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LETTER TO THE EDITOR

The thrifty gene hypothesis: maybe everyone is right?

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As always, Professor Claude Bouchard provides an elegant up-to-date exposition of the Neel 'thrifty gene' hypothesis, but disappointingly concurs with discarding it completely.[1] Perhaps an expansion of the hypothesis could satisfy everyone?

As stated, the presence of strong genetic influences in obesity has been demonstrated to everyone's satisfaction. However, the excellent identical twin studies quoted by Professor Bouchard required confirmation from studies of both identical and non-identical twins, to reject the possibility that similar *in utero* environmental influences in twins caused later adiposity, rather than the genetic one.[2] In such a twin study, using further decomposition analysis, we also showed that there are multiple genes involved in governing total and central fatness, some shared and some separate.[3]

However, the rejection of Neel's 'thrifty gene' hypothesis may be too early. Rather, I suggest its expansion to hypothesize a selection by evolution of genes that are 'superior for survival' in dangerous times. Survival in hard times was based (as Professor Bouchard details) on qualities now probably disadvantageous to our hopes of a long life (to which we all now feel entitled). Unfortunately, species preservation demands only our survival to rear our young safely, not to reach a comfortable old age.

I propose the following list as a teleological 'survival' grouping, in accord with both the Neel concept and genes that Professor Bouchard reports in his review.

The survival gene clusters we should expect to identify will govern the following activities:

(1) rapid food consumption; (2) efficient fat storage; (3) activity bursts for food gathering or protection (glycolytic predominance, less rapid switch to fat oxidation); (4) hyperactive innate immune response (Toll-like receptor 4 system), possibly with faster thrombus formation; (5) greater flight or flight response (sympathetic nervous system responsiveness); (6) low level of 'unpurposeful' activity.

The association between the innate immune response system, a primitive cellular response as if to a threat of hypoxia (also related to reactive oxygen species), and the tendency to glycolytic rather than fat oxidative metabolism is consistent with an 'overresponsive' hypoxia-inducible factor 1α pathway.[4] Furthermore, the very recent data suggesting that the gut flora cause obesity and insulin resistance would be consistent with my hypothesis of a hyperactive state of T-cell like receptor 4 immunity, itself causing the immune hyperresponse to gut microbiota, thus demonstrating the predicted links between immunity and obesity genes.[5,6] Thrombocytes may apparently be similarly T-cell like receptor 4 responsive to lipopolysaccharides and such over-responsiveness would no longer be beneficial to man.[7]

In behavioural traits, the low non-exercise activity thermogenesis reported in 'couch potatoes' has been suggested to be genetic in origin.[8]

Professor Bouchard speculates that genotyping will eventually simplify susceptibility to obesity and associated phenotypes. I agree, because the genes useful for survival and fat sparing can already help explain later atheroma (via novel mechanisms such as T-cell like receptor 4 interaction with oxidized low-density lipoprotein and lipopolysaccharides) and possibly, microvascular disease (via tumour growth factor β under hypoxia-inducible factor 1α regulation). For example, a human polymorphism of T-cell like receptor 4 was reported in 2002 associated with poorer immunity to infection as well as decreased atheroma.[9]

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