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DEBATE

Thrifty genes for obesity, an attractive but flawed idea, and an alternative perspective: the 'drifty gene' hypothesis

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Almost 50 years ago Neel proposed a hypothesis to explain the prevalence of obesity and diabetes in modern society—the 'thrifty gene' hypothesis. The fundamental basis of the hypothesis was that, in our early evolutionary history, genes, that promoted efficient fat deposition would have been advantageous because they allowed their holders to survive at periods of famine. In modern society, such genes are disadvantageous because they promote fat deposition in preparation for a famine that never comes, and the result is widespread obesity and diabetes. In recent years I, and others, have questioned some of the fundamental assumptions of this hypothesis—particularly focusing on whether differential survival of lean against obese in famines provides sufficient selective pressure for the spread of so-called 'thrifty genes'. These arguments have been criticized because famines not only affect survival but also fecundity, and obese people would be expected to sustain fecundity longer in the face of food shortages. In this paper, I show that the reduced fecundity argument is flawed because famines are almost universally followed by periods of enhanced fecundity, which offsets the decline observed during the famine itself. The net effect of famines on fecundity is consequently insufficient to rescue the thrifty gene idea. Elsewhere, I have suggested an alternative scenario that subsections of the population have a genetic predisposition to obesity due to an absence of selection, combined with genetic drift. The scenario presented earlier was based on evidence from prehistory concerning the release of our ancestors from heavy predation pressure around 2 million years ago. I suggest here that this is one of a number of potential scenarios based on random genetic drift that may explain the specific aetiology of the obesity epidemic. Together, these alternatives, based on central notion that genetic drift rather than positive selection was a dominant factor, may be called the 'drifty gene' hypothesis.
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Introduction

Neel[1] proposed the 'thrifty gene' hypothesis as a solution to a conceptual problem. Diabetes and obesity have very clear negative impacts, yet they also have a large genetic component.[2–4] How could natural selection favour the spread of genes causing such negative conditions? It was proposed that such genes may be disadvantageous in modern societies, but in our ancient history they were advantageous during periods of famine. Since its publication, the original article has been cited over 850 times, and it has spawned many additional articles that have reiterated the same basic idea.[5–20] The primary attraction of the 'thrifty gene' idea is that it is simple, and therefore seemingly obvious that it must be correct. In this paper, I will detail and expand on an argument I have made elsewhere,[21–24] that the hypothesis is superficially attractive, but erroneous. I have also proposed an alternative to the thrifty gene hypothesis, which I have called the 'predation release' hypothesis.[24] I will elaborate here that this is one of the several potential alternative scenarios that have at their heart the notion that genes favouring obesity have not been positively selected in our past, but have rather been subject to random drift because of an absence of selection. These alternatives might be collectively called the 'drifty' gene hypothesis. As by definition genes cannot be under selection, and also drifting with no selection, the drifty gene and thrifty gene ideas are mutually incompatible.

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The thrifty gene hypothesis

Before outlining why the thrifty gene idea is wrong, I will clarify what a thrifty gene is and how it is hypothesized, they were once advantageous. A thrifty gene results in a phenotype that is '…exceptionally efficient in the intake and/or utilization of food'.[1] It is suggested that our historical environment was punctuated by periods of famine. Prentice,[9] for example, stated that 'Famine has been an ever present selective pressure on human populations' and Chakravarthy and Booth[12] stated that 'it was not unusual for our…ancestors to undergo periods of feast (during food abundance) intermixed with periods of famine…' Prentice[16] detailed many cases of historical famines as direct supportive evidence. Given this scenario of alternating feast and famine, Prentice[17] suggested that '…adaptations that allowed an organism to rapidly lay down fat in times of food surplus would have a survival advantage in the reciprocal periods of…famine'. Following Neel,[1] these genes are presumed to act through selection on food intake. Effects on expenditure are not discounted but considered less likely.[16] Thrifty genes are suggested to be positively selected for in the historical feast–famine environment because during the feast periods they make people fat. This fat provides the energy necessary for individuals to survive during subsequent famines. As stated by Neel[1] 'Subsequently, during famines, individuals with the ''thrifty'' genotype would have a survival advantage because they relied on larger, previously stored energy to maintain homoeostasis, whereas those without ''thrifty'' genotypes would be at a disadvantage and less likely to survive'. The emphasis was therefore initially placed on enhanced survival, but a second advantage, noted later, was that thrifty genes might also sustain fecundity during famine. As stated by Prentice[16] '…this selection would have been mediated through suppression of fertility as well as actual mortality' (see also Wells[18]). In an environment characterized by feast and famine, thrifty genes are postulated to be positively selected because of the survival and fecundity advantages conferred by fat deposited between famines. In modern society, where there is perpetual abundance of food, these genes prepare their holders for famines that never materialize, and the consequence is widespread obesity.

Why this argument is flawed

Haldane[25] was among the first to develop a quantitative treatment of the expectation for the spread of an advantageous dominant mutant allele (A) compared with the alternative allele (a). Given a selective advantage (k) of only 0.001, that is, an increased survival or fecundity benefit of only 0.1% for the carriers of the A allele versus homozygote 'aa', the number of generations required for the allele A to spread from 1% of population loci to 99% was calculated as 16 500 generations. Modern humans evolved from Hominid ancestors in Africa around 2 million years ago. With a generation time of about 20–30 years, this equates to about 100 000–70 000 generations. Consequently, if advantageous mutations (A) in potential thrifty genes arose at random throughout this period, and these genes provided a selective advantage greater than 0.1%, then the majority of these genes (around 80%) would be fixed at $>99\%$ prevalence. The remaining 20% of mutations would have occurred during the last 16 500 generations and would not yet have increased to $>99\%$ prevalence. If the thrifty gene idea is correct, we should all have inherited advantageous mutations in thrifty genes, and if these mutations cause obesity, as the hypothesis suggests, we should all be obese. Yet even in the United States, only 20–30% of individuals are obese.[26,27] Indeed 30% of Americans are not even overweight and are resistant to weight gain.[28]

One potential solution to this problem with the thrifty gene hypothesis might be that famine has been a factor driving the evolution of thrifty genes for a much shorter period of time. There is a difference of opinion among proponents of the thrifty gene idea on this issue. Chakravarthy and Booth[12] exemplify a position that all the selection for thrifty genes occurred prior to the Neolithic. This parallels the statement by Prentice[16] that 'Famine has been an *ever present* selective feature of human populations'. On the other hand, Prentice[17] argues that famine has only been a selective force since we developed agriculture 12 000 years ago. As detailed above, if positive selection had been acting on thrifty genes for 70 000–100 000 generations, we would all be fat. What about the alternative idea that famine has only been selecting thrifty genes for the past 12 000 years (400–600 generations)? Clearly, any gene that only provided a selective advantage (k) of 0.001 would have no chance of spreading over this period: in which case we would all be thin.

An alternative way to look at this problem is to turn the question around and ask what selective value would be necessary for an allele to spread to 30% of the population over 600 generations? (that is, to produce obesity in 30% of individuals). Modelling the spread of dominant alleles suggests that k would need to be around 0.03 to generate an allele shift from 1 to 30% in 600 generations. That is, a difference in survival or fecundity of 3% between homozygous or heterozygous carriers of the A allele and homozygotic aa carriers in each generation. In the rest of this article, I will make the case that the difference in survival or fecundity per generation between obese and non-obese subjects, as a consequence of famine exposure, is insufficient to generate the observed genetic background to the current epidemic.

Periods of food insecurity are relatively common and historically have occurred about once every decade.[29,30] These periods, however, with no mortality are unimportant for genetic selection. Famines, with significant mortality, have been relatively rare. Demographic surveys suggest famines occur about once every 150 years (Dupaquier[31] and Ho[32]), that is about once every 5–7 generations. If famines provided the selective force, each famine would need to involve a mortality difference between the A and a allele carriers about 5–7 times higher than the critical k value

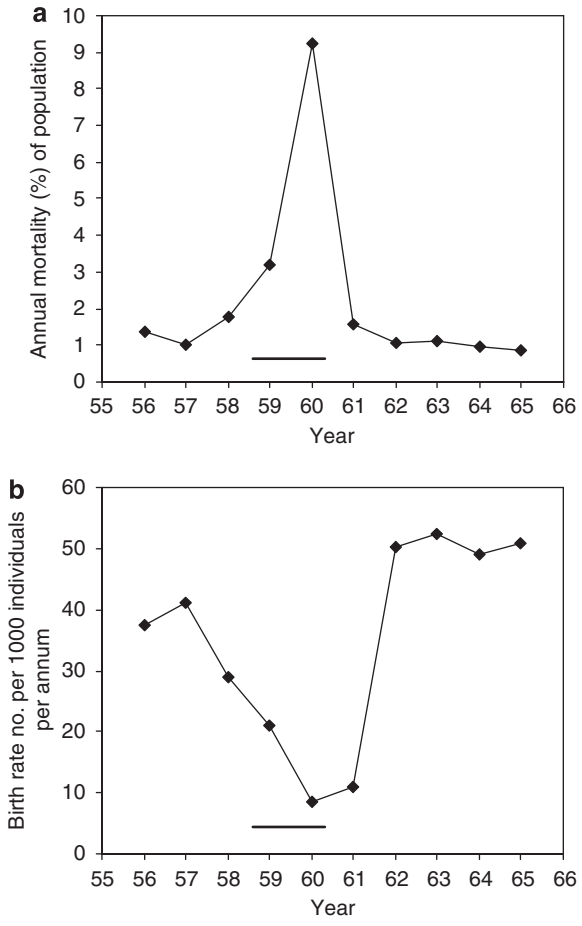

Figure 1 Annual mortality (**a**) and birth rates (**b**) in WuHu, AnHui province, China between 1956 and 1965. The 'great leap forward' famine shown by the bar started in mid-1958 and lasted until the end of 1960. Data plotted from tables in St Clair *et al.*[33]

per generation of 0.03. The difference in mortality between obese (AA or Aa carriers) and lean (aa carriers) during famine would need to be between 15 and 21%.

It is frequently suggested that famine mortality ranges between 20 and 60%. However, estimates of the impact of famine on mortality are routinely exaggerated, often by confounding mortality effects with emigration. More recent famines, where there has been better record keeping, suggest that normally mortality during even-prolonged multi-annual famines seldom exceeds 10% of the population (see references Speakman[22,23]). For example, Figure 1a shows the mortality during the Chinese 'great leap forwards' famine between 1958 and 1960 in the six districts around WuHu in Anhui.[33] These data are particularly useful because restrictions on movement during this famine mean that mortality is not confused with emigration. Total mortality across the two main famine years (1959 and 1960) was 12.1%, but the pre- and post-famine mortality averaged 1.2% per year, thus 9.7% in total might be directly attributable to the famine. Records are available for many famines and a similar pattern emerges. The level of reported mortality (at 5–12%) falls short of the 15–21% increase in mortality necessary to select for thrifty genes.

Although the mortality rates in famine do not appear high enough to select for thrifty genes, the difference between the observed mortality during famines of 5–12% and the required mortality between carriers and non-carriers of the thrifty genotype of 15–21% is not that great, and perhaps within the range of error in both these figures. However, if we make the generous assumption that these figures actually match, absolutely all the mortality during famines would have to fall on the carriers of the non-thrifty 'aa' allele. Any obese subjects carrying the Aa or AA thrifty genotypes would need to be completely spared any mortality. The thrifty gene hypothesis suggests that the carriers of the 'thrifty genes' survive because they deposit fat between famines. The implication of this is that the primary factor causing famine mortality is running out of energy reserves—that is, starvation, and that fatter people run out of reserves more slowly. Records of famine mortality, however, show conclusively that the majority of individuals, during the majority of famines, do not die of starvation (for example, references [34–37]). There are a few exceptions where starvation is the primary cause of death, but these appear to be unusual famines on small islands.[38] Most people, in most famines, die of diseases, particularly cholera and typhoid, and disorders like diarrhoea.

The causes of famine mortality are predictably complex. However, an important factor why people get these diseases and disorders during famines is, in part, because they are hungry, and this forces them to make disastrous choices in their food selection. People will routinely eat carrion and decaying corpses, and these habits greatly increase the probability of gastrointestinal problems like diarrhoea. There is a general breakdown in sanitary conditions, and water supplies often become contaminated. This leads to conditions in which cholera[39] and typhoid spread. Measles and typhus (for example, Raoult *et al.*[40]) are also common among famine victims. Given the reasons why most people die in famines, it appears unlikely this mortality would be biased entirely towards initially lean subjects, completely sparing the obese.

It might be argued that although the ultimate cause of death is normally disease, the mortality might still be biased towards lean individuals. This is because lean people are closer to starvation, and so may make poorer food choices in desperation, and they may have poorer immune systems making them more susceptible to disease. Some evidence does support this viewpoint, as severe wasting is a predictor of disease risk and mortality among famine victims (Lindtjorn *et al.*[41] and Collins and Myatt[42]). Body mass index (BMI) is not a good predictor of risk of mortality because starvation odema often inflates BMI.[42]

How wasting relates to initial body weight or fatness, however, remains unclear—and factors such as age, social status, gender and competitive aggression may be more significant factors driving wasting than initial body condition (for example, the entitlement hypothesis for famine

mortality; Sen[43]). Unfortunately, we have no data on a population of individuals measured pre-famine for their body fatness (or even BMI) and an indication of how these differences translated into famine survival. However, we do have abundant data on death during famine, and the patterns are repeated in almost all the famines for which we have data. The people who die are children under the age of 10 years, and the elderly over the age of 40 years.[44–47] Regarding people aged over 40 years, they will, in most cases, have already passed on their genes; hence, their mortality could only have indirect effects, perhaps influencing the probability of mortality among their children or grandchildren, because of the absence of extended care. Moreover, mortality in children under 10 years cannot possibly have been biased towards the lean over the obese because childhood obesity was virtually unknown in all populations until very recently.

Summary of effects of thrifty genes on mortality. Summarizing the above arguments, if one takes the position adopted by Prentice[17] that selection favouring thrifty genes has only occurred for the past 12 000 years, the levels of mortality during famines and the demographics of this mortality do not provide a sufficient selective force to favour the spread of thrifty genes into 30% of the population. This leaves us with several alternatives. First, the Chakravarthy and Booth[12] proposal that famines stretched back to the dawn of the genus *Homo* may be correct, but in that case we would all have inherited thrift in our genes and would all be obese—which patently we are not. Second, mortality during famines may not be the important factor. The obese may not die more frequently in famines but they may be able to continue breeding, and consequently derive a fecundity advantage. Third, the whole idea may be wrong, and the genetic basis of the obesity epidemic may be due to some completely different process. I have argued elsewhere for this third possibility.[24] I will conclude this paper by considering the alternative suggestion that it is differences in fecundity between obese and lean subjects during famine that provide the selective pressure for thrifty genes, and will then elaborate on the alternative process presented previously.

Famine and fecundity. The suggestion that obese persons retain higher fecundity during famine has much to commend it. The suggestion is that levels of body fat have important implications for reproductive function, and that when body fatness falls below a critical level, reproductive functions are shut down.[48–50] Obese people entering a famine would in theory reach this threshold for sustained reproductive condition later, and would consequently retain fecundity for longer. The evidence that famines have profound effects on fecundity is much stronger than the weak evidence concerning mortality effects summarized above. For example, Figure 1b shows fecundity during the 'great leap forward' famine in China for the same area as the mortality statistics in Figure 1a.[33] The birth rate prior to

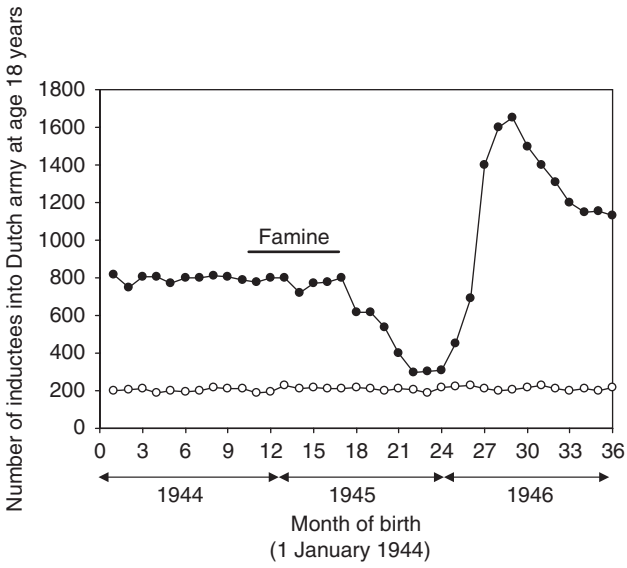

Figure 2 Numbers of inductees into the Dutch army at age 18 in relation to month of birth, from an area exposed to the Dutch winter famine (filled circles) and an area spared from the famine (open circles). The famine indicated by the bar started in November 1944 and lasted until May 1945. Data interpolated from graphs in Stein.[51]

the famine in 1956–1958 averages about 36 births per 1000 people, but during the famine years of 1959 and 1960 and the following year of 1961, it falls to 21.0, 8.6 and 11.1 births per 1000 people, respectively (averaging only about 13 births per 1000). This level of fecundity is 60% lower than that prior to the famine. If this fecundity was biased towards individuals who before the famine were obese, the obese carriers of a thrifty 'A' allele would have easily sufficient selective advantage for the spread of the thrifty genes over the 10 000 years since the dawn of agriculture ($k = 0.15$–0.21).

However, there is a problem with this calculation. Following the famine, the birth rate does not return to the pre-famine rate of 36 births per year but instead leaps up to around 50 births per year, and this elevated rate is maintained for at least the 4 years that records are reported by St Clair *et al*.[33] This rebound effect following the famine completely offsets the reduced fecundity during the famine years. If a window of average fecundity is considered, which spans the period of the famine and the immediate post-famine years, the resultant effect of the famine on fecundity is virtually zero. In the case of the famine at WuHu (Figure 1b), the average fecundity between 1956 and 1958 was 35.6 births per year per 1000 people, and between 1959 and 1965 was 34.8 ($t = 0.1$, $P = 0.92$). This could be an isolated incidence where the background changes in lifestyle of the population were leading to elevated birth rates over time, but studies of several different famines reveal similar effects. For example, rates of conscription of 18-year-old males from families with manual occupations into the Dutch army, 18 years after the Dutch winter famine of 1944–1945 (Figure 2), show a dip in recruitment, which would match a

fall in conceptions during the famine, followed by a bulge in recruitment corresponding to the immediate post-famine period.[51] These changes were not observed in adjacent areas of the country not subject to the famine (Figure 2). The net effect of the famine, taking into account not only the decline in fecundity during the famine but also the post-famine recovery, is again virtually zero. The small differences in overall fecundity, even if they are biased towards obese people, are insufficient to rescue the thrifty gene hypothesis.

There are several further problems with the fecundity argument. Evidence suggests that the stimulus causing shutdown of the reproductive system is not actually the absolute levels of body fatness, but the immediate experience of energy imbalance and intracellular fuel oxidation status.[52,53] Famine infertility probably therefore affects obese people as much as lean people, as they are both exposed to severe negative energy imbalance. Moreover, decreases in reproductive activity will also, in part, reflect changed social conditions. For example, couples are frequently separated for protracted periods during famines because one partner leaves to search for food. These social factors would be unlikely to be biased with respect to body condition. In addition, evidence suggests that obesity has negative effects on reproductive performance in both animal models[54] and humans.[55–58] Even if there was a bias in fecundity towards obese individuals during famines, this would probably be offset by the detrimental effects of obesity between famines, which span much longer periods.

However, let us consider that I am wrong. Let us imagine that famines have caused the selection of thrifty genes and my interpretations of the levels and patterns of famine mortality and fecundity are faulty. How could we test that idea directly? The easiest way to test the 'thrifty gene' hypothesis is to examine the levels of obesity among populations in the periods between famines. If there has been selection for 'thrifty genes', then a population carrying these genes must become obese between famines. If they do not exhibit an obese phenotype, then it is impossible to see how they could derive an advantage from their thrifty genotype. The advantage of having thrifty genes in all the formulations of the hypothesis published to date is that individuals between famines get fat.

I have previously summarized some data on the body condition of modern hunter gatherer and subsistence agriculture communities (for example, references[59–63]) showing that between famines these people do not get fat.[22,23] However, one could make the argument that these are the wrong populations to investigate because these societies have never developed organized agriculture, and so have never been exposed to 'real famines' *sensu*.[17] The absence of an increase in fatness in these populations may actually therefore support an interpretation that famine and the selection of thrifty genes has only occurred over the past 12 000 years in societies that developed agriculture. However, if one examines historical levels of obesity (prior to the recent epidemic) in societies that have developed agriculture, during periods between famines, one finds the same pattern. For example, in the United States in the late 1890s, levels of obesity were only around 3%,[64] yet these populations had not experienced a famine since 1816 ample time for those individuals expressing a thrifty genotype to utilize their genes to deposit a sizable fat store.

An alternative perspective: 'drifty' genes

It is interesting that despite the recent flurry of papers reiterating the thrifty gene hypothesis (cited above), and its continued citation popularity, Neel himself, based on his experience working with tribes in South America, had already recognized by the late 1980s that the hypothesis was wrong. For example, Neel[65] stated that 'The data on which that rather soft hypothesis was based has now largely collapsed'. The fundamental problem with the thrifty gene hypothesis is that it infers that obesity was historically advantageous and hence under positive selection pressure. Yet, basic calculations, that have been known for 80 years, about what happens to allele frequencies under such positive selection, show that if alleles endow any minute advantage at all, the duration over which selection has been operating means that we would all have inherited these genes and be obese. Consequently, obesity must either be under some counterbalancing selection, such as reduced fecundity highlighted above or greater susceptibility to disease, or alleles in genes that predispose us to obesity have spread by a different process.

Such an alternative process is genetic drift.[66] This occurs when the mutant alleles in question are not under selection but selectively neutral. In a previous paper, I have highlighted one such scenario. That is, a situation where our body fatness was historically regulated by system that involves upper and lower intervention limits, as appears to be the case in some wild animals today (for example, El Bakry *et al.*,[67] Peacock and Speakman,[68] and Krol *et al.*[69]). The lower intervention limit is set by the risk of starvation, and the upper intervention limit is set by the risk of predation. I have argued that 2 million years ago, we went through a transition in our exposure to predation risk because at that time we developed social behaviour, weapons and fire. This effectively removed any selection maintaining the position of the upper intervention point. Over the past 2 million years, the genes defining the upper intervention point have been subject to random mutation and drift. Consequently, when embedded in modern societies where energy is freely available, individuals move to their drifted upper intervention points. A simple model suggests this may generate a pattern of susceptibility to obesity that reasonably mimics the form of the modern epidemic.[24]

The predation release hypothesis is, however, only one of the several scenarios based on drifting unselected genes that may explain the current demographics of the obesity epidemic. An alternative scenario, for example, could be that

historically we were never exposed to high levels of dietary fat. Mutations that negatively affected function of the genes that regulate the oxidation of fat might therefore also have been under random mutation and drift. The capacity for fat oxidation would consequently vary between individuals, but as long as dietary fat levels remained low, there would be no negative consequences of this variability. These mutations would only be exposed as giving their bearers a predisposition to obesity when dietary fat levels increased. Supporting this suggestion, individual variation in basal fat oxidation rates are a consistent predictor of predisposition to obesity in both humans[70–76] and animals.[77,78]

The common point in these two scenarios is that they do not rely on any assumption that obesity was historically advantageous. Rather they make the opposite assumption that genes predisposing to obesity were NOT under any positive selection. In this situation, random mutations occur in the genes and the frequencies of these mutant alleles drift at random. These genes may then be called 'drifty genes', and it is due to their influence that some of us are unfortunate in the genetic lottery and inherit a predisposition to conditions that in our modern society have such devastating effects.

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