Epigenetics and Childhood Obesity

To the Editor: In his article in the January 2015 issue of *Mayo Clinic Proceedings*, Archer[1] has, in a novel yet age-old construct, succinctly hypothesized the putative role of epigenetics in a complex multifactorial condition, childhood obesity. His hypothesis is in harmony with the results of a recently published systematic overview of the most recent research findings in the area of epigenetics and obesity, which revealed that the propensity toward adult obesity has early developmental origins and follows an intergenerational cycle.[2]

Epigenetics, an increasingly recognized discipline, is defined as heritable regulation of gene expression without a change in the base sequence of DNA.[3] Epigenetic marks can alter the transcription of a particular gene, thereby determining whether the gene is "turned on or off" at a given point in time. Epigenetic mechanisms that are best studied so far include addition or deletion of methyl groups to DNA (this occurs predominantly at CpG sites), posttranslational modifications to histone proteins, and noncoding RNA. Although the DNA sequence of genes in an individual (the genome) is largely stable, the epigenome is dynamic and has the potential to be reversibly modified by exposure to a range of environmental factors.

Over the past decade, increasing effort has been made to understand the role of epigenetic modifications in other complex conditions like cancer, autoimmune rheumatic diseases, and obesity. To date, DNA methylation, either at global, site-specific, or genome-wide levels at single nucleotide resolution, is by far the most studied epigenetic mark in obesity with the help of high-throughput screening methods. Archer's proposed maternal resource hypothesis is a very useful addition to the insight about developmental origins of health and disease via epigenetic modifications programmed by the perinatal environment.

Epidemiological studies, including Project Ice Storm[4] (a study of the effects of prenatal maternal stress exposure to a storm that impacted Quebec in 1998), have already documented the lasting impact of the prenatal conditions via methylation patterns of offspring.[5] Recently, no connection was found between the *FTO* gene and obesity in the Framingham cohort born before 1942 and very strong correlation in those born after 1972, findings that take Lamarck's notion of environment shaping phenotype to an interesting level.[6,7]

The first steps are already being made in identifying potential epigenetic biomarkers for obesity that could be detected at birth. Eventually, this finding may help in predicting an individual's obesity risk at a young age, before the phenotype develops (the "tipping point." as coined by Archer[1]), and opens possibilities for introducing targeted strategies to prevent the condition. It is also now clear that several epigenetic markers are modifiable by changing maternal habits during pregnancy, to turn the unfavorable epigenomic switch off and pass it in an off mode to several subsequent generations.

As Einstein said, "a problem cannot be solved on the same level at which it arose."[8] With Archer's commendable article, we are going beyond Darwinism back by a few centuries to Lamarck's soft inheritance theory, or even all the way to the Vedas, the oldest books in the library of mankind that say, "You are the architects of your destiny" and of the generations to come. Once we unravel all we can about epigenetics as well as we have done with genetics, we may realize we are no closer to understanding the mysteries of our existence and human behavior. What is clear from the burgeoning field of epigenetics is that the historical argument of nature vs nurture might best be reconciled by a context of nature via nurture.

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In reply—Epigenetics and Childhood Obesity

I sincerely welcome the letter from Drs Kaushik, Pettus, and Malkani and the opportunity to continue the increasingly vigorous scientific discourse that my theory[1] has fomented in disciplines as disparate as pediatrics, sociology, evolutionary genetics, and public

health. It is not often that a scientist finds his or her work[1] associated with quotes from Einstein and Vedic texts. Although I sincerely appreciate the compliment these authors offer me, I think it necessary to address 2 important issues: first, their interpretation of my use of the term *nongenetic*, and second, the assumption that the genome and/or epigenome are productive levels of analysis with respect to obesity and type 2 diabetes mellitus (T2DM).

In my article, the term *nongenetic* is not synonymous with the term *epigenetic*. In my reply to a previous letter to the editor,[2] I offered a detailed explanation of my use of the term *nongenetic*, and I direct readers to that response. I will not belabor that point here but will provide further support for my position that genetic/epigenetic research is an incongruous level of analysis for the examination of obesity and T2DM and as such represents an extremely costly, unnecessary, and irrelevant tangent for clinically relevant scientific progress.

Scientific Progress and Relevant Levels of Analysis

Science can be described as the pursuit of explanation and prediction (ie, lawful relations) and when possible, control of the natural world. Given that the foundation of medicine is the prediction and control of biological processes, science is the essence of the clinician's professional life. Although scientific examinations may be performed at many levels of analysis (eg, from cells to society), for many biological phenomena there is a single level of analysis that subsumes both ultimate and proximate causes and therefore is the most relevant to achieve the scientific (and clinical) ends of explanation, prediction, and control. For example, if a physician seeks to explain to a parent why his or her child has fetal alcohol syndrome (FAS), the most relevant level of analysis is the mother's behavior because it is the mother's prenatal ethanol consumption[3,4] (ie, the ultimate cause) that alters the trajectory of the child's prenatal and postnatal development (ie, the proximate causes). It is patently obvious that gene expression was substantially altered, but the level of analysis with the most explanatory and predictive power is the mother's prenatal behavior.[4] The molecular level of analysis (eg, genetic/epigenetic) offers the clinician no additional information relevant to the explanation, prediction, or control (eg, prevention) of FAS. Thus, as with childhood obesity, gene expression is merely one of the many components in the proximate causal pathway of the FAS phenotype that are subsumed by the ultimate cause.

Levels of Analysis Relevant to Scientific Progress in Obesity and T2DM Research

Funding for biomedical research has increased exponentially over the past few decades as the National Institutes of Health research expenditures increased from less than $5 billion in 1970 to approximately $30 billion in 2010.[5,6] This increase was greater than that for all other scientific disciplines combined. Nevertheless, the sheer volume of tangential and irrelevant information produced by the massive influx of funding has obscured both scientific common sense and basic knowledge as the competition for grants, publications, and professional tenure gained prominence over problem solving. Fundable but trivial research became more important than the scientific ends of explanation, prediction, and control.

I wrote the article on the maternal resource hypothesis to provide a synthesis and integration of a century of knowledge in the hope that it will assist in overcoming the information overload and the pursuit of trivial research that currently pervades obesity and nutrition science. To that end, my theory explicitly states that the *ultimate cause* of childhood obesity and predisposition to T2DM is nongenetic evolution via *accumulative maternal effects*. The *proximate* causal elements are (1) maternal prenatal energy metabolism, of which body composition and physical activity are the greatest determinants, and (2) maternal postnatal physical activity, which substantially influences the child's lifelong physical activity behaviors and consequent disease risk. As such, all other levels of analysis (eg, genetic, epigenetic, microbiomic, economic) are merely interesting but costly and irrelevant tangents to scientific progress in preventing obesity and T2DM.

Accumulative and "Corrective" Maternal Effects

The scientific literature on maternal effects and metabolic functioning in both humans and other animals (eg, sheep, rodents) is unequivocal.[7-12] Ovum transfer, animal breeding, and cross-fostering studies have clearly documented that the intrauterine milieu and early postnatal periods can induce or ameliorate metabolic dysfunction in a single generation, independent of genotype. Recently, an embryo transfer study by Garg et al[13] found that the inheritance of pathologic metabolic phenotypes can be ameliorated when the embryo is transferred and gestated in a "normal metabolic environment." These results taken together provide unambiguous empirical support for the maternal resource hypothesis and my contention that genetic/epigenetic research is an incongruous level of analysis for the examination of obesity and T2DM and represents an extremely costly, irrelevant tangent for clinically relevant scientific progress.

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Continued Caution Recommended in Use of Intravenous Iron Preparations

To the Editor: We read with interest the report of the well-performed study of Avni et al[1] on the safety of intravenous (IV) iron administration published in the January 2015 issue of *Mayo Clinic Proceedings*. After carefully analyzing more than 100 published randomized, controlled trials (RCTs) that included more than 10,000 patients, the authors concluded that there is no increased risk of serious adverse effects (SAEs) with IV iron preparations compared with other oral iron preparations or placebo and that IV iron formulations are safe and may be given to iron-deficient individuals without fear of infection or cardiovascular events. Although the authors rightfully acknowledged in their discussion the substantial limitations of RCTs to detect rare SAEs, we think that several aspects of the studies included in the meta-analysis and postmarketing signals represent serious limitations to such a strong recommendation.

First, as rightfully mentioned by the authors, risk of bias analysis found that allocation concealment was unclear in almost half of the trials and that only 18% of the assessed studies were double-blind trials. Also, most included trials (80%) did not specify how severity was defined. Although beyond the control of the authors, the fairly low quality of included studies could decrease the validity of their findings. Finally, for many relative risks for SAEs, confidence intervals were borderline, which could also be regarded as an additional limitation for their recommendation.

Second, the authors did not take into account postmarketing signals coming from spontaneous reporting to pharmacoepidemiology surveillance programs. This factor was not the purpose of their research and thus is fully understandable. However, many cases of SAEs including anaphylaxis and death were reported to several national pharmacoepidemiology surveillance programs. After a careful reevaluation of the risks and benefits of IV iron, the European Medicine Agency and the Agence Nationale du Médicament et des Produits de Santé in France drastically tightened the procedures for IV iron administration.[2] This change had immediate practical consequences for the prescribers and their patients.[3] Swissmedic (the official body responsible for collecting all postmarketing adverse effects reports in Switzerland) announced 239 severe reactions following carboxymaltose administration only between 2010 and 2013. There were 3 deaths, including 1 secondary to an anaphylactic reaction. Causality between IV iron administration and death was less evident for the other cases (one cerebral haemorrhage 3 weeks after iron administration and one fetal death). Furthermore, 185 anaphylactic reactions, including 21 cases of shock were reported.[4] For ferumoxytol, 3 SAEs and 1 death were reported.[4] Following several reports of SAEs including deaths following ferumoxytol administration, Health Canada endorsed important new safety information on ferumoxytol in November 2014.[5]

One of the goals of postmarketing reporting is to capture SAEs that are too rare to be observed in RCTs or are only apparent when the drug in question is administered to other populations with different characteristics, such as children, pregnant women, or elderly people. The same applies for severe drug interactions (and potential SAEs), which are rarely captured in RCTs in which coadministration of other drugs is much rarer than in real life. Between 2002 and 2011, 19 such drugs were withdrawn from the market after pharmacoepidemiological studies signaled SAEs.[6]

In summary, the analysis of Avni et al[1] is correct. All IV iron formulations remain effective drugs. However, in view of their findings and of the current postmarketing signals, their conclusions should be somewhat more nuanced. Serious infusion reactions are reported more often with IV iron preparations, either in RCTs or in postmarketing surveillance programs, and this issue should not be forgotten. Prescribers should continue to use intravenous iron cautiously, as has already been recommended.[2,3,5]