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In reply- Maternal, Paternal, and Societal Efforts Are Needed to "Cure" Child Obesity

Edward Archer, Ph.D, MS.

Office of Energetics Nutrition Obesity Research Center University of Alabama at Birmingham

Letter to the Editor

I welcome Drs. Ferraro and Adamo's discourse and readily admit that whenever educated readers wholly fail to comprehend the main thrust of a theory, the fault frequently lies with the author (i.e., me). Given this possibility, I now seek to remove whatever opacity led to their miscomprehension.

Science is the pursuit of lawful relations, not mere correlations; and the only test of a scientific theory ishow well it explains *all* the available evidence, not isolated findings. With these premises as a foundation, my theory links the socio-environmental changes over the past century to the lawful relations between the physiologic mechanisms driving epidemiologic trends and the subsequent evolutionary consequences.

In simple terms, the human body may be conceived as an ecosystem in which tissues compete for nutrient-energy. Within this framework, obesity is *not* a complex phenomenon but merely the result of the competitive dominance of fat cells over other tissues in the absorption and sequestering of energy. This competitive advantage is engendered via prenatal physiologic and postnatal behavioral 'maternal effects' (i.e., alterations in fat, muscle, and pancreatic beta cell development and learned physical inactivity). These environmentally-induced phenotypic effects have evolutionary consequences because they are transmitted progressively to the next generation through an altered maternal phenotype, independent of changes to the genome.

As stated in my title and throughout the paper, the twin epidemics of obesity and type II diabetes mellitus (T2DM) are the result of *non-genetic* evolution; at no point was there an "implied contribution of epigenetics...driving the intergenerational cycle of obesity." Quite the contrary, I wrote extensively on the near-complete failure (i.e., lack of explanatory and predictive power) of the gene-centric (i.e., DNA and epigenetic) paradigm and stated explicitly that the problem of the "missing heritability...will not be found in the genome." Furthermore, I posited that the rapid and ubiquitous phenotypic evolution evidenced over the past century was the result of "the progressive intergenerational transmission of acquired characteristics over multiple successive generations."

My empirically supported physiologic theory of inheritance and evolution (based on accumulative maternal effects) posits that a fertilized oocyte with *any human genome* placed in the intrauterine milieu of a woman with an obese, inactive phenotype (i.e., with an evolutionary/familial history of high maternal resources and high levels of physical

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inactivity/sedentary behavior) will be born with compromised metabolic functioning. This inherited phenotype assures the adipogenic nutrient partitioning that leads to obesity and T2DM and is transmissible to the next generation via maternal effects (e.g., excessive gestational weight gain). In other words, phenotype begets phenotype because the intrauterine environment overwhelms any genetic variance across generations (i.e., the environmental determinism of obesity/T2DM; please see text of figure 4 of[1]). The empirical support for 'maternal effects' is unequivocal across species,[2] including humans. For example, Brooks et al.[3] examined ovum donations in humans and found that the "*only discernible factor*" influencing infant birth weight was the *surrogate* mother's body mass. Given these findings, and the fact that metabolically relevant mitochondrial DNA are (asexually) inherited via the maternal germ-line,[4] I find little evidence to support the dogmatic speculation that paternal genes will have significant differential effects where it appears that maternal genes do not.

With respect to fetal development, genes are merely a necessary but not sufficient component of the development of obese/T2DM phenotypes, akin to atmospheric oxygen and water. They can be conceptualized as the 'tools' of the fertilized oocyte, and their use (i.e., expression) is strictly environment-dependent.[5-9] As such, if we assume that a hammer is necessary to build a house, it should be obvious that the hammer does not *cause* a house to be built, nor determine its dimensions. Nevertheless, gene-centric dogma is based on the unsupported speculation that DNA (the hammer) is the cause of the obese/T2DM phenotypes (the house *and* its dimensions). Not surprisingly, if the only tool one has is a hammer, one will think everything is a nail; hence the myopic nature of genetic determinism, the irrelevance of genetic testing for obesity/T2DM, and failure of the gene/DNA-centric paradigm to explain recent epidemiologic trends.

Conversely, the most clinically relevant and scientifically important aspect of my paper is the empirical support presented for the 'inheritance of acquired characteristics through use and disuse' as a significant and universal mechanism of inheritance and evolution. This theory has been presented for millennia without strong evidence (e.g., Hippocrates,[10] Aristotle[11], Jean-Baptiste Lamarck[12] and Charles Darwin[13]). Thus, I posited an empirically supported "*in utero training effect*" for fat cell development (i.e., the 'use' phase of "*use and disuse*") and the post-natal effects of inactivity (i.e., the '*disuse*' of skeletal muscles leading to insulin resistance, increased adiposity, etc.) leading to the intergenerational transmission of obesity and T2DM. The clinical and research implications of my theory are obvious given that it provides an unambiguous framework to intervene on the intergenerational transmission of obesity and T2DM: significantly increase the skeletal muscle energy flux of females across their lifespan.

My theory of inheritance and evolution: 1) directly challenges and potentially refutes the hyper-reductionist gene-centric Modern Synthesis,[14] 2) flouts the central dogma of molecular biology[15] and Weismann Barrier,[16] and 3) subsumes and extends the ground-breaking (and brilliant) work of both Barker[17] and Pedersen.[18] From a clinical standpoint, because gene expression is environmentally determined,[5-9,19] genes are a merely a marker of what was and what is, not what will be.[7] Therefore, gene-centric research is a costly, unnecessary tangent to clinically relevant scientific progress. As the great evolutionary

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geneticist Richard Lewontin wrote in 2006, it is time to dispel the "naive current prejudice that DNA has in it all the information necessary to specify the organism."[20] I could not agree more and look forward to scientific and clinical progress.

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References

1. Archer E. The Childhood Obesity Epidemic as a Result of Nongenetic Evolution: The Maternal Resources Hypothesis. Mayo Clinic Proceedings. 2015; XX(XX):1–16. [xxx1].
2. Fox, CW.; Mousseau, TA. Maternal effects as adaptations for transgenerational phenotypic plasticity (TPP).. In: Mousseau, TA.; Fox, CW., editors. Maternal Effects as Adaptations. Oxford University Press; New York: 1998.
3. Brooks AA, Johnson MR, Steer PJ, Pawson ME, Abdalla HI. Birth weight: nature or nurture? Early Hum Dev. May 12; 1995 42(1):29–35. [PubMed: 7671843]
4. Hoekstra RF. Evolutionary origin and consequences of uniparental mitochondrial inheritance. Hum Reprod. Jul; 2000 15(Suppl 2):102–111. [PubMed: 11041518]
5. Bissell, MJ.; Mian, IS.; Radisky, D.; Turley, E. Tissue Specificity: Structural Cues Allow Diverse Phenotypes from a Constant Genotype.. In: Muller, GB.; Newman, AB., editors. Origination of Organismal Form: Beyond the Gene in Development and Evolutionay Biology. A Bradford Book/MIT Press; Cambridge MA: 2003. p. 103-118.
6. Crabbe JC, Wahlsten D, Dudek BC. Genetics of Mouse Behavior: Interactions with Laboratory Environment. Science. Jun 4; 1999 284(5420):1670–1672. 1999. [PubMed: 10356397]
7. Rosenquist JN, Lehrer SF, O'Malley AJ, Zaslavsky AM, Smoller JW, Christakis NA. Cohort of birth modifies the association between FTO genotype and BMI. Proceedings of the National Academy of Sciences. Dec 29.2014 2014
8. Kilpelainen TO, Qi L, Brage S, et al. Physical Activity Attenuates the Influence of FTO Variants on Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children. PLoS Med. Nov.2011 8(11):e1001116. PubMed. [PubMed: 22069379]
9. Vimaleswaran KS, Li S, Zhao JH, et al. Physical activity attenuates the body mass index-increasing influence of genetic variation in the FTO gene. Am J Clin Nutr. Aug; 2009 90(2):425–428. PubMed. [PubMed: 19553294]
10. Hippocrates. Stevenson, DC., editor. On Airs, Waters, and Places. Available online at http://classics.mit.edu//Hippocrates/airwatpl.html/2000
11. Aristotle. On the Generation of Animals. Harvard University Press; Cambridge: 1943.
12. Lamarck, JB. Zoological Philosophy: Exposition with Regard to the Natural History of Animals; [Philosophie Zoologique, Ou Exposition Des Considérations Relatives À L'histoire Naturelle Des Animaux.]. Macmillan; London: 1809/1914.
13. Darwin, C. The variation of animals and plants under domestication. 1st ed.. John Murray; London: 1868.
14. Huxley, J. Evolution: The Modern Synthesis. Allen & Unwin; London: 1942.
15. Crick F. Central dogma of molecular biology. Nature. Aug 8; 1970 227(5258):561–563. [PubMed: 4913914]
16. Weismann, A. The Germ-Plasm. Charles Scribner's Sons/Electronic Scholarly Publishing; 1893. Available at: http://www.esp.org/books/weismann/germ-plasm/facsimile/
17. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. Jul; 1992 35(7):595–601. PubMed. [PubMed: 1644236]

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18. Pedersen, J. The pregnant diabetic and her newborn: problems and management. Munksgaard; Copenhagen: 1967/1977.
19. Bhat R, Bissell MJ. Of plasticity and specificity: dialectics of the microenvironment and macroenvironment and the organ phenotype. Wiley interdisciplinary reviews. Developmental biology. Mar-Apr;2014 3(2):147–163. PubMed. [PubMed: 24719287]
20. Lewontin RC. Commentary: statistical analysis or biological analysis as tools for understanding biological causes. Int J Epidemiol. Jun; 2006 35(3):536–537. PubMed. [PubMed: 16672311]