Disease definition

Evolving a definition of disease

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Perspective on the paper by Reinehr *et al* (***see page 1067***)

Koch and Pasteur provided modern medicine with its primary model of disease – that it has a specific and organic cause. Treatment is generally developed from an understanding of that agent of causation. Generations of medical students have been taught the causes of disease in their pathology classes: genetic, infection, trauma and so on. But for some situations such a model is inadequate. The boundaries between normality and abnormality blur, and can be situational and dependent on when and where an individual lives. Persistence of intestinal lactase function was the co-evolutionary outcome when groups of *Homo sapiens* started herding cattle and using their milk for food.[1] So while northern Europeans and some Africans see lactase intolerance as a disease, and the label implies as much, for much of humanity non-persistence of lactase activity is the evolutionary norm and of no significance in a world, historically at least, largely free of cows' milk. So we have a problem in defining disease – the answer may indeed be contextual.

The ''metabolic syndrome'' is a term often given to a multisystem cluster of cardiovascular risk factors, including central obesity, glucose intolerance, dyslipidaemia and hypertension, associated with endothelial dysfunction and insulin resistance. The use of the term has been debated,[2 3] in no small part because the failure to identify a single causative agent has suggested to critics that it is merely the accidental co-clustering of common abnormalities, and this uncertainty is reflected in the numerous and various definitions of the syndrome that are found in the literature. In this issue of the journal, Reinehr and colleagues use eight different definitions of metabolic syndrome to ascertain the prevalence of the cluster in a relatively homogenous population of children and adolescents from northern Europe who were selected for their attendance at an obesity clinic. They conclude that prevalence varies widely according to definition, question the predictive value of the concept in this age group, and plead for an internationally accepted uniform definition.[4]

But perhaps this variation is not surprising – are we not looking at the metabolic status of individuals from the wrong perspective? When we consider our metabolic capacity, perhaps we should look not at disease but at normality. Life is a matter of energetics, and human life history traits are to a large part the outcome of natural selection acting to optimise energy allocation.[5] Species come to match the environments in which they were selected, but that match is only there if the environment the individual is living in is similar to that of the evolutionary past. Importantly, selection is about fitness, the capacity of the individual organism to transmit its genes, directly or indirectly, to the next generation. Thus fitness and health are not the same concepts, a matter of key importance in understanding the development of poor health in a long-lived species such as humans.

Adaptive evolution of our species involved selection for traits well matched to nutrient environments and patterns of energy expenditure quite different to modern times.[6] While some humans have always had long lives, longevity as a norm is a very recent feature. Selection pressures were for successful reproduction as a youthful (by modern criteria) adult, not health into middle and long age.

These considerations point away from a disease-focused perspective on the origins of the metabolic syndrome. Is the syndrome a reflection of ''normal'' humans living beyond their metabolic adaptive capacity, beyond or at the margins of the environments to which they were matched through evolution? There can be no doubt that nutritional environments and patterns of energy expenditure have changed dramatically in recent decades. The nature of this change means that humans are being exposed to evolutionarily novel environments, and for an increasing number of individuals this novelty extends beyond the capacity of their metabolic homeostasis. Yet selection has not had time to adjust, nor has there been strong selective pressure because generally such later-life metabolic dysfunction does not compromise reproduction or only appears once reproduction is largely complete, although, as the study of Reinehr and colleagues underscores, obesity and metabolic disease are increasingly emerging at younger ages. Thus the metabolic syndrome can be envisaged not as a reflection of abnormal biology but of our evolved biology placed within an extreme environment which we were not selected to live within.

Then the question must become: what determines individual variation in metabolic adaptive capacity? Attempts to find genetic linkages have been disappointing, both for the metabolic syndrome and for its individual components such as type 2 diabetes where, despite claims for significant linkages,[7] the evidence for strong causal relationships to particular genes is lacking[8] except in rather rare conditions such as maturity-onset diabetes of the young.[9] Conversely, there is growing evidence for developmental components, both from the increasing prevalence of metabolic disorders in younger people and from studies implicating developmental factors in the origins of the mismatch between an individual's physiology and his or her environment. Epidemiological studies point to relationships between early life, be it fetal growth[10] or patterns of infant nutrition,[11] and the later appearance of components of the syndrome. Experimental studies show that it is relatively easy across numerous species to induce a biology similar to that of the human syndrome by exposing the fetus or infant to altered nutrition,[12] particularly if mismatch is exacerbated by later exposure of the offspring to an energy-dense diet.[13] What might be the mechanism?

Developmental plasticity provides a mechanism beyond selection by which an organism can match its biology to its environment.[14] Plasticity is in part underpinned by epigenetic mechanisms whereby early environmental signals induce persistent but specific changes in patterns of gene expression and potentially alterations in organ development. Such processes explain why one genotype can produce a range of phenotypes, in this case with respect to metabolic traits.[15 16] The developing organism responds to cues and adjusts its trajectory of development so as to enhance its lifetime fitness in the current and hence anticipated environment.[17] Yet early growth is limited by nutrient availability, which itself is limited by the mechanisms of maternal–fetal transfer or by the capacity of maternal lactation.[18] Thus the fetus or infant may be setting its metabolic phenotype to an environment cued by its assessment of future nutritional availability, but given the limited nutritional information reaching the fetus or

infant and the capacity of the external environment to change rapidly, it may be adjusting its trajectory of development while still plastic to an environment that is very different to that it will actually later experience. Nutrition once independent of the mother is not limiting, as the growing obesity epidemic dramatically demonstrates.

Thus two related evolved processes may underpin the rising incidence of metabolic abnormality – evolutionary novelty and developmental mismatch. In this context, the metabolic syndrome cannot be seen as a pathological failure of homeostasis but rather the outcome of normally adaptive physiology in an maladaptive context.[19]

These concepts of normality challenge the medical model of disease and raise issues about the purpose of defining the metabolic syndrome. Doing so might allow us to communicate in shorthand about a symptom cluster, but it would be misleading to consider that a uniform definition will tell us anything about the underlying biology or be universally applicable, even if population-specific cut-offs are included.[3] Reinehr and colleagues compare different symptom/signled definitions and obtain a spectrum of prevalences. But one would anticipate such variation as even within a population of common ancestry there will be varying degrees of compromise between the individual and its environment, and between populations there will be ethnic differences in the association between individual components of the cluster.[20] Variation will be influenced by genotype, because genetic variation will provide the basis for differing sensitivities to nutritional and other cues and environmental factors,[21] by epigenotype,[15] and by other factors that depend on the individual's developmental history[16] and indeed that of his or her immediate ancestors, there being a number of routes of non-genomic transfer of information that can affect development.[22] Thus individuals can have a broad range of metabolic traits in a given environment, reflecting how their particular adaptive capacity is able to match that environment.

Our challenge may not be in defining the metabolic syndrome, a definition that may primarily serve epidemiological surveillance, but rather in defining well and poorly matched individuals in an environment. Biology is based on two fundamental pillars – understanding the gene and understanding the processes of evolution and development. Medicine has incorporated the former well; the latter needs greater consideration.

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