Why are we failing with the epidemic of obesity and other chronic diseases? A further look at aetiopathogenesis

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Abstract

It is timely to be addressing this question: in some respects medicine and the delivery of healthcare has driven itself slowly to an impasse, whilst the biological sciences that should underpin our understanding of healthcare are undergoing a revolution. That there could now be seriously conflicting scientific opinion over the role of saturated fats in the aetiopathogenesis of coronary heart disease is a terrifying indictment of our limited understanding of the role of the modern diet in disease.

Currently there remains a substantial disconnect between the new directions indicated by the biological sciences, and our entrenched views concerning treatment of the epidemic chronic diseases such as obesity. As the new knowledge unfolds it seems likely that a better understanding of diet in all respects will move to centre stage as we endeavour to solve these problems.

The last decade has seen the field of epigenetics emerging from the fog, and with it entirely new biological structures for understanding the aetiology of disease.\textsuperscript{1,2} This development has thrown open an important window upon our understanding of the mechanisms by which diet, nutrition, and many other environmental factors influence gene expression and ultimately health and disease.\textsuperscript{3} The specialty within which the study of epigenetics has found immediate relevance has been that of fetal development and—more specifically—the developmental origins of adult disease.\textsuperscript{4}

It increasingly appears that the fetus is the ‘canary in the coalmine’: maternal physiology and biochemistry, and anything that influences it, can potentially be transfused into lifelong patterns of gene expression and consequent risk for metabolic disease.\textsuperscript{5,6} From the moment of conception the physiological attributes of the expected environment are being used to program changes in chromatin structure and expression of the genome, through the intermediary of even the most subtle nuances in the maternal microenvironment. The major window of this epigenetic imprinting takes place up until the time of birth.

The clustering comorbidities of obesity, diabetes, cardiovascular disease, and even mood disorder are becoming epidemic in the developed world. Questions are now being asked about the relationship between the surge of these disorders and the modern western diet, as well as other aspects of the environment that coexist with these pathologies.

Consider the example of obesity, which is clearly a multifactorial condition. Many different potential genetic, epigenetic, environmental, nutritional, and lifestyle factors all potentially contribute to an apparent variety of developmental trajectories that lead to this condition.
Rather than reflecting fixed change in the genome itself, the explosion of the epidemic of obesity and metabolic disease suggests factors that are environmental and epigenetic. Molecular epidemiology has failed to find any single strong identifiable genetic links; instead, there is an association with a broad range of genes subject to many single nucleotide polymorphisms. Generically-applied dietary and lifestyle advice to address obesity that takes no account of this heterogenicity is of limited value. Unfortunately, some past public health advice in this respect has not been good. The plethora of animal and human studies which highlight many different facets of developmental programming known to influence adult obesity have recently been well reviewed. For example, it now appears from both animal and human studies that the macronutrients in a pregnant woman’s diet can influence the incidence of obesity in the later life of her offspring.

Manipulating the macronutrient component of the maternal diet in animal studies (in which diet can be rigorously controlled) has been shown to induce obesity in the offspring. Thus the quantity, the quality, the composition, and the timing of nutritional interventions in animal models have all been shown to potentially influence adult obesity. If there are aspects of the maternal diet that either augment or attenuate the transgenerational transmission of obesity risk, then it is urgent that these issues be clarified.

To add yet another layer of complexity, it has been demonstrated that changes in 1-carbon metabolism may provide a broad amplification or reduction of the risk generated by these macronutrient modifications. In animal studies, the modification of DNA methylation by methyl donor supplementation has been shown to prevent transgenerational amplification of obesity in the well worked Agouti mouse model of genetic predisposition to obesity. Restriction of folate, vitamin B12, and methionine from the peri-conceptual diet of sheep-induced obesity in the offspring. The influence of diet upon epigenetics extends beyond the provision of macronutrients and methyl groups.

There are some 25,000 bioactive compounds in the human diet, such as bioflavanoids, that also directly influence many aspects of epigenetic regulation—although their role, if any, with obesity is unknown. Furthermore, the fetus may be especially sensitive—on account of its open window of epigenetic ‘work in progress’—to the consequences of endocrine disrupting chemicals, now known to include obesity. In another environmental-dietary nutrient type interaction, bisphenol A-induced epigenetic changes were shown to be negated by additional methyl group supplementation during gestation. Thus diet, in terms of its macronutrient composition, the availability of methyl groups, and its xenobiotic content have all been shown to influence epigenetic mechanisms relevant to fetal programming and obesity.

Increasingly, we see that a single environmental, genetic, or epigenetic input may lead to many diseases, and a single disease may have many inputs. Thus, environmental inputs as diverse as psychosocial stress, toxic exposure, and nutrient deficiency are capable of programming the pre-natal hypothalamic-pituitary axis in a manner that increases vulnerability to disease processes as diverse as diabetes, obesity, cardiovascular disease, and depression. These epigenetic influences are now understood to be transferable to a subsequent generation.
To illustrate this, a lot of very disparate lines of research have converged on epigenetic modification of the expression of the glucocorticoid receptor. Thus, psychosocial stress (both during pregnancy and in the neonatal period) has been shown to induce differential methylation in the promoter region of the glucocorticoid receptor.

In animal studies, these changes were reversible with methionine, the precursor of the methyl donor S-adenosyl methionine.\(^{18,19}\) It has since been shown that partner violence in pregnancy and childhood maltreatment also increases methylation of the glucocorticoid receptor promoter region.\(^{20,21}\) However, epigenetic effects in the same receptor have also been demonstrated to be a target of modifications in the protein content of the diet in pregnancy,\(^{22}\) again reversible with dietary methyl supplementation.\(^{23}\)

Thus, glucocorticoid receptor sensitivity seems to be a key point at which the hypothalamic–pituitary axis (HPA) reactivity is set or programmed by aspects of the intrauterine milieu. Meaney\(^{24}\) proposed that “the HPA axis is both a target for environmental influences and a mediator of the relationship between early life events and health in adulthood.”

Apparently, anything the fetus translates as stress—be it nutritional, psycho-social, or due to toxic exposure—is translated into an integrated set of physiological responses centred around altered HPA-axis functioning, including heightened stress response, increased central nervous system corticotrophin releasing factor (CRF), and adaptations centred around increased production and storage of energy.\(^{25}\)

The broad environmental inputs into fetal HPA axis programming are all ultimately translated (at least in terms of GR receptor function) into a simple binary code of HPA-axis functioning, which manifests across multiple endocrine, metabolic, and central nervous systems. When dysregulated, this seems to be associated with that familiar cluster of epidemic comorbidities in adult life.

A ‘money laundering’ effect occurs by which it becomes impossible to tease out the diverse environmental inputs (apparent risk factors) from the adult disease outcomes. Thus, for example, in terms of glucocorticoid receptor methylation, prenatal dietary effects on methylation pertinent to obesity may be relevant to the aetiology of lifelong depression, and factors relevant to depression might also affect obesity. There will be a summation of effects, and this will occur across many receptors and many genes yet to be studied as closely. It is also clear that these epigenetic effects can be transmitted to a second generation.\(^{26}\)

It now appears that, in many instances, causality may be better conceived as a network, and that these networks are not constrained to a single organ system; nor is the understanding of them contained in a single medical specialty-based silo of knowledge.\(^{27,28}\) The increased recognition of the protean effects of underlying inflammatory mechanisms and methylation imbalances across a wide spectrum of diseases are two examples of an evolving understanding of pathophysiology.

Interest is now focusing on ‘intermediate patho-phenotypes’ or ‘endophenotypes’ (a term co-opted recently within the field of biological psychiatry). This relates to underlying mechanisms of disease, often underpinned by genetic or epigenetic variations, and often brings a commonality to disorders that have seemed otherwise unrelated in terms of existing diagnostic classifications.
As we dig deeper into the aetiology and pathophysiology of these chronic conditions, current diagnostic groupings of diseases start to look less relevant, and increasingly the molecular signatures of disease are providing better information relevant to treatment and prognosis than histopathology.\(^2\)\(^9\) The unexpected benefits of statins—by virtue of their anti-inflammatory actions on patients with chronic obstructive pulmonary disease (COPD) and in the prevention of malignancy-related thromboembolic disease, and the diverse influence of omega-3 fatty acids and vitamin D across a range of disease processes—also illustrates aspects of this emerging complexity when we consider treatment.

The chronic diseases that the health system is failing to address, such as obesity and treatment resistant depression, are all subject to significant genetic influence from dozens, if not hundreds, of genes. These genes are subject to a multitude of single nucleotide polymorphisms, the expression of which is associated with a broad range of effects that can be cross-referenced to lists of seemingly unrelated diseases.

Downstream of this biological investigators are now working with vast transcriptomic, proteomic, and metabolomic datasets in individual health and disease which contain useful functional information and which again create new groupings of previously unrelated disorders.\(^3\)\(^0\) Targeted profiling of these polymorphisms and other diagnostic processes that identify relevant intermediate patho-phenotypes has the potential to lead to more individualised care for patients within these broad diagnostic categories. Such profiling can enable very important differences to be made in the provision of advice to patients concerning pharmacological agents, diet, nutrients, lifestyle, and even exercise.

Fundamentally, it informs the ability to individualise treatment in order to achieve optimum therapeutic efficacy. It also holds the promise of an improved ability to prevent disease, and a roadmap towards the application of public health genomics has been proposed.\(^3\)\(^1\) But this approach cannot easily be assimilated into the trusted methodologies of evidence based medicine—particularly not the randomised controlled trial (RCT), which studiously and philosophically avoids the individualisation of treatment. Thus, work in these areas currently exists only on the fringe of mainstream medicine.

The RCT aims, by weight of numbers, to systematically eliminate individual differences. Thus, an effective intervention for a small undefined sub-group within a heterogeneous study population may be concealed. The more that individuality is probed by the RCT methodology, the smaller the numbers and the weaker its power to discern an effect. The ability of that RCT to ‘see’ an effect in a vast heterogeneous population will depend entirely on its ability to precisely identify and group small numbers of patients in some of the new ways alluded to above.

Thus the current pervading medical paradigm sees the acknowledgement of the biological reality of individuality as problematic—at the very moment that the biological sciences are making sense of it. In trying to treat these new epidemics we risk being like a shoe salesman trying to fit the same shoe size to every customer because we have evidence pertaining to the size of the average foot. To move forward with these diseases there must first be a necessary mind shift to accepting that bigger and bigger trials with single treatment or intervention modalities is not going to provide us with the answers, or certainly not with the speed which is now required.
To “deliver the right treatment to the right patient; and the right prevention to the right population” there are three inescapable conclusions. The first is the necessity of a better understanding of the emerging role of diet in all of the mechanisms alluded to above. The second is that dietary interventions must be first targeted both pre pregnancy, during pregnancy and in the first postnatal year. The third is that ultimately, more effective treatment can only be delivered by interventions better individualised and targeted to specific underlying mechanisms of disease, not just treatments allotted by traditional diagnostic categorisation.

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