia could be a result of hypothyroidism. Hyperlipidemia appears to be common in hypothyroid animals, where there is a decrease in lipid utilization or catabolism (Hoch, 1974).

Similar etiology was suggested for increased insulin levels and localized lymphoblastoid infiltration of the pancreas (Carter and Smith, 1984) because it was observed that amelioration of thyroid function by Synthroid administration reduces insulin levels (Carter and Smith, 1983). Increased mortality that occurred 20 and 30 days posthatching may be the result of a severe drop in glucagon levels (Carter and Smith, 1983; Carter *et al*., 1983a), which determines severe hypoglycemia (Mikami and Ono, 1962).

IV. *CHLAMYDIA PNEUMONIAE*

Chlamydia pneumoniae (CP) is the first bacteria reported to be associated with increased body mass index (BMI) in humans. Experimental inoculation of animals with CP to study the effect on body weight has not been reported.

A. CP GENERAL INFORMATION

Chlamydia is a eubacteria that causes widespread infection in humans (Hogan *et al*., 2004). CP respiratory infection occurs in almost all humans during lifetime (Hogan *et al*., 2004) and results in 10% of community-acquired pneumonia and 5% of bronchitis and sinusitis cases (Kuo *et al*., 1995). Association between CP and coronary heart disease (CHD) is equivocal. Some studies show an association between CP and CHD (Danesh *et al*., 1997; Kuo *et al*., 1993; Saikku *et al*., 1988), while others found none (Caligiuri *et al*., 2001; Hoffmeister *et al*., 2000). Hoffmeister *et al*. (2000) reported that indicators of atherogenic lipid profile, like decreased HDL-C, HDL-C to total cholesterol ratio, apoAI, and increased apoB, were associated with current infection with *Helicobacter pylori*, but not with CP or Cytomegalovirus (Hoffmeister *et al*., 2001).

B. CP ASSOCIATION WITH HIGHER BMI

Some studies reported an association between CP infection and increased BMI (Dart *et al*., 2002; Ekesbo *et al*., 2000), while others did not find any relation (Blanc *et al*., 2004; Falck *et al*., 2002; Muller *et al*., 2003).

Ekesbo *et al.* (2000) reported that a group of subjects with combined serology for CP and *H. pylori* had significantly higher BMI compared to the control group (27.3 kg/m^2 vs 25.8 kg/m^2). Greater age, lower socioeconomic status, and greater fasting levels of insulin also characterize the antibody positive subjects. The authors suggested that "Obesity might be a marker not only for lower social class but also for greater than normal susceptibility to such infections" (Ekesbo *et al.*, 2000). Similar correlation was found in another study where subjects positive for IgG to CP had significantly higher mean BMI compared to the seronegative subjects 26.6 kg/m^2 versus 25.5 kg/m^2, respectively (Dart *et al.*, 2002). There was no association between CHD or coronary artery stenosis and infection with CP. Antibody positive subjects had increased BMI, smaller LDL particle, and greater insulin levels. However, after multivariate analysis, only BMI continued to be associated with seropositivity (Dart *et al.*, 2002).

C. MECHANISM OF CP EFFECTS

Dart *et al.* (2002) postulated that CP infection is causally related to increased BMI, although the mechanism is completely unknown.

Obesity is associated with impaired immunity (Fried *et al.*, 1998; Tanaka *et al.*, 1993; Visser *et al.*, 1999) and as suggested by Ekesbo *et al.* (2000) obesity might be the indicator for increased susceptibility to *H. pylori* and CP infection (Ekesbo *et al.*, 2000). However, Dart *et al.* (2002) found no preponderance of antibodies to *Chlamydia trachomatis* and *Chlamydia pssittaci* in the same subject population. Lack of relationship of BMI with prevalence of antibodies to *C. trachomatis* and *C. pssittaci* indicated that increased BMI did not necessarily predispose the subjects to "catch" infection. Experiments with animal models designed to investigate the adipogenic potential of CP and human sero-epidemiological data are needed to further determine the role of CP in obesity.

V. SCRAPIE AGENT

Scrapie agents have been reported to cause obesity in mice, and the effect is dependent on the strain of scrapie. Relevance of the findings to humans has not been established.

A. GENERAL INFORMATION

Scrapie is a neurodegenerative disease with a long incubation period, known to occur in sheep and goats, however, mice and other small rodents can be infected with it (Hunter, 1972). Certain scrapie strains induce obesity in

experimentally infected animals, although the main manifestation of scrapie infections is abnormal behavior and motor dysfunction in mice (Kim *et al.*, 1987) and hamsters (Carp *et al.*, 1990). Incubation period determined by the mouse gene Sinc and manifestation of disease varies with the scrapie and mouse strain (Dickinson and Meikle, 1971).

B. SCRAPIE-INDUCED OBESITY

Weight increase in scrapie-infected animals was observed as a preclinical manifestation as early as 1968 by Pattison and Jones (1968) and was followed by Outram and Markovits in 1972 and 1981, respectively (Markovits *et al.*, 1981; Outram, 1972).

Mice infected with certain strains of scrapie determine a significant increase in body weight in the preclinical phase of the disease (Carp *et al.*, 1984). Regardless of the mouse strain, the scrapie strain ME7 injected in the hypothalamus-induced obesity (Carp *et al.*, 1984, 1998; Kim *et al.*, 1987, 1988). This effect was also observed for 22L scrapie strain injected in certain type of mice (Carp *et al.*, 1984, 1998; Kim *et al.*, 1987), but not for 139A (Carp *et al.*, 1984, 1998; Kim *et al.*, 1987, 1988) or 22A scrapie strains (Carp *et al.*, 1984).

Hypothalamic injection of ME7 injection induced obesity in SJL, C57NL, A2G, SAMP8, SAMR1, and AKR mice (Carp *et al.*, 1984, 1998; Kim *et al.*, 1987, 1988). Twelve weeks postinfection with ME7, SJL mice weighed significantly more than the control group and this difference reached maximum after 4 weeks. Infected animals showed 80% and 68% increase in body weight when injected in the hypothalamus or cortex, respectively, versus 41% in the control group. The weight increase was due to fat accumulation, and not due to edema (Carp *et al.*, 1998; Outram, 1972). Surprisingly, spleen, liver, kidney, brain, and uterus weights were lower than those in the control (Carp *et al.*, 1984; Kim *et al.*, 1988). Adrenal gland was the only organ with significantly greater weight in the infected group. This increase was due to marked enlargement in zona fasciculate and slight enlargement in zona glomerulosa of the cortex, without any cytopathic changes (Kim *et al.*, 1988).

Weight gain in ME7-infected mice paralleled increase in food consumption (Kim *et al.*, 1988). The weight gain appeared 67 days postinfection and continued throughout the preclinical phase of the disease (Kim *et al.*, 1988). Unexpectedly, at the same time there was an increase in food consumption in scrapie strain 139A-infected SJL mice, which did not become obese. The author suggests a possibly separate mechanism for food consumption and weight gain (Kim *et al.*, 1988).

ME7 injected in the hypothalamus, but not in cortex, induces obesity in C57NL mice. ME7 produced the same pattern of vacuolation in nine

different brain regions, regardless of the injection site (Kim *et al.*, 1987). The only difference was in the brain region predominantly affected: ME7 affected the forebrain region, 22L affected the cerebellum, and 139A the white matter (Kim *et al.*, 1988).

22L strain of scrapie injected in the cortex or hypothalamus of SJL mice induced obesity (Carter and Smith, 1984; Kim *et al.*, 1987). However when injected in SAMP8, SAMR1, AKR (Carp *et al.*, 1998), and CBA mice (Carp *et al.*, 1984), the scrapie strain did not produce any differences in body weight. SJL-infected mice showed 73% and 70% increase in body weights when injected in hypothalamus or cortex, respectively, versus 36% increase in the control group. Furthermore, the weight difference became significant earlier, compared to when inoculated with 22L (10 weeks vs 12 weeks postinjection) (Kim *et al.*, 1987).

A significant decrease of GLUT-1 in thalamus, cerebellum, and hippocampus along with reduced glucose tolerance and hyperglycemia in ME7-infected mice suggested disregulation in function of the affected brain regions (Carp *et al.*, 1989; Kim *et al.*, 1988).

C. MECHANISM OF SCRAPIE-INDUCED OBESITY

Involvement of the brain is strongly implicated in scrapie-induced obesity. Kim *et al.* (1987) speculated that scrapie-induced obesity is related to changes in CNS and neuroendocrine dysfunction and that the condition was also dependent on the route of inoculation. ME7 induced obesity in C57NL mice only when injected in hypothalamus, but not cortex, whereas hypothalamic and not cortical route of inoculation was required for increasing body weight in SJL. Similar weight gain and patterns of vacuolation were obtained whether ME7 was injected unilaterally or bilaterally in the hypothalamus of SJL mice, suggesting that scrapie can spread to the opposite hemisphere after replication at the site of injection (Kim *et al.*, 1987).

Role of brain function alterations was further supported by the findings of Vorbrodt *et al.* (2001), who reported a decrease in GLUT-1 density in certain brain regions, reduced glucose tolerance and hyperglycemia in ME7-infected mice. Glucose is of critical importance for normal functioning of the nervous system and impaired glucose transport could untimely lead to impaired brain function. The authors recommend further studies to elucidate the regional difference in GLUT-1 expression and the effect on brain function (Vorbrodt *et al.*, 2001).

In addition to the role of higher centers, a hypothalamic-pituitary-adrenal axis-mediated mechanism for scrapie-induced obesity has been suggested (Kim *et al.*, 1988). Adrenals in the scrapie-induced mice were significantly larger than controls and adrenalectomy performed before ME7 injection

prevented weight gain in mice, which support the hypothesis. Although one of the possible downstream effects of impaired higher brain center functions is food intake dysregulation, increased food intake did not necessarily explain obesity in all models of scrapie strains. ME7- and 139A-infected SJL mice showed increase in food consumption, however only ME7 induced obesity (Kim *et al.*, 1988). Kim *et al.* (1988) suggested that the pathways involved in increasing food consumption and weight gain may be separate in these models.

Moreover, the duration of scrapie incubation does not seem to play a role in the development of obesity. Carp *et al.* (1984) showed that Sinc mouse gene, which determines the incubation period, is not involved in scrapie-induced obesity. 22L strain was injected into three mouse strains with the same s7s7 Sinc genotype, which resulted in obesity in SJL mice, but not the other two strains (Carp *et al.*, 1984).

VI. *BORNA DISEASE VIRUS*

A. GENERAL INFORMATION

Borna disease virus (BDV) is an enveloped, nonsegmented, negative-stranded RNA virus belonging to the Mononegavirales order (Kao *et al.*, 1993; Rott and Becht, 1995; Stitz *et al.*, 1995). Although it can produce a strong immune response and the disease can be fatal, BDV may persist in the nervous system with no major symptoms (Ludwig and Bode, 2000; Narayan *et al.*, 1983; Solbrig *et al.*, 1995). Experimental infection with BDV has been shown in chickens, mice, rats, rabbit, hamsters, and rhesus monkeys models (Ludwig *et al.*, 1988; Richt *et al.*, 1992). Rats infected with BDV showed behavior changes and learning deficits (Ludwig and Bode, 2000). BDV causes encephalopathy in a broad range of animals like horses, sheep, cattle, cats, and dogs (Ludwig and Bode, 2000). BDV incidence was reported worldwide: in UK (Thomas *et al.*, 2005), Iran (Bahmani *et al.*, 1996), Japan (Terayama *et al.*, 2003), China (Yang *et al.*, 2003), Germany (Bechter *et al.*, 1987), and the United States (Kao *et al.*, 1993). Ludwig and Bode (2000) postulated that a cross species transmission of BDV from animals to humans may be possible. BDV received considerable attention when de la Torre (1994) demonstrated that BDV can infect human brain, by detecting BDV-specific antigen in four autopsied human brains. Fifty BDV studies were reported in humans before the beginning of 2000, including case studies, serological, or viral prevalence studies. Chalmers *et al.* (2005) reported in their review that seroprevalence in humans varied from 0% to 48% and viral prevalence from 0% to 82%. Mental disorders like depression

and schizophrenia are associated with BDV-specific antibodies prevalence (Chen *et al*., 1999; Ferszt *et al*., 1999; Richt *et al*., 1997) and BDV RNA in the peripheral blood (Chen *et al*., 1999). Chen *et al*. (1999) provided some evidence for a possible human to human transmission of BDV infection, by showing that psychiatric patient's family members and the mental health workers had higher prevalence of BDV antibodies than control. However, Ferszt *et al*. (1999) postulated that the higher prevalence of BDV antibodies in depressive patients may be a nonspecific aspect of immunosuppression. Although the BDV pathogenesis is not yet clear, a pathogen once thought to only infect animals certainly appears to infect humans as well.

B. *BORNA DISEASE VIRUS*-INDUCED OBESITY

Gosztonyi *et al*. (1991) described an obesity syndrome induced by BDV in rats. Induction of obesity was dependent on age and genetic characteristics of animals and virus strain (Gosztonyi and Ludwig, 1995; Gosztonyi *et al*., 1991). Weanling or adult rats developed acute encephalitis 1–4 months post-BDV infection. Two moths later, surviving animals developed marked obesity. Virus-specific antigen and inflammatory infiltrate were present in brains of obese rats, and decreased progressively with time, reaching very low levels 18–24 months postinfection (Gosztonyi and Ludwig, 1995; Gosztonyi *et al*., 1991). The lymphomonocytic inflammatory infiltration was found in the hypothalami of all infected rats. Progressive neural degeneration located mainly in the dentate gyrus was accompanied by marked hydrocephalus. Spongy degeneration foci were present in the cerebellum, followed by reactive astrocytosis. Obese rats had massive visceral fat deposition with increased triglyceride and hyperplasia of Islets of Langerhans, with moderate increase in blood glucose (Gosztonyi and Ludwig, 1995).

C. MECHANISM OF BDV-INDUCED OBESITY

Herden *et al*. (2000) compared the effect of two different BDV variants, one that induces obesity (BDV-ob) and one that induces the biphasic course of the disease (BDV-bi) in order to determine the mechanism of BDV-induced obesity. No antigenic variation was present between the two different phenotypes. Four-week-old Lewis rats were inoculated intracerebrally with the infectious brain homogenate of BDV-ob or BDV-bi representing the control group. Fifty-six days postinfection animals infected with BDV-ob reached significantly higher body weight ($p < 0.0001$) compared with the control group. No neurological signs were observed in the obese group, whereas the control group developed the biphasic form of infection with ataxia, hyperactivity, and weight loss followed by apathy and somnolence. Both groups

developed nonpurulent meningoencephalitis with mononuclear perivascular and parenchymal infiltration. These were generalized in the control group, but restricted to the ventromedial tuberal hypothalamus, septum, hypocampus, and amygdala in the obese group. Viral antigen expression presented a similar pattern of distribution. BDV-ob infection produced low levels of replication, in contrast with BDV-bi where replication was persistent for more than 210 days. Therefore, Herden *et al.* (2000) hypothesized that BDV-induced obesity may be due to inflammatory lesions and viral antigen expression in brain, especially in the hypothalamus, which is known to regulate body weight and food intake.

VII. GUT MICROBIOTA

A. GENERAL INFORMATION

Microbiota is a collection of microorganism, growing in the human gut. It is mostly composed of anaerobic bacteria, which are essential for processing dietary polysaccharides (Xu and Gordon, 2003). These bacteria act in a symbiotic relationship with the human gut, consuming as well as distributing energy by processing nutrients inaccessible to humans in other ways (Backhed *et al.*, 2005). Moreover, it regulates human immune system (Braun-Fahrlander *et al.*, 2002), fortifies the mucosal barrier, and stimulates angiogenesis (Hooper, 2001; Hooper *et al.*, 2003; Stappenbeck *et al.*, 2002).

B. MICROBIOTA-INDUCED OBESITY

Backhed *et al.* (2004) reported that gut microbiota regulates fat storage. Fourteen days postconventionalization with normal microbiota, germfree mice developed more body fat and insulin resistance, with surprisingly lower food intake. These effects were seen in male and females in two different mouse strains (B6 and NMRI) (Backhed *et al.*, 2004).

Eight- to ten-week-old male germfree mice, which experience colonization for 14 days, showed 57% increase in total body fat with 61% increase in epididymal fat and 7% decrease in lean mass with no difference in body weight. Lipid profile did not change after colonization. A similar change was determined by colonization of germfree animals at birth or for different amount of time; however, increasing colonization time did not amplify the effect on adipose tissue (Backhed *et al.*, 2004).

Subsequently, germfree mice were colonized only with *Bacteroides thetaiotaomicron*, which is predominant in gut microbiota and has the ability to degrade plant polysaccharides (Hooper *et al.*, 2001). *B. thetaiotaomicron* is

associated with induction of host monosaccharide transporters (Xu and Gordon, 2003). After a 14 days colonization period, these mice developed 23% more body fat than their germfree counterparts showing a similar change to the complete colonization effect, but to a smaller extent (Backhed *et al*., 2004).

Ley *et al*. (2005) reported that obesity correlates with a shift in microbiota composition. Obese mice showed 50% decrease in *Bacteroides* and significant increase in Firmicutes ($p < 0.05$), independent on kinship or gender. Offspring shared cecal microbiota with their mothers, independent of their ob phenotype. The authors suggest that changes in microbiota of ob/ob animals "may represent an unheralded contributing factor to their fuel partitioning" (Ley *et al*., 2005).

C. MECHANISM OF MICROBIOTA-INDUCED OBESITY

Colonization for 14 days produced a 27% decrease ($p < 0.01$) in metabolic rate, whereas high energy phosphate stores remained unchanged. Thus, obese colonized animals consume more oxygen without increasing high energy phosphate stores, which suggest the presence of inefficient metabolism (Backhed *et al*., 2004).

The microbiota determined a 2.3-fold increase in hepatic triglyceride content, with no change in cholesterol, but significantly increased expression of *de novo* fatty acid synthesis pathway genes (Backhed *et al*., 2004). Moreover, colonization decreased the expression of fasting-induced adipocyte factor (Fiaf) (Backhed *et al*., 2004), also called angiopoietin-like protein 4, an inhibitor of lipoprotein lipase (LPL) *in vitro* (Yoshida *et al*., 2002). This effect is not dependent on mature lymphocytes or PPAR-γ (Backhed *et al*., 2004). The authors suggest that the microbiota act via Fiaf to increase hepatic lipogenesis as well as increase adipose tissue LPL. Thus, the extra energy harvested from the gut by microbiota is converted to lipids in the liver and LPL helps deposition of this lipid in adipocytes and adiposity ensues (Backhed *et al*., 2004).

VIII. ADENOVIRUSES

Four adipogenic pathogens are adenoviruses. Adenoviruses were first isolated in 1953 by investigators attempting to establish cell lines from the adenoidal tissue of children after tonsillectomy (Shen and Shenk, 1995). Adenoviruses are widespread in nature, infecting birds, mammals, and humans. In humans, adenoviruses are frequently associated with acute upper respiratory tract infections, enteritis, or conjunctivitis. Presence of serum antibodies

to adenovirus is common in the general population (Foy and Grayston, 1976). Adenoviral DNA is detected in adult human lymphocytes, and the number of positive cells increases with the age of the person (Horvath *et al*., 1986).

There are six major subgroups among the 50 human adenoviruses maintained by the American Type Culture Collection (ATCC). Each subgroup has a number of specific serotypes. Adenoviruses are nonenveloped DNA viruses with icosahedral symmetry and a diameter of 65–80 nm (Pereira *et al*., 1963). All adenoviral genomes have the same general organization, that is the genes encoding specific functions are located at the same position on the viral chromosome (Shen and Shenk, 1995). The genome consists of a single linear, double-stranded DNA molecule consisting of five early transcription units (E1A, E1B, E2, E3, and E4), two delayed early units (IX and IVa2), and one major late unit which generates five families of mRNAs (L1–L5). Adenoviruses can be readily propagated in primary cell cultures or cell lines, replicate within the nucleus of the infected cells, and produce characteristic cytopathic changes in the cell.

IX. SMAM-1

Avian adenovirus SMAM-1 causes adiposity in chickens and shows association with human obesity. It is the first virus to be linked with human obesity. Increased adiposity with hypolipidemia are the peculiar features of this syndrome.

A. SMAM-1 GENERAL INFORMATION

Adenoviruses are responsible for approximately 8% of the viral infection worldwide (Rubin, 1993). Avian adenovirus SMAM-1 was discovered during a poultry epidemic in early 1980s (Ajinkya, 1985) and it is serologically related to avian adenovirus Chick Embryo Lethal Orphan virus (CELO).

B. SMAM-1-INDUCED OBESITY

Three-week-old chickens experimentally inoculated with SMAM-1 developed excessive visceral fat compared to the uninfected controls 3 weeks postinoculation. Another group of chickens sharing the cage with the infected group (in-contact group) also developed significant visceral adiposity, suggesting a horizontal transmission of the virus in cage mates (Dhurandhar *et al*., 1990, 1992). Visceral fat was greater by 53% and 33% in the infected and in-contact group, respectively. Interestingly, SMAM-1-induced adiposity was accompanied by paradoxically lower serum cholesterol and triglyceride levels.

Food intake of the chickens could not explain the adiposity (Dhurandhar *et al*., 1990, 1992).

At baseline, body weights were similar for all groups; however, after 5 weeks the infected group weighted significantly less than the control (924.8 ± 102.1 g vs 995.7 ± 97 g). Furthermore, weight gain between the third and sixth week was 473.8 ± 90.7 versus 571.8 ± 63.5 in the infected and control groups, respectively. The in-contact group tended to have lower body weight after 6 weeks, but the difference was not significant (Dhurandhar *et al*., 1992).

One week postinoculation, the infected and in-contact group had significantly lower cholesterol and triglyceride levels when compared to the control. Cholesterol values were 46.1 ± 10.3 mg/dl versus 56.5 ± 10.8 mg/dl and triglycerides 19.9 ± 7.9 mg/dl versus 67.1 ± 18.5 mg/dl in the infected and control groups, respectively. After 2 weeks, cholesterol as well as triglycerides remained lower for the infected and the in-contact groups, but only cholesterol showed statistical significance 3 weeks postinoculation (Dhurandhar *et al*., 1992).

Livers were significantly heavier for the infected and in-contact groups. Livers and kidneys of the infected animals were enlarged and pale brown. Histopathology of the livers showed severe congestion, fatty infiltration, and presence of intranuclear inclusion bodies. The in-contact group showed similar but less severe changes. Bursae, thymus, and spleen were atrophied in the infected and in-contact group (Dhurandhar *et al*., 1992).

Subsequently, Dhurandhar *et al*. (1997a) reported an association between SMAM-1 seropositivity and human obesity. This was the first virus reported to be associated with human obesity. Using an agar gel precipitation assay, Dhurandhar *et al*. (1997a) reported 20% prevalence in 52 obese subjects from India screened for the presence of antibodies against SMAM-1. Similar to the syndrome caused by SMAM-1 in chickens, the seropositive human subjects had significantly higher body weight and BMI and significantly lower blood lipid levels.

These subjects were men and women from an outpatient treatment program in Bombay, India, with a mean age of 39 and a mean BMI of 31.6 kg/m^2. The antibody positive subjects had significantly greater BMI (35.3 ± 1.5 kg/m^2) compared to antibody negative subjects (30.7 ± 0.6 kg/m^2, $p < 0.001$). A similar difference was seen in body weight. The antibody positive subjects weighted significantly more than the antibody negative ones (95.1 ± 2.1 kg vs 80.1 ± 0.6 kg, $p < 0.02$). The differences were valid even within gender. Serum cholesterol was 15% lower ($p < 0.02$) and triglyceride 60% lower ($p <001$) in the antibody positive subjects compared to antibody negative counterparts (Dhurandhar *et al*., 1997a). In addition, two of the positive serum samples cross-reacted with each other, suggesting presence of active viremia. The findings were surprising as avian adenoviruses have been

thought to be serologically different from human adenoviruses (Asch *et al.*, 1979; McFerran *et al.*, 1975), and therefore, unable to infect across species.

C. MECHANISM OF SMAM-1-INDUCED OBESITY

Dhurandhar *et al.* (1992) suggested that SMAM-1 infection could impair normal liver function, causing fatty liver and decreasing cholesterol and triglyceride levels. Consequent to impaired hepatic lipogenesis, increased visceral fat accumulation may be due to either increased compensatory lipogenesis or reduced lipolysis in fat cells. Moreover, since chickens are very sensitive to glucagon, the authors expressed the possibility that glucagon deficiency could be responsible for greater accumulation of visceral fat due to reduced lipolysis (Dhurandhar *et al.*, 1992). Both theories have not been tested.

The authors postulated that high infectivity of SMAM-1 and the temporal association between the appearance of SMAM-1 in chickens in India and worldwide increase in obesity may suggest the role of SMAM-1 in human obesity (Dhurandhar *et al.*, 1997a). However, further research is necessary to demonstrate such a role.

X. ADENOVIRUS TYPE 36

Animals experimentally infected with Adenovirus type 36 (Ad-36) develop greater adiposity but a relative hypolipidemia. Sero-epidemiological studies show association of Ad-36 antibodies with human obesity. *In vitro* experiments in 3T3-L1 preadipocytes showed that Ad-36 promotes their proliferation, differentiation, and lipid accumulation. However, the exact mechanism of adipogenic action *in vivo* is yet unknown. Adipogenic effects of Ad-36 are described below in detail.

A. Ad-36 GENERAL INFORMATION

Ad-36 was first isolated in 1978 in Germany from the feces of a 6-year-old girl suffering from diabetes and enteritis (Wigand *et al.*, 1980). Ad-36 infection was thought to occur rarely, but work indicates that 11–30% of the individuals screened in the United States are seropositive for Ad-36 antibodies (Atkinson *et al.*, 2005).

B. Ad-36-INDUCED ADIPOSITY

Ad-36 promotes adiposity in animals and shows association with human obesity.

1. Animal models

In separate experiments, chickens, mice, or marmosets (nonhuman primates) inoculated with human adenovirus Ad-36 developed a syndrome of increased adipose tissue and paradoxically low levels of serum cholesterol and triglycerides (Dhurandhar *et al.*, 1992, 2000, 2001). Food intake of the infected and the uninfected controls was not significantly different. Using a capillary electrophoresis assay (Kolesar *et al.*, 2000), Ad-36 DNA was detected in the adipose tissue of the infected animals but not in the skeletal muscle. The amount of Ad-36 DNA present in the visceral fat correlated with the amount of total visceral fat in the chickens ($r = 0.41$, $p = 0.025$). Sections of the brain and hypothalamus of Ad-36-inoculated animals did not show any overt histopathologic changes.

Dhurandhar *et al.* (2001) demonstrated the transmissibility of adenovirus infection and adiposity in a chicken model by parenteral route. Four groups of 3-week-old chickens (infected donors and recipients, and control donors and recipients) were used. The infected and the control donors were inoculated with Ad-36 or media. Thirty-six hours postinoculation, blood from the infected or a control group was transfused intravenously in the respective recipient groups. Infected donors and recipient animals developed significantly greater total body fat than the control groups, despite similar food intake. The visceral fat depots in the infected donors and receivers were heavier (142% and 80% greater, respectively) compared to the control.

When obesity was defined as body fat $\geq$85th percentile of that in the control group, 64% of the infected donors and 72% of the infected recipients were considered obese versus only 18% in control donors and recipients together. Serum cholesterol was significantly lower in the infected and infected-recipient animals compared to the control group, showing that Ad-36 infection and subsequent obesity was transmissible.

Subsequently, two more studies were conducted to demonstrate the adiposity-promoting effect in nonhuman primates (Dhurandhar *et al.*, 2002). The first study used stored plasma samples from adult male rhesus monkeys, which were collected every 6 months over a period of 84 months at the University of Wisconsin Regional Primate Research Center in Madison, Wisconsin. The results showed spontaneous appearance of Ad-36 antibodies followed by weight gain in the year following seroconversion versus the year preceding it (1.8 kg vs 0.1 kg, respectively). Lipid profile was improved, showing a decrease in serum cholesterol by 35 mg/dl. In the second study, male marmosets, separated into two weight- and age-matched groups, were inoculated intranasally with either Ad-36 or medium. Twenty-eight weeks postinoculation, the infected animals showed a fourfold gain in body weight and an increase in visceral fat (7.3 ± 2.5 g vs 4.4 ± 0.9 g, $p = 0.089$).

Ad-36 inoculation induced adiposity in male Wistar rats despite similar food intake. Twenty-seven weeks postinoculation, Ad-36-infected rats attained greater body weight (628.3 + 45.1 g vs 587.5 = 30.6 g, $p < 0.008$). Their epididymal-inguinal, retroperitoneal, and visceral fat pads were 60%, 46%, and 86% greater, respectively ($p < 0.0001$). Paradoxically, Ad-36 group developed higher insulin sensitivity compared to the control (Yu and Dhurandhar, 2005). Leptin levels were greater and corticosterone and norepinephrine lower in the infected group, suggesting that Ad-36 may affect the hypothalamo-pituitary-adrenal axis (Pasarica *et al.*, 2006; Shin *et al.*, 2004).

2. *Association with human obesity*

Sera of 360 obese (BMI $\geq$ 30 kg/m^2) and 142 nonobese (BMI $<$ 30 kg/m^2) subjects from Wisconsin, Florida, and New York were screened for the presence of Ad-36 antibodies using a constant-virus-decreasing-serum neutralization assay, a gold standard for detecting neutralizing antibodies. The effect of Ad-36 seropositivity on the risk of obesity was highly significant (Atkinson *et al.*, 2005), which was independent of age, sex, and the data collection site, Ad-36 antibodies were more prevalent in obese subjects (30%) than in nonobese subjects (11%). Seropositive obese as well as nonobese subjects had significantly greater BMI versus their respective seronegative counterparts (Atkinson *et al.*, 2005).

Prevalence of Ad-36 antibodies in human population may vary by the geographic locations. Only 5% of the subjects screened in Denmark had antibodies to Ad-36 (Raben *et al.*, 2001). Ad-36 is the first human virus reported to show an association with human obesity. Due to ethical reasons, it is not possible to infect humans with a virus, which precludes unequivocal demonstration of causative role of Ad-36 in human obesity. Future experiments are likely to generate indirect and circumstantial evidence.

C. MECHANISM OF Ad-36-INDUCED OBESITY

The adipogenic mechanism of Ad-36 is unclear, but several *in vitro* and *in vivo* studies provide some insight about the molecular effect of Ad-36 on adipose tissue metabolism. Studies show that Ad-36 has similar effects as thiozolinediones, a class of antidiabetic drugs. Ad-36 increases replication (Pasarica *et al.*, 2005), differentiation (Vangipuram *et al.*, 2004), lipid accumulation (Vangipuram *et al.*, 2004), and insulin sensitivity (Yu and Dhurandhar, 2005) and reduces leptin secretion (Vangipuram *et al.*, 2007) and expression (Yu and Dhurandhar, 2005) in fat cells. 3T3-L1 preadipocytes as well as human primary preadipocytes when infected with Ad-36 show increased levels of glycerol 3-phosphate dehydrogenase (GPDH), a differentiation specific

enzyme (Vangipuram *et al.*, 2004). These effects were not observed with Ad-2, a nonadipogenic human adenovirus. These findings suggest considerable involvement of the adipose tissue in adipogenic effect of Ad-36. Increased differentiation of 3T3-L1 preadipocytes (Vangipuram *et al.*, 2004) and upregulated expressions of adipogenic regulator genes (like PPAR-γ, CEBP β and α, and GPDH) in visceral fat of infected animals (Yu *et al.*, 2004) suggest an effect of Ad-36 on fat cell differentiation.

Moreover, Ad-36 increases proliferation of preadipocytes, generating more cells capable of accumulating lipids, which may explain the adipogenic effect *in vivo* (Pasarica *et al.*, 2005). Greater number of preadipocytes and adipocytes due to Ad-36 infection may also contribute to the enhanced insulin sensitivity in Ad-36-infected rats (Yu *et al.*, 2004). As expected, adipose tissue of Ad-36-infected rats showed enhanced expression of genes of insulin-signaling pathway and *de novo* lipogenesis such as GLUT-4, insulin receptor, fatty acid synthetase (FAS), and acetyl CoA carboxylase (ACC-1) (Yu *et al.*, 2004). Thus, it appears that Ad-36 increases number of fat cells, enhances glucose uptake by adipocytes, and promotes its conversion to lipids via *de novo* lipogenesis in 3T3-L1 cells.

XI. ADENOVIRUS TYPE 5

A. Ad-5 GENERAL INFORMATION

Adenovirus type 5 (Ad-5) sequence was completely described in 1992 (Chroboczek *et al.*, 1992). Ad-5 has been extensively used for gene therapy (Kanerva and Hemminki, 2005) because these vectors are safe and efficient and can accommodate large antigen-encoding structures (Wu *et al.*, 2005). Ad-5 causes respiratory tract infections in humans (Limbourg *et al.*, 1996).

B. Ad-5-INDUCED OBESITY

So *et al.* (2005) showed that Ad-5 induces adiposity in mice. Three-week-old female CD1 mice were injected intraperitoneally with either Ad-5 or saline solution. *Ad libitum* access at food and water was provided. After 22–23 weeks, infected animals attained significantly greater body weight compared to the control group (14.8 g vs 13.5 g; $p < 0.05$) despite similar food intake. The infected group had a mean adiposity of 6.7%, compared with 2.4% in the control group ($p < 0.05$) representing a 279% increase, as measured by *in vivo* ^{1}H magnetic resonance spectroscopy (^{1}H MRS), which is a new rapid and noninvasive technique used to determine body composition. Compared to the control group in the upper quartile for body weight, 66.7% of the infected animals were heavier versus only 16.7% in the control group. *In vivo* ^{1}H MRS

showed that there was no difference in the intrahepatic lipid levels (So *et al.*, 2005). Serum lipid levels were not reported in this study.

C. MECHANISM OF Ad-5-INDUCED OBESITY

The infected group accumulated more body fat, which accounted for the increased body weight. The authors suggest that like Ad-36, increased preadipocyte differentiation by viral infection (Vangipuram *et al.*, 2004) may be responsible for the increased body fat. Alternatively, the authors proposed the effect of inflammation on lipid metabolism. PPAR-γ is a pivotal transcription factor responsible for adipocyte differentiation and is also involved in modulating inflammatory response (Clark, 2002). The authors speculated that increased adiposity may be a side effect of the anti-inflammatory response elicited by Ad-5 infection.

XII. ADENOVIRUS TYPE 37

Human adenovirus type 37 (Ad-37) was discovered by de Jong *et al.* (1981). It causes keratoconjunctivitis and genitourinary tract infections in humans (de Jong *et al.*, 1981). Ad-37 was shown to cause adiposity in chickens (Atkinson *et al.*, 2002). Visceral fat pads were three times heavier for the Ad-37 group compared to the control ($p < 0.0009$). Interestingly, unlike Ad-36, it did not reduce serum cholesterol levels. Food intake of the animals could not explain the adiposity. No information is available about the possible mechanism involved.

XIII. ADIPOGENIC POTENTIAL OF OTHER ADENOVIRUSES

The adipogenic potential of Ad-36 is not shared by all adenoviruses. Avian adenovirus CELO or human adenoviruses type 2 or 31 did not promote adiposity in animal models (Atkinson *et al.*, 2002; Dhurandhar *et al.*, 2000). Unlike Ad-36, Ad-2 and Ad-31 did not show association with human obesity. For Ad-31 and Ad-2 the antibody prevalence between the obese and the nonobese subjects was similar (76% vs 81% for Ad-2 and 70% and 80% for Ad-31). BMIs and serum lipids were virtually identical for AB+ and AB− subjects (Atkinson *et al.*, 2005). Moreover, almost equal distribution of seropositivity among the obese and nonobese subjects for Ad-2 and Ad-31 suggested that the greater prevalence of Ad-36 antibodies in obese subjects is not a result of obesity.

Of the 50 known serotypes of human adenovirus, Ad-36, Ad-37, and Ad-5 are adipogenic and Ad-2 and Ad-31 are not adipogenic. Adipogenic

potential of the remaining serotypes is unknown. Further information about the mode of action and elucidating the mechanism involved may help in screening the remaining serotypes for their adipogenic effects.

XIV. ROLE OF PATHOGENS IN HUMAN OBESITY

Although some of the adipogenic pathogens are conventionally considered to be nonhuman pathogens, possible use of a human host by these pathogens cannot be ruled out. Such was the case with BDV, which was originally considered to be a virus of horses and sheep but now shows clear evidence of human infections (Chalmers *et al.*, 2005; de la Torre, 1994; Gosztonyi and Ludwig, 1995; Ludwig and Bode, 2000). Similarly, humans showed antibodies to SMAM-1, the adipogenic avian adenovirus (Dhurandhar *et al.*, 1997a). Moreover, human adenovirus Ad-36 appears to have little selectivity for species and infects chickens, mice, nonhuman primates, rats, and hamsters (Dhurandhar *et al.*, 1997a, 2000, 2001, 2002; Pasarica *et al.*, 2006). Changing of host by pathogens has been well documented. For instance, CDV changed species to infect feline species and considerably reduced Serengeti's lion population (Morell, 1996). Therefore, nonhuman adipogenic pathogens cannot be ruled out as nonpathogenic for humans.

Although several pathogens have been unequivocally shown to cause obesity in animal models, determining their contribution to human obesity is of greatest significance, but equally challenging. Unlike the animal models, human cannot be experimentally infected with these pathogens due to ethical reasons. This limitation precludes any direct demonstration of a cause and effect relationship of a pathogen and adiposity and the evidence will have to be indirect and circumstantial. Moreover, insidious onset of obesity makes it difficult to link it to a particular episode of infection experienced in the past. If an adipogenic pathogen uses "hit-and-run" mechanism to induce obesity, the pathogen may not even be detectable in the body, by the time adiposity is noticed. Therefore, elucidating the mechanism of adipogenic action of a pathogen is important. In addition to treatment, prevention could be a long-term goal of researchers investigating Infectobesity. Vaccines against adipogenic pathogens could be expected to provide protection against obesity due to that specific pathogen.

XV. INFECTION, INFLAMMATION, AND OBESITY

The rapid increase in obesity, its comorbidities, and the associated health care costs have prompted a search for newer and better approaches for its prevention and management (WHO, 2000). Such efforts may be facilitated by

understanding the etiology of obesity. Of the nine etiologic factors (Sclafani, 1984), the viral etiology of obesity first reported in 1982 (Lyons *et al.*, 1982) has been largely ignored. In the last two decades, 10 adipogenic pathogens were reported (Atkinson *et al.*, 2002; Backhed *et al.*, 2004, 2005; Carter *et al.*, 1983a,b; Dart *et al.*, 2002; Dhurandhar, 2004; Dhurandhar *et al.*, 1990, 1992, 2000, 2001, 2002; Gosztonyi and Ludwig, 1995; Kim *et al.*, 1987; Lyons *et al.*, 1982; So *et al.*, 2005). These astonishingly high number of reports include human and nonhuman viruses, scrapie agents, bacteria, and gut microflora. Some of these pathogens are associated with human obesity (Atkinson *et al.*, 2005; Dart *et al.*, 2002; Dhurandhar *et al.*, 1997a), but their causative role has not been established.

Although a causative role of certain infections in obesity is a relatively novel concept, adipose tissue involvement with modulators and mediators of immune response is well documented. For instance, Cousin *et al.* (1999) showed that preadipocytes function like macrophages and possess phagocytic and microbicidal activity. Leptin, an adipocyte-secreted hormone involved in body weight regulation, also enhances proliferation and activation of human circulating T lymphocytes and stimulates cytokine production (Martin-Romero *et al.*, 2000). In addition, adipocytes themselves secrete various cytokines (Fried *et al.*, 1998; Sewter *et al.*, 1999) and, in turn, preadipocytes and adipocytes are subject to cytokine-directed modulations (Gregoire *et al.*, 1992; Kras *et al.*, 2000). With such an 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 (MCSF), which promotes the production of macrophages, is also secreted by adipocytes and when over expressed *in vivo* induces significant adipose tissue hyperplasia (Levine *et al.*, 1998). It is unknown if the obesity-promoting pathogens stimulate MCSF production to increase the growth of adipose tissue.

MCSF is an example of pro-inflammatory cytokine. Relationship of infections with inflammation is well known. Moreover, a recent body of evidence shows association of obesity with cytokines and markers of inflammation. Elevated levels of IL-6 (Roytblat *et al.*, 2000) and C-reactive proteins (Visser *et al.*, 1999) are observed in obese individuals. Interestingly, Duncan *et al.* (2000) showed that markers of inflammation can *predict* weight gain in middle-aged adults. It remains to be determined if inflammation is a cause or effect of obesity.

XVI. CONCLUSIONS

In conclusion, Infectobesity or "Obesity of infectious origin" would be a relatively novel, yet extremely significant concept, if shown to be relevant to humans. An adequate understanding of such pathogens is needed for the

better management of obesity. A new perspective about the infectious etiology of obesity may stimulate additional research to assess the contribution of hitherto unknown pathogens in human obesity and possibly to prevent or treat obesity of infectious origins.

ACKNOWLEDGMENTS

This work was partly funded by NIH grant 1R01 DK066164-01 to NVD.

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