Abstract
Many features of human susceptibility to chronic noncommunicable diseases can be mapped onto the framework of the match/mismatch hypothesis. From an evolutionary perspective, it is highly likely that the human genome has been under selective pressure to survive and reproduce against a background of seasonal food shortages and frequent episodic famines, leading to the attractive, but unproven, concept of ‘a thrifty genotype made deleterious by famine’. From an ontogeny perspective, it has been clearly demonstrated that fetal undernutrition leads to a thrifty phenotype that enhances metabolic risk if the individual is later exposed to an energy-abundant environment. Data from developing and rapidly emerging countries permit insights into both of these pathways. Many populations are rapidly emerging from conditions broadly representative of human history over the past 600 or so generations (i.e. since the dawn of agriculture) and are transitioning within very few generations to a state of dietary abundance and low physical activity. And within this framework, many individuals make an even more rapid personal transition from the womb of a malnourished mother to a state of affluence. These journeys provide exceptional opportunities to interrogate thrifty genotype/phenotype theories, but such prospects are frequently impaired by a lack of robust data.

Introduction
In a preceding chapter, Uauy et al. [pp. 39–52] have made the case that the very rapid demographic and nutrition transition affecting many emergent countries is precipitating a ‘double burden’ of disease. This double burden – the unfin-
ished agenda of infectious diseases and the emergent agenda of chronic diseases – is a major threat to the development of nations.

The fact that developed nations have previously travelled down this road of abundant, low-cost, highly-refined, energy-dense diets combined with sedentary lifestyles, leading to fat gain and its associated morbidities, should hold lessons that could be used to slow the growing pandemic of noncommunicable diseases (NCDs). Conversely, knowledge gleaned from studying the rapid dynamics of change in developing countries may help to us to understand causal pathways with potentially important lessons for affluent societies. What are these lessons, and can we learn them fast enough to have a meaningful impact on global public health?

**Diabetes: The Leading Exemplar of Double Burden Diseases**

Among the wide range of chronic NCDs that hold a threat for emergent nations, diabetes stands out as the one that is most intimately linked to the societal changes that are transforming the disease landscape as countries pass through the nutrition and demographic transitions. Projections for the global increase in type 2 diabetes mellitus (T2D) leading up to 2030 are listed in table 1 which shows that, with the exception of the US, the countries with the leading burden will be those that are only now passing through the demographic transition. There are two synergistic components driving this change: first, the increases in

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**Table 1. International Diabetes Federation projections for diabetes prevalence rates by 2030**

<table>
<thead>
<tr>
<th>Country/territory</th>
<th>2011</th>
<th>Country/territory</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. China</td>
<td>90.0</td>
<td>1. China</td>
<td>129.7</td>
</tr>
<tr>
<td>2. India</td>
<td>61.3</td>
<td>2. India</td>
<td>101.2</td>
</tr>
<tr>
<td>3. United States of America</td>
<td>23.7</td>
<td>3. United States of America</td>
<td>29.6</td>
</tr>
<tr>
<td>4. Russian Federation</td>
<td>12.6</td>
<td>4. Brazil</td>
<td>19.6</td>
</tr>
<tr>
<td>5. Brazil</td>
<td>12.4</td>
<td>5. Bangladesh</td>
<td>16.8</td>
</tr>
<tr>
<td>6. Japan</td>
<td>10.7</td>
<td>6. Mexico</td>
<td>16.4</td>
</tr>
<tr>
<td>7. Mexico</td>
<td>10.3</td>
<td>7. Russian Federation</td>
<td>14.1</td>
</tr>
<tr>
<td>8. Bangladesh</td>
<td>8.4</td>
<td>8. Egypt</td>
<td>12.4</td>
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<tr>
<td>9. Egypt</td>
<td>7.3</td>
<td>9. Indonesia</td>
<td>11.8</td>
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<tr>
<td>10. Indonesia</td>
<td>7.3</td>
<td>10. Pakistan</td>
<td>11.4</td>
</tr>
</tbody>
</table>
child survival and adult longevity that allow longer exposure to any detrimental lifestyle factors, and, second, the rapid development of obesity.

It is well-proven that unhealthy weight gain lies on the causal pathway to metabolic syndrome, impaired glucose tolerance and ultimately to T2D. It is also clear that certain populations (e.g. South Asians, Polynesian Islanders, Pima Indians) are at a higher risk than others [Misra and Bhardwaj, this vol., pp. 133–140]. In the Pima Indians and Polynesians, much of this increased risk is mediated through their very high rates of early-onset obesity [1]. In South Asians, there is good evidence that they are more prone to obesity-related pathology at a lower body mass index (BMI) due to a relative excess of intra-abdominal adipose tissue [Misra and Bhardwaj, this vol., pp. 133–140]. Thus, BMI cutoffs are set at a lower level for South Indians [2].

The dyad of obesity and diabetes (sometimes termed ‘diabesity’) will be used as the key exemplar below, but the arguments are equally applicable to a range of other chronic diseases such as hypertension.

Exploiting Genetic Differences to Map Causal Pathways in Chronic Diseases

A question that arises from these observations is whether the differences summarized above are due to genotypic differences or life-course (including inter-generational) phenotypic differences, or a combination of the two. The issue of genetic variation clearly needs to be addressed when drawing comparisons between nations. The putative existence of ‘thrifty genes’ [3] is frequently invoked to explain the rapid transition towards obesity in urban Africans and South Asians, yet some of the known obesity-predisposing gene variants are less common in these populations. Intriguingly, for the human fat mass and obesity-associated (FTO) gene, which is the strongest of the known obesity-associated gene variants, the more recent variant allele favors leanness, not weight gain [4].

It is also a misconception to suggest that areas associated with recent famines and food-shortages (i.e. Africa and the Indian subcontinent) would have been under greater pressure to select thrifty genes. Historically, all populations worldwide have been under gene selection driven by famine [3], and the majority of this selection has probably been mediated through traits that influence fertility and reproductive success under marginal nutritional conditions [5]. Any such favorable genotypes may contribute to obesity, by favoring deposition of reproductively useful fat reserves in times of plenty [3], and to T2D, by favoring peripheral insulin resistance to benefit conception at low levels of BMI [5], and by displacing resources towards the fetus.
We [e.g. 3, 5, 6] and others [e.g. 7, 8] have written extensively about the possible role of thrifty genes in determining risk of obesity and T2D and speculated that definitive proof would shortly be available. However, the wait may need to continue as, although both traits are highly heritable, and large-scale genome-wide association studies (GWAS) have found multiple highly significant associations, even the most persuasive of these (i.e. FTO) has a very small influence on BMI, and when summed together all of the GWAS hits can still only explain a very small proportion of the heritability. New approaches involving integration of ENCODE analysis, systems biology approaches to genome-phenome analysis, and the analysis of genome-epigenome interactions may all yield future dividends. In the meantime, it will be more profitable to concentrate on potentially modifiable influences on chronic diseases.

Exploiting Phenotypic Differences to Map Causal Pathways in Chronic Diseases

The wide diversity of disease phenotypes (i.e. subvariants of insulin resistance/diabetes and hypertension), especially in populations of African origin, may be particularly helpful in efforts to map pathways of disease causality through GWAS and phenome-wide association studies. Recognition of this fact has resulted in increased investment in building cohorts and genetic repositories from such populations (e.g. H3A and the African Partnership for Chronic Disease Research) and will ultimately pay dividends in both developed and less developed populations.

Exploiting Rapid Development to Study Life-Course and Intergenerational Influences on Chronic Diseases

The basic thesis encapsulated in the developmental origins of adult disease (DOHAD) hypothesis is now generally well accepted [Singhal, this vol., pp. 123–132; Adair, this vol., pp. 111–120], but there remains much to be learnt about the mechanisms by which early life exposures affect chronic disease outcomes. The compression of the timeframe in which emerging societies are being exposed to affluent diets and lifestyles offers special opportunities to interrogate these mechanisms further, and considerable research is in progress concerning the long-term effects of nutritional deficits and excess as an individual passes through the various phases of the nutrient supply chain (histiotrophic, placental, mammary, weaning and through to adult diet). Matriline
(and possibly patriline) influences on the capacity of such processes offer the opportunity for intergenerational effects on chronic disease outcomes, and these are also easier to study in rapidly transitioning societies, but with lessons applicable globally.

**Exploiting the Nutritional Deprivations of Underdeveloped Societies to Understand Epigenetic Regulation of Disease**

Epigenetic variations are currently viewed as likely mediators of the known associations between early-life nutritional exposures and later disease – the DOHAD thesis. This topic represents another good example of where research in rapidly developing nations can have global implications. Some of the first proof-of-principle studies in humans are demonstrating that alterations in nutrients involved in maternal methyl-donor supply (choline, betaine, methionine, folate, vitamins B₂, B₆ and B₁₂) do affect methylation patterns of the offspring [9–11]. Such studies are often more tractable in populations with naturally low intake levels. The phenotypic and health implications of these changes are far from being understood, but a key emergent message is that different dietary practices can lead to a range of imbalances in methyl-donor metabolic cycles and that there will not be a single solution to optimizing such diets. For instance, B₁₂ deficiency (especially against a background of folate repletion) appears to be a major issue in rural Indians [12] but not in rural Africans [13].

**Future Prospects**

The ultimate aim of all such research is to inform public health interventions that can reduce the penetrance of chronic diseases for future generations. Whether such interventions can be effective against the inherent propensity for gluttony and sloth in human populations remains to be seen.

**Disclosure Statement**

The author has no conflicts of interest.
References