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The villain with a thousand faces

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Type 2 diabetes (T2D) is unquestionably diverse in its phenotypic manifestations as well as heterogeneous and complex in regard to its multi-system involvement, molecular etiology, pathophysiology and natural history. The diversity and heterogeneity are increasingly apparent as the condition manifests itself in different ethnic and racial populations around the world (Balasubramanyam, Tandon, & Yajnik, 2011). Yet most physicians, including endocrinologists, persist in treating this complex condition as a monolithic entity, resulting from the convergence of two vaguely defined and poorly quantifiable “core defects” (insulin resistance and relative insulin deficiency), assertively defined by a single glycemic parameter, and managed by treatment approaches shaped more by habit or consensus than by rational targeting or comparative evidence. In trying to understand T2D, we have remained stubborn “lumpers”, whereas science and society require us to be skillful “splitters”.

Phenotypic dissection of T2D is an essential preliminary step both for identifying key molecular mechanisms of disease and for optimal clinical management. In regard to identifying mechanisms, if T2D patients are treated as an undifferentiated group, even powerful, high-throughput “omics” approaches identify disappointingly small elevations of risk associated with individual risk factors, e.g., odds ratios of 1.28 to 1.47 (95% CI) with risk allele frequencies of about 10–30% in different ethnic/racial groups for *TCF7L2*, the leading candidate from genome-wide association studies (GWAS) (Kahn, Suvag, Wright, & Utzschneider, 2012). Technical and analytical advances in GWAS of common gene variants with restriction of the study population to a single geographic area and ethnic group have permitted discovery of new genetic risk factors, as seen in the recent identification of *SLC16A11* as a risk allele in Mexico, but have not increased the effect size of the association (OR 1.20 to 1.29) or its frequency in the population (The SIGMA Type 2 Consortium, 2014). Detailed phenotypic subtyping of T2D has the potential to reveal higher frequencies of molecular or genetic risk factors – for example, within the aggregation of a subtype of adults with Ketosis-Prone Diabetes (the “A-β-” subgroup), defined by absence of islet autoantibodies and HLA risk alleles despite presentation with diabetic ketoacidosis, the frequency of gene variants linked to monogenic diabetes was 24% (Haaland et al., 2009), compared to frequencies of <5% obtained in screens of patients with undifferentiated T2D. The more circumscribed the phenotype in a complex disease, the greater the likelihood of molecular discovery. In regard to clinical management, our treatment paradigms remain speculative so long as they do not target unique characteristics of different forms of T2D.

Even if an interplay of insulin response and insulin sensitivity is the necessary final pathway to hyperglycemia (Balasubramanyam et al., 2011), one cannot assume that new onset diabetes in an elderly northern European, a young, lean Indian villager, an older Mexican-American or West African presenting with DKA, and a middle-aged Chinese with beta cell autoantibodies but not requiring insulin, is the result of a singular disease process requiring a common treatment approach.

But how does one subclassify T2D based on clinical parameters? The most easily discernible phenotypes - ones that are obvious or easy to measure, such as ethnicity, race or BMI - are crude and imprecise. Complex interactions of nature, nurture and the “thousand natural shocks that flesh is heir to” can obscure ethnic-specific differences in the pathophysiology of T2D. Classification based on categories of body weight or BMI are bedeviled by the powerful secular trend towards obesity among populations in all parts of the world – BMI is a moving target, and even within a restricted subset of T2D such as Ketosis-Prone Diabetes, a classification based on this parameter is less precise than one that incorporates multiple variables (Balasubramanyam et al., 2006). Parameters such as the distribution of fat or amounts and efficiency of muscle mass may have better discriminant function, but these are not simple to measure longitudinally in large study cohorts.

Despite these challenges, it is critical to develop systematic approaches to T2D phenotypic sub-classification, and several research groups have attempted to do so using simple clinical measures (Balasubramanyam et al., 2006). In the present issue of JDC, Coleman et al. 2014 report characteristics of lean compared with obese T2D patients in a retrospective, cross-sectional review of patients in a US urban public hospital, and suggest that the group differences could be prognostically useful in regard to beta cell functional reserve, insulin requirement and natural history. The investigators analyzed a very large number of subjects, fortuitously matched in regard to key demographic features. The clinical criteria to limit inclusion of T1D patients were quite stringent. Lean T2D patients were distinct from obese T2D patients in being predominantly male, with greater likelihood of requiring insulin, lower frequencies of lipid markers of metabolic syndrome, and a higher prevalence of pancreatitis and alcoholism. Each of these differences raises interesting hypotheses for the cause of diabetes and more rapid decline in beta cell function among the lean group. The male predominance is especially interesting, as there are only a few diabetes syndromes that demonstrate a gender-associated susceptibility, e.g., some mitochondrial gene mutations (Maassen, van den Ouweland, t Hart, & Lemkes, 1997) and the "A-β + " subgroup of Ketosis-Prone Diabetes (Nalini et al., 2010). Men also predominated among lean patients requiring insulin, suggesting an interaction between gender/sex hormones and beta cell function, consistent with evidence from mouse studies (Liu & Mauvais-Jarvis, 2010). Another provocative finding is that while African-Americans and Hispanics were equally likely to belong to the lean and obese groups, Asians belonged mainly to the lean group - further evidence for unique forms of T2D among Asian populations.

Joseph Campbell's classic “The Hero With a Thousand Faces” unified world mythology in the “monomyth” of an archetypal hero who represents universal themes of searching, suffering and redemption. But Campbell was careful to not to obscure the critically important cultural and historical variations that affect this concept. In dealing with T2D, an

equally multifaceted villain, we have grasped the final common metabolic and endocrine defects. What remains is to understand the different paths our patients take to arrive at those defects. We have at our disposal increasingly precise molecular and analytical methods, but these cannot accomplish the task of deciphering T2D until we properly deconstruct the human phenotypes under study.

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