

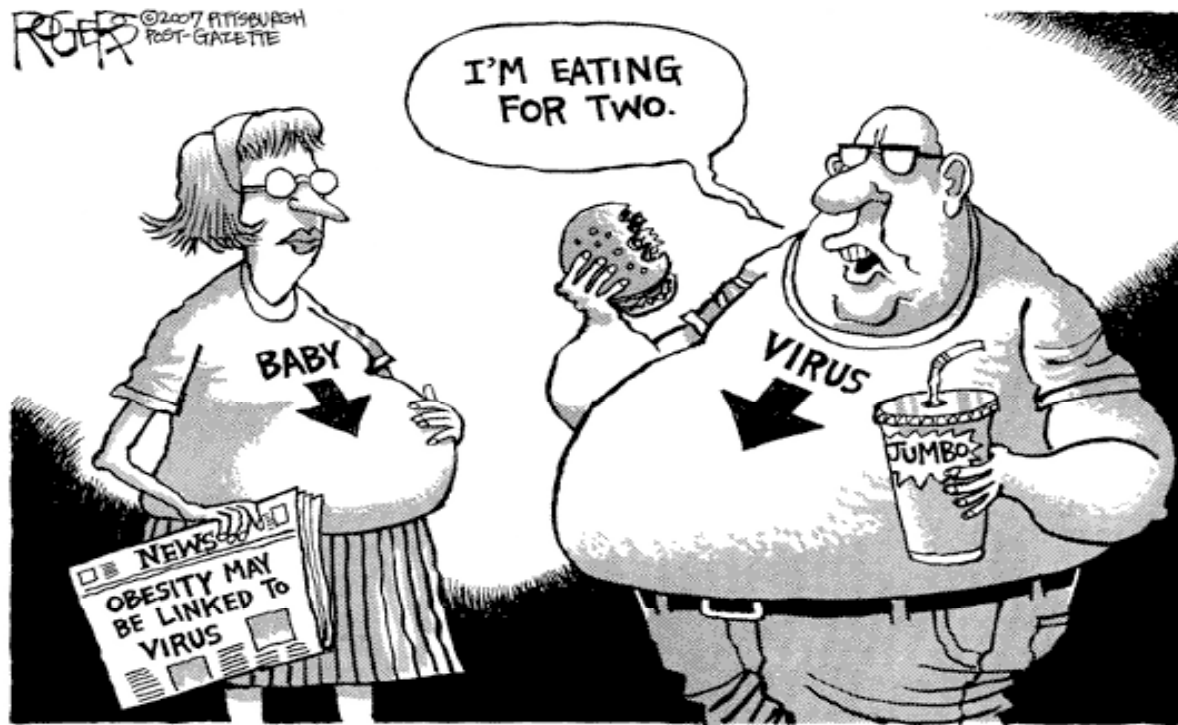
Has Obesity Gone

**VIRAL?**

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Infectious Diseases

Achoo...you're fat.





# Obesity Epidemic

- Percentage of US states with an obese population less than 20%? ZERO.
  - Consideration classically given to lifestyle choices, society, genetics, endocrine etiologies, etc.
- If lifestyle choices and eating behaviors remain paramount, what physiologic and/or microbiologic factors also contribute to obesity?

# Media Glory



- MTV True Life “I love being Fat”
- NBC’s “The Biggest Loser”



## Media cont'd.

- It is “OK” to be fat
  - Dating websites, support groups, advocacy sites.
- Overzealous non-discrimination in schools, workplaces, etc.
- More obese sitcom characters with central roles







# Predisposition to Obesity

- Is it possible there is a viral etiology that predisposes one to obesity? Who is at risk? Which virus(es)?
- Is there something microbiologically different about the obese? Variations in natural flora?
- Lame blame, or true culprits?



# “Chronic Fatigue”

- Epstein-barr virus (EBV)
- Cytomegalovirus (CMV)
- Herpes Simplex Virus (HSV)
- Xenotropic murine virus-related virus (XMRV)
- Lyme Disease



# The True Viral Culprits?

- PubMed Statistic – as of September 2009 there are over 1,000 publications on the topic of viruses in obesity
- 5 animal viruses, 3 human viruses
  - Animal: SMAM-1, canine distemper, Rous-associated virus type 7, Borna disease virus, scrapie agent
  - Human: Adenovirus 36, adenovirus 37, adenovirus 5

# SMAM-1

- Of the animal viruses, only SMAM-1 has been linked to obesity in humans

- “Original” obesity virus
- Avian adenovirus (India)
- Acts directly on adipocytes



- In the 1970s/1980s there was a high die-off of commercially raised chickens in India
  - Viral source was SMAM-1, causing decreased immune function and increased accumulation of body fat in affected chickens

# Dr. Nikhil Dhurandhar

- 2<sup>nd</sup> generation Obesity specialist in India
- Together with a veterinary pathologist friend were baffled that poultry “sick enough” to die of a virus could be fat
- Isolated SMAM-1 and injected it into uninfected lab chickens
  - 6 weeks later, 50% fatter





# SMAM-1 cont'd.

- Because of these observations
  - Dhurandhar et. al. concluded that infection with this virus lead to obesity regardless of food consumption
  - Uninoculated chickens became infected as well from presumed droplet exposure
  - Livers enlarged, loaded with triglycerides
  - Paradoxical decrease in total cholesterol



# Next step...

- Dr. Dhruandhar obtained blood samples from 52 of his obese patients
  - 10 were positive
  - The 10 that were positive were the among the heaviest of the 52 total test subjects
  - These 10 patients also had lower than average cholesterol – similar to what was seen in the test chickens



# Onto the US...

- Dr. Dhruandhar relocated to the US and was able to collaborate with other obesity researchers
- Difficulty in importing SMAM-1 from India for further research
- Dr. Dhruandhar and Dr. Richard Atkinson of the University of Wisconsin, Madison decided instead of waiting to look into human adenoviruses



# Human adenovirus connection?

- Numerous studies conducted on many adenovirus isolates
  - Of ~57 total human adenoviruses, 3 are proven obesogenic
  - Adenovirus 36 and 37 cause obesity in chickens
    - Adenovirus 36 also causes obesity in mice, rats, hamsters, and monkeys
  - Adenovirus 5 causes obesity only in mice



# Adenovirus 36 (Ad-36)

- Ad-36 is the only human adenovirus shown to definitively be associated with human obesity
  - Acts directly on adipocytes
  - Stimulate enzymes and transcription factors that cause accumulation of triglycerides and differentiation of preadipocytes into mature adipocytes
  - Numerous studies on chickens, mice
  - Bloodborne and airborne transmission noted

# Ad-36 cont'd.

- Two experiments on non-human primates
  - One had 15 rhesus monkeys – 7 infected, 8 eventually infected
    - After initial positive serology for Ad-36, 18mo later there was a universal 15% body weight increase compared to controls
  - Second smaller study on marmosets





# Ad-36 – Human Research

- Ad-36 is a D species adenovirus first isolated in 1978 and usually implicated in respiratory and eye infections in humans
- 2005 study of 502 adults of varying weights (obese and non-obese) from Madison, WI; NYC; and Naples, FL found Ad-36 antibodies in 30% of obese individuals and 11% of lean individuals



# Ad-36 Human Research

- The Ad-36(+) individuals were 9 BMI units heavier than Ad-36(-) study subjects
- In pediatric studies:
  - OBESE children weighed 35# more on average with Ad-36(+) serologies than those who tested negative
  - Children (regardless of obesity) were 52# heavier on average with Ad-36(+) status
- Stem cells from fatty tissue in liposuction patients, when exposed to Ad-36, became mature adipocytes in 1 week
  - No change in non-exposed stem cells

# Ad-36 Human Research

## ■ Twin Studies

- 89 serodiscordant twin pairs were evaluated in New York City
- Ad-36(+) twins were slightly, but statistically heavier and fatter than their Ad-36(-) co-twin
- No differences found if discordant to Ad-2, Ad-31, or Ad-37





# What do we do with this info?

- Correlation? Causation? Should we be testing Ad-36 serologies on our obese patients?
- Vaccine potential?
- Excuse?
- Most experts agree, when it comes to obesity there is a very simple equation:
  - $\text{Calories IN} > \text{Calories BURNED}$
  - In the end, this is the ultimate “cause” of obesity



# Calories in, calories out...

- So if the ultimate issue is still dietary, do the gut flora of the obese vary from the lean?
- Recent evidence indicates there are trillions of bacteria that normally reside in the human GI tract – collectively called the gut microbiota
  - Are the gut microbiota of the obese more efficient?
  - Possible predisposition to obesity?
  - Can altering this flora become a treatment for obesity?



# Gut Microbiota

- 1800 genera and between 15,000 and 36,000 species of bacteria alive and well in our gut
- It has been suggested that the gut flora of the obese are “more efficient” at the extraction of calories and ultimate storage of fat



# Gut Microbiota cont'd.

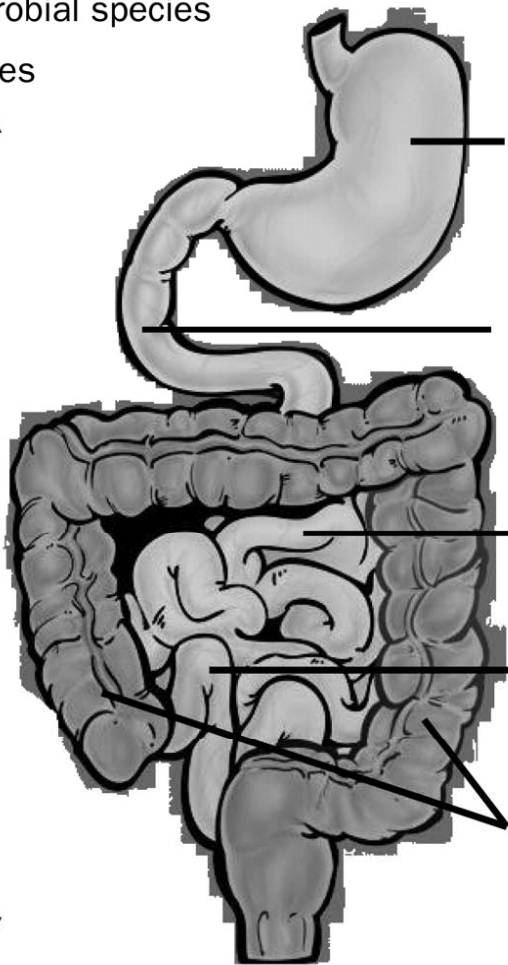
- The gut flora of obese humans contain fewer bacteroidetes and more firmicutes than those of the lean
  - Firmicutes include peptostreptococcus, enterococcus, clostridium, lactobacillus
- This differential likely accounts for differences in caloric extraction and the efficiency of digestion in the obese
  - Even if the obese person is NOT overeating!

# Usual Gut Flora Numbers

500-1000 Microbial species

Aerobes

Anaerobes



Stomach  
 $<10^2$  cfu/mL  
pH, 1-2

Digestion and  
acid secretion

Duodenum  
 $10^{1-3}$  cfu/mL  
pH, 6-7

Small  
intestine

Digestion and absorption  
of carbohydrates, proteins,  
and fats

Jejunum  
 $10^{3-4}$  cfu/mL  
pH, 6-7

Ileum  
 $10^{7-9}$  cfu/mL  
pH, 6-7

Absorption of bile acids  
and vitamin B<sub>12</sub>

Colon  
 $10^{10-12}$  cfu/mL  
pH, 5-7

Large  
intestine

Absorption of water,  
electrolytes, and short-chain  
fatty acids



# Gut Flora cont'd.

- An individual's indigenous gut bacteria composition is established in the first year of life
  - Adult gut microbiota closely resembles what you were born with – UNTIL...
  - You partake in the typical high-fat, processed American diet

# American Diet



**MCDONALD'S**

Making people fat since 1940



# What happens?

- First – long-term exposure to high-fat, processed foods slowly changes the gut flora
  - A shift occurs in that gram positives begin to outnumber gram negatives in the stool
  - Gram positives (higher variability) are more efficient at extracting dietary energy from foods
  - When mice are purposely colonized with higher numbers of gram positive gut flora – a 60% weight increase was noted in 2 weeks



# Human Studies

- Ley et. al. studied the stool composition in 12 obese patients participating in a 1 year weight-loss program
  - Average bacteroidetes content before fat-restricted diet was 3% of fecal flora
  - Average bacteroidetes content after fat-restricted diet was 15% of fecal flora
  - Firmicutes numbers decreased parallel to weight loss
  - Agreed, additional cause-and-effect research needs to be completed



# Wait a minute?

- Antibiotics? Prebiotics? Probiotics?
  - In animal models, use of antibiotics delays the onset of Type-1 diabetes. Rats that did NOT develop diabetes had fewer bacteroidetes.
- Prebiotics – enhance the growth of our beneficial gram-positives
- Probiotics – nonpathogenic live microorganisms (lactobacillus, etc.) that confer health benefits



# Contradiction?

- YES – Antibiotics decrease those gram negatives and pre/probiotics increase gram positives
- Differences accounted for by variations in the systemic inflammation mechanisms, variations in behavior of individual lactobacillus species, gut transit times, tendency of probiotics to induce satiety, etc.

# Future Directions

- More studies needed
  - Does the enhanced caloric extraction ability of the gut flora in the obese translate to truly meaningful weight differences?
  - In fact, are these differences in gut microbiota the CAUSE or RESULT of obesity?
- Exact mechanism of relative bacteroidetes and firmicutes proportions still not definite
- Pre/probiotic benefits in the obese still being evaluated





# Summary

- Has Obesity gone VIRAL?
  - Yes. It's everywhere we look.
- Is there a viral etiology?
  - Perhaps. Correlation at best with SMAM-1 and Adenovirus-36.
- Are there differences in gut microbiota?
  - Yes. Decreased bacteroidetes and increased firmicutes lead to more efficient extraction of calories in the obese

# So What?



- Mr. Doe comes into your office after reading an article that the “cold” he had last year may have lead to his 55# weight gain.
- What do you tell him?
- Any reason to do adenovirus serologies?
- What will you do with the results?



# Conclusions

- There may very well be a viral predisposition to obesity
  - The ultimate “treatment” remains to create a caloric deficit
    - 3500 calories burned = 1 pound lost
- Those with Ad-36(+) may have a more difficult time losing weight
  - Instead of excuses, more strict commitment/adherence to a diet/exercise program
  - Manage as a chronic illness like diabetes
  - Future vaccine?
- Low-fat diets can change gut flora over time and decrease the relative number of “efficient” gut flora yielding less storage of fat/calories
- Probiotics? Why not?!