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Obesity? So what?

About its history, causes and treatments

What is obesity?

We all know what obesity is. If we see a person who is overweight or obese we recognise it as such immediately- without thought and without medical training. But what if you were to stop and think about it? How much would you know and what exactly would you think? It is possible that thoughts that immediately spring to mind are that they are greedy, lazy or both [Figure 1]. Is that fair? No it isn't and they convey a certain lack of informed opinion.



Figure 1. Of course, obesity and the related stigmatisation are not new to modern society. In 12th Century Japan scroll painting was a popular art form. One particular scroll, the yamai-zdshi, the picture scroll of illnesses, shows an obese woman, who was a money lender in Kyoto and who became so fat because of her extravagant living that she could hardly walk requiring two maids to help her walk; two men are gazing at her in amazement and probably laughing at her size and infirmity.

In this article we would like to provide you with a natural history of obesity as a medical, social and economic malady. We will start with the medical definitions of obesity, its prevalence as a worldwide phenomenon and why we should be worried about it. We will then touch on the causes of obesity, an oddly controversial subject; we are bound by the first law of thermodynamics [Box 1] that essentially means that what goes in (food) must balance what goes out (expenditure). Imbalance in this equation leads either to obesity or to excessive weight loss; so what is controversial about that? It has been notoriously difficult to prove in a scientific, empirical sense.

Humans are horribly difficult to study in their natural (or perhaps unnatural as we will see later) environment. Also most studies are cross-sectional (comparisons between one group and another in a given moment in time); longitudinal studies (where individual are followed for many years and disease progression

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can be tracked) are less plentiful, largely because of their huge cost. In the final section we will talk about treatment options, why we need treatment options (will power alone just doesn't work) and then a very brief look into the future to give a flavour of where research is taking us.

Box 1

The First Law of Thermodynamics.



This states that the change in internal energy (U) of a system is equal to the heat added to a system (Q) minus the work done by the system (W):

$$U = Q - W$$

Energy balance is analogous to this. Energy balance would be U , food intake Q and energy expenditure W . When food intake is equal to energy expenditure there is equilibrium and body weight will remain constant. However, if Q exceeds W then the system would be in positive energy balance and weight gain will occur. There are no exceptions!

Obesity as a medical condition

Although obesity is plain to see, it doesn't need special lab tests and expensive examinations, there still needs to be a way of measuring it to determine whether people are benefiting from treatment for example. Weighing is an option, bathroom scales are relatively cheap, but consider the definition of obesity. Obesity is increased weight due to excess fat stores. When we weigh ourselves we weigh everything, bone, blood, muscle and guts as well as adipose tissue. A body builder may weigh as much as someone with obesity. A measure used in the clinic and in the study of obesity is the body mass index (BMI) that takes body surface area into account and is calculated according to the equation: $BMI = \text{body weight (kg)}/\text{Height (m}^2)$

BMI has been used by medical agencies such as the WHO to define normal, under and overweight in a population [Table 1].

This is not a perfect measure either, large muscle mass can give a high BMI also but it has served a fairly handy and cheap index in population studies. Waist circumference is also used and is the measurement most statistically associated with the metabolic consequences of overweight, a cluster of problems known collectively

as the “Metabolic Syndrome” (ref), which dramatically increase the risk of heart disease and diabetes. This is a subject of a review all to itself.

BMI kg/m ²	WHO definition
< 18.5	Underweight
18.5-25.0	Ideal weight
> 25.0	Overweight
> 30.0	Obese

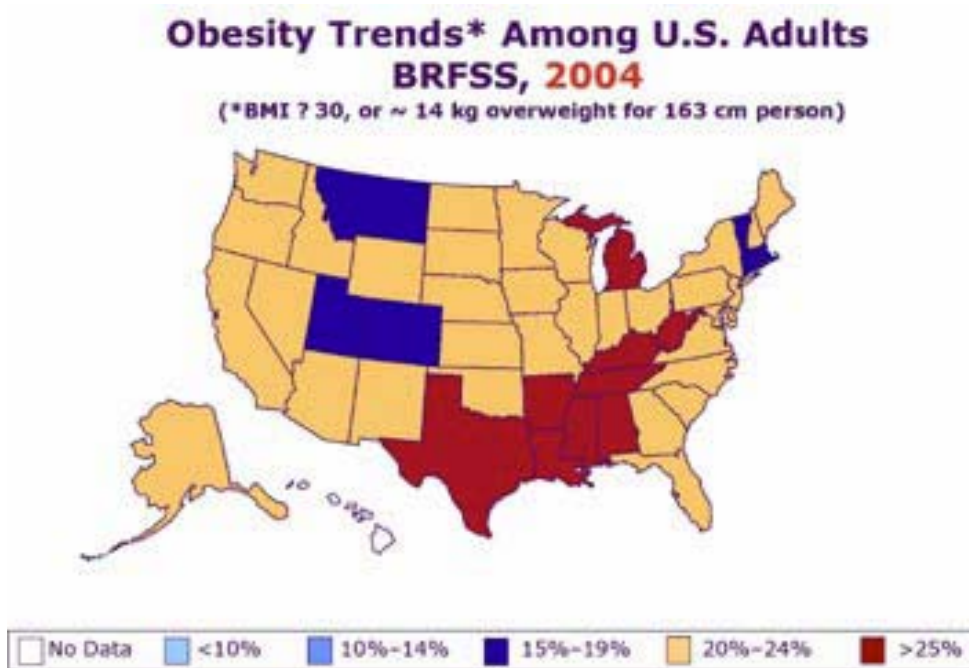
Table 1, WHO definitions of obesity. These data apply more broadly to European and North American, North African and some Pacific populations. The BMI definitions of obesity and overweight for Asian populations are lower. Also, it is difficult to compare children using BMI because of the confounding influences of linear growth.

BMI has been used to survey large populations for incidence of obesity and the results are shocking. Since the mid 1980s, the Centre for Disease Control (CDC) in Atlanta, Georgia has been monitoring obesity rates in all states of the USA every year. Figure 2 (next page) shows the difference between 1994 and 2004 and it is clear that there has been a huge increase in the incidence over that time. The year by year results are shown in a very dramatic and visually impacting series of slides which can be found at their website

(<http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index.htm>).

Obesity is not just a problem in the USA. Europe too, with countries like the UK and Germany having rates over 20% of the population. Although Scandinavian countries fare much better, it doesn't pay top be complacent, rates are increasing there too at 10%. This doesn't sound much, but 1 million people in Sweden out of a population of 9 million people is a dangerous trend. Emerging countries are now beginning the mad rush to be obese. Lifestyle “improvements” and affluence are beginning to pervade these societies – a trend called “coca colonisation”.

The most sad and most disturbing feature of obesity is the dramatic rise in childhood obesity – and this gets media attention, and a lot of it. Kids in their young teens are now, in the 21st century, developing metabolic diseases such as diabetes and atherosclerosis, which was previously in the domain of adulthood 20-30 years ahead of them. This is a life sentence on medication, surgery, ill health and social problems. We know that obesity leads to obvious diseases such as diabetes, cardiovascular disease, cancer (the main cancers associated with obesity are breast, colon, prostate, endometrium, kidney and gallbladder) but it also leads to psychological stress; the obese are highly stigmatized members of our society.

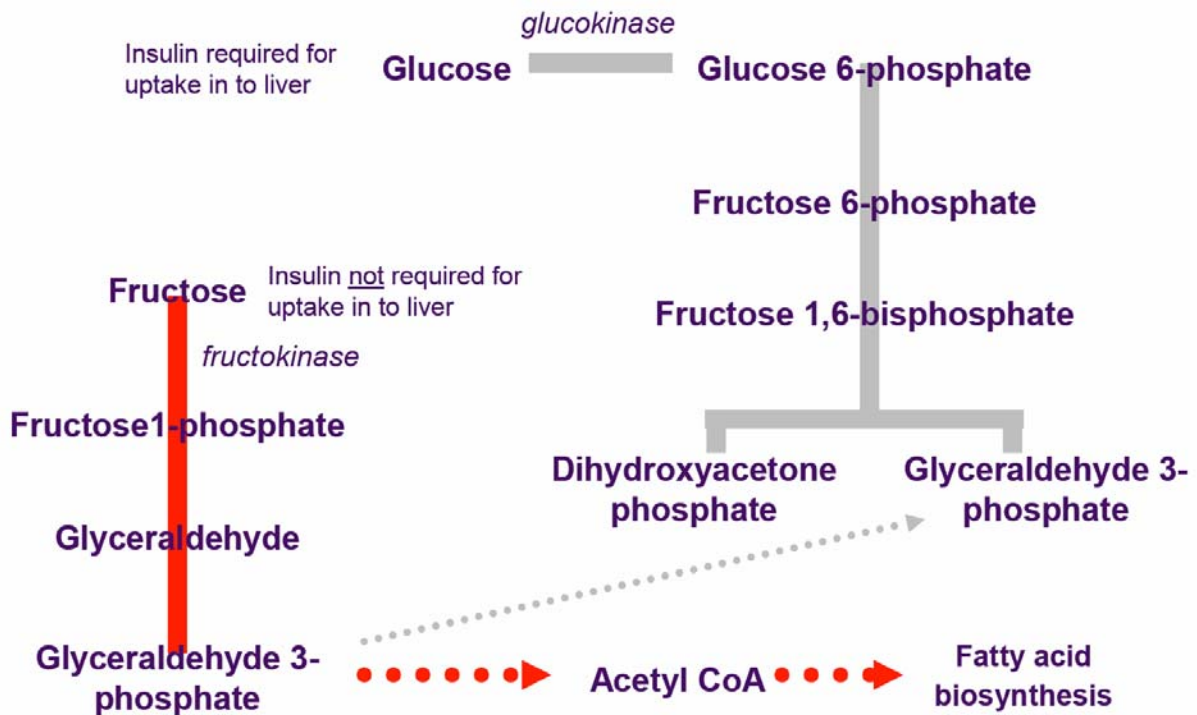


The causes of obesity

The causes of obesity can only be due to an increase in food intake, a decrease in physical activity or a bit of both. The controversy is how, with this knowledge, the obesity pandemic has increased so dramatically over such a short period of 20 years. We have had our gene set for tens of millennia, 30 years is a mere blink of the eye. Thus, although our genes may predispose us to weight gain, the inescapable conclusion is that our modern environment has done for us. In 1962, James Neel proposed the thrifty gene hypothesis, the title of his publication explains the thesis "Diabetes Mellitus: A "thrifty" genotype rendered detrimental by "progress".

The “progress” being the driver and involving a complex interaction between physical activity decline (look at the number of labour saving devices we own; cars, TV, automatic washing machines, 1 stop shopping, even internet shopping) combined with the increased range of cheap to produce energy-dense and palatable foods, there is a vested interest in promoting increased food consumption. There are also changes in mass food production using cheap, but saturated fats in palm oil or high fructose corn oil in soda drinks. Greg Critser in his excellent book “Fat Land” describes this with a great deal of clarity and is recommended further reading.

We would like to spend a minute or two with an example, high fructose corn syrup. In nature we have developed a highly regulated system to control the metabolism of glucose [Box 2]. Firstly, in order to get into the metabolically important tissues such as liver, muscle and adipose tissue, glucose needs insulin to provide a door and unlock it. It does this by promoting the movement of the door, the glucose transporter called Glut4, from the interior of the cell to the cell surface. Once there, glucose can enter the cell, for example a liver cell. In the liver cell glucose is modified by the addition of phosphate that allows it to be further metabolised to make glycogen to store energy or to consume it completely for energy. The enzyme responsible for this is called glucokinase, an enzyme that is highly controlled.



BOX 2. Our only use of a biochemical pathway. This is to illustrate the interdependence of fructose and glucose. Normally, the fate of glucose is production of simple sugar phosphates can be burned by the mitochondria as fuel. Fructose, in the fed state, blocks this and diverts these intermediates away from burning into the production of fats which will be, eventually, stored very visibly on the hips and tummy.

Fructose is not so well mannered. It can enter cells, uninvited, through another transporter called Gluts that always sits on the cell surface. Fructose is not a substrate for glucokinase (but is for a similar enzyme called hexokinase found in muscle) and follows the pathway to glyceraldehyd-3-phosphate [see box]. Normally, in the liver in a situation of refeeding after a fast, the glyceraldehyd-3-phosphate will enter the Krebs cycle. In today's environment, this situation is rare ("progress"), we eat when we are hungry but we never really find ourselves in a truly fasted state (how many people graze on snacks throughout the day?). In this case the glyceraldehyd-3-phosphate provides convenient building blocks for making fatty acids. Since calories in carbonated drinks are plentiful and additional to any meal being eaten, they are adding to adipose stores. Other factors that have been cited as causal or adding to the obesity pandemic are environmental pollution and an avian virus called AD36.

Thus, the possible changes in our environment that have revealed our capacity for weight gain are social and technological to reduce physical activity in the general population, the pressure to consume increased amounts of energy dense foods by business and food policy and perhaps even pollution and viruses.

Why treat obesity?

First of all it is beneficial. Reduction in overweight by as little as 5-10% can result in dramatic improvements in metabolic health – and therefore life expectancy. But there is a problem. Mark Twain hit the nail on the head with his observation "quitting smoking is easy... I've done it a thousand times." Many, many studies have documented excellent weight loss through diet and exercise. Only very few of these people maintain their weight loss for any length of time, the rest of us end up where we started, or worse, heavier. This, in a nutshell, is why we need treatment. We simply cannot keep the weight of by diet and exercise alone unless we are very lucky and highly motivated – it is easy to stop. Today, the gold standard treatment for obesity is bariatric surgery, a procedure where the capacity of the stomach is dramatically reduced. Good and consistent weight loss is achieved, but it is a risky procedure. Nevertheless, the number of these procedures has increased at a rate almost paralleling obesity, from around 18,000 in 1992 to over 100,000 in 2003. It is also an expensive option at around \$20-50,000 per patient and studies in Sweden have shown that cost of drugs for gastrointestinal conditions is higher in this group of patients. What about drugs? Oh dear! This is a sorry tale. The history of drug treatment of obesity is chequered and tragic. In the 1930s, a treatment called dinitrophenol, DNP, which increased metabolic rate proved fatal for many. In the 1950s, amphetamines were used as appetite suppressants resulting in drug dependence. Subsequently

drugs related to amphetamine, but without the dependency liability, culminated in the combination of two drugs, fenfluramine and phentermine (though this latter agent has been shown to have problems with dependency), the so-called "fen-phen" combination. A series of articles claiming large weight loss resulted in the of-label prescribing of this combination. The purpose of the combination was that the weight loss effects of each of the drugs were multiplied when given together. So, it seems, were the side effects. Several deaths occurred due to valve disease in the heart that was attributed to fenfluramine, which was withdrawn from the market in 1997. Today there are only 2 drugs available for the long-term treatment of obesity, orlistat and sibutramine. Orlistat prevents the breakdown of fats in the gut, which then prevents their absorption into the body. Sibutramine reduces appetite and increases energy expenditure. Both drugs are moderately effective at weight loss, relatively safe and they do improve health outcomes.

Soon, it is hoped that there will be a third antiobesity drug on the market, rimonabant (Acomplia™). Rimonabant works by blocking the activity of the cannabinoid receptor-1 (CB-1), and in so doing affects the amount of food desired; it might also have an effect on energy expenditure. Why CB-1? Receptors for the active ingredient of cannabis, 9-tetrahydrocannabinol, have been known for some time and the connection of CB-1 receptors with the cannabis-induced "munchies" was made fairly recently. At the end of the last millennium, rimonabant was shown to reduce appetite in clinical trials (it was being tested as an antipsychotic agent), which resulted in a change in its intended development to that of obesity. It is thought that by inhibiting CB-1 receptors the hedonistic, or pleasurable, drive to eat is blunted. It is hypothesised that our "desires" will lean towards blander food and it may also have a greater effect in obese subjects than in the lean. We know from clever imaging studies that activity in an area of the brain called the striatum is increased much more in obese subjects than in lean subjects when presented with sweet food after a fast. This area is also associated with addictive disorders and it is an area that contains CB-1 receptors. Thus, there is the tantalising possibility that the drug could be moderating an addiction to food. The story of these three agents also sums up obesity drug discovery over the past 30 years. Two of them were begun development for entirely different indications, sibutramine for depression and rimonabant for schizophrenia. Both were "rebadged" on the opportunistic findings that they induced weight loss. To us this indicated that during the late 20th century a signal lack of interest in the greater part of the industry in dedicating early drug discovery efforts to obesity. This all changed in December 1994 when the discovery of leptin, a peptide hormone secreted from adipose tissue which appeared to signal as a satiety signal and was the single gene defect that explained obesity in certain

genetic strains of mice, was published in Nature. We also know now that the functions of leptin are far more complicated than first imagined. It was thought at the time that this was the discovery of a potential wonder drug for obesity.

Sadly (again) things didn't work out; except for a few individuals who lack leptin, obesity is actually characterised by very high plasma levels of leptin. However, to be positive, the discovery of leptin had a profound effect on the field with enormous interest and effort into studying the mechanisms of appetite control, energy metabolism and fuel utilization. Figure 3 illustrates this.

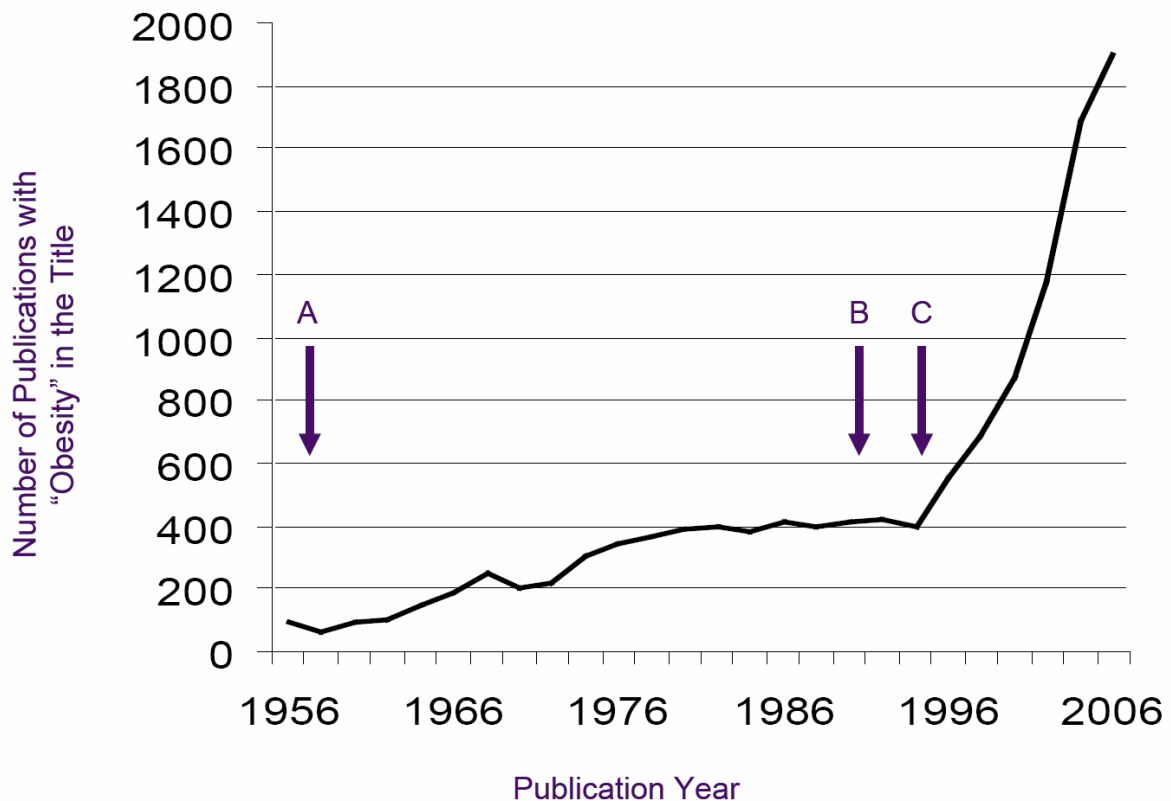


Figure 3. Rising trends in Obesity research. This figure shows the publication activity over the last 50 years. A = year of authors' birth; B = authors' entry into research in metabolic diseases; C = publication of the seminal paper from Jeff Friedman's group in New York, "Positional cloning of the mouse obese gene and its human homologue, Zhang, Y., et al., Nature 372: 425-432 on the 1st December 1994. This paper has had a profound effect on the research activity into energy balance. Sadly leptin never itself fulfilled its promise of an obesity panacea. Its legacy has been the revitalisation of a fascinating area of research which will result in new therapies gained from the learnings inspired by the leptin discovery.

Medline, a database of medical literature, was searched looking for the keyword "obesity" in the title. One can immediately see that the authors' entry into the obesity research arena had no impact whatsoever but, 6 years later (at least we were "pre-leptin" obesity, a minority who are feeling pretty smug now) on the appearance of the now classic leptin paper, prompted an exponential growth in publication activity implying a greatly increased interest in the field. This in turn has spawned numerous target proteins that the pharmaceutical and

biotech industries are currently putting their resources behind drug discovery efforts to hopefully add to the sparse antiobesity drug options.

Conclusions

The future, as it looks today, seems far more promising than it did in the early 1990s in terms of treatments. However, despite all of these potentially high tech solutions, one thing must be borne in mind. There is no better treatment than prevention and this is especially critical to protect our young who are already increasingly falling victim to obesity. Healthy eating and active lifestyle should be the norm but there is constant environmental pressure that promotes over consumption. Healthy eating in correct portion sizes is not good for business. The food industry has a major role to play here, arguably the main role, in preventing obesity but instead it appears to be pushing harder on the consumer more philosophy, whether it be processed foods, junk food or alcohol and the evidence for the success of this campaign is seen on 30-50% of most western populations. Even "diet" foods are advertised so well that they are over consumed; take the example of the United Kingdom. The incidence of overweight and obesity in the British Isles is around 40%, pretty high, yet reports seem to show that the Brits spend the most on diet fads. We hope now that your thoughts around the global epidemic of obesity will be a little more informed. There are a number of web-based resources that are included here if you want to dig deeper into this fascinating and, perhaps, frightening area.

Further Reading

In this section we have tried to avoid very technical references, with the exception of the seminal article (in our opinion) in obesity research and a couple of our own reviews which includes references to the scientific literature for those of you that are interested in digging deeper into this area of research.

The Nature series of journals often carry obesity related articles and the journals, Obesity Research; Obesity Reviews; The International Journal of Obesity and Related Metabolic Disorders; Diabetes, Obesity and Metabolism are four examples of the more specialised journals.

For excellent journalistic treatment of the subject the following books are highly recommended, they are highly readable and are available through Amazon.com:

Pool, R. (2001) Fat. Fighting the Obesity Epidemic. Oxford University Press. ISBN 0-19-511853-7.

Critzer, G. (2003). Fatland. Penguin Books. ISBN 0-141-01540-3.

Useful websites dealing with the metabolic syndrome:
www.wellcome.ac.uk/bigpicture/obesity

<http://www.americanheart.org/presenter.jhtml?identifier=4756>

The seminal Nature article on the identification of the leptin gene: Zhang, Y.; Proenca, R.; Mafei, M.; Barone, M.; Leopold, L.; Friedman, J.M. (1994) Positional cloning of the mouse obese gene and its human homologue. *Nature* 372: 425-432.

For general reference and a deeper look into the science of obesity drug discovery, which, of course reflect the authors scientific bias, but consider these a beginning:

Clapham, J.C.; Arch, J.R.; Tadayyon, M. (2001) Anti-obesity drugs: a critical review of current therapies and future opportunities. *Pharmacology and Therapeutics* 89(1): 81-121.

Clapham, J.C. (2004) Treating Obesity: The pharmacology of energy expenditure. *Current Drug Targets*. 5(9): 309-323.

Even further discussions can be found at:

Atkinson R L et al. (2005) Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *International Journal of Obesity* 29, 281–286.

<http://www.nature.com/ijo/journal/v29/n3/abs/0802830a.html>

Keith et al. (2006) Putative contributors to the secular increase in obesity: exploring the roads less traveled. *International Journal of Obesity* 30, 1585–1594.

<http://dx.doi.org/10.1038/sj.ijo.0803326>



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