Is type 2 diabetes a category error?
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Type 2 diabetes is a disease in search of a definition. It has no hallmark clinical features, is generally diagnosed by default (no other cause for diabetes being evident), has very heterogeneous pathophysiological features, and varies widely between populations in clinical presentation and consequences. Despite this obvious heterogeneity, laboratory and clinical research is typically done as if type 2 diabetes were one disease entity with uniform characteristics, thus assuming standard causal mechanisms and universal treatment pathways. I propose that this conventional perception of type 2 diabetes is based on a category error.

A category error occurs when we assign a problem to a category inappropriate to its solution. The visitor to Oxford who inspects the colleges, lecture rooms, and libraries and asks “but where is the University?” is making a category error. The University, as Ryle points out, “is just the way in which all that he has already seen is organized”: attempts to explain it in terms of bricks and mortar are predestined to failure.1

18th century physicians set out to classify disease much as their contemporary Linnaeus classified plants, on a similar assumption that diseases were invariant and had originated in the hand of the Creator. The task of the clinician was to identify the so-called essence of the disease—ie, its constant and archetypal features, and to separate these from what they termed the accidents, or incidental features that varied from one patient to another.2 The second half of the 20th century witnessed the emergence of a new type of disease whose cause (essence) has not been identified by mechanistic search, and is accordingly characterised by incidental features that vary from patient to patient. These are the multifactorial diseases, and they are defined by their attributes and consequences rather than by their causal mechanisms, which remain unknown. The essence of such diseases cannot be pinpointed, leaving us with statistical approximations in terms of genetic or epidemiological characterisation of the average patient. Like visitors to Oxford, the epidemiologists describe a typical student, the geneticists reveal that Oxford has 38 colleges and six permanent private halls, but neither can find the University.

Carl von Noorden regretfully noted in 1907 that diabetes can only be defined in terms of glucose.3 A century has passed since then in largely fruitless attempts to escape from this circular definition. The recurring difficulty is that glucose is a continuously distributed variable, and that the cutoff between healthy glucose and harmful glucose needing intervention is virtually impossible to define, let alone encapsulate for all populations, age groups, and environments. For practical purposes, harmful glucose is identified by its association with vascular and other outcomes deemed to be diabetic. The diagnostic thresholds for intervention in diabetes, prediabetes, gestational diabetes, and so forth are also decided by votes cast in expert committees. Because all glycaemic definitions of diabetes become circular, many investigators have tried to establish a non-glycaemic point of reference in terms of genes, mechanisms, or non-glucose markers of disease. Although this search has yielded many discoveries, including monogenic subtypes of diabetes, it has yet to provide a new diagnostic criterion for type 2 diabetes. A scientific definition needs an external point of reference, and a problem that cannot be defined in scientific terms cannot have a scientific solution.4 Much progress has been made by investigators careful to define their own terms of reference, but others have tried to build on a foundation of sand.

Investigators did not distinguish between type 1 and type 2 diabetes before the 1970s,5 and indeed no progress could be made while diabetes was viewed as a single entity. The heterogeneity of type 2 diabetes presents similar problems. Many attempts have been made to subclassify the diseases according to ethnic origin, genotype, or pathophysiology, and many differences have emerged. The continuum between obese insulin-resistant and lean insulin-deficient individuals has long been recognised, for example, as have phenotypic differences in fat distribution and insulin sensitivity. Attempts to study these elements have however been limited by the methods available, since β-cell function and β-cell reserve are hard to assess, as is insulin resistance (another circular definition).

Despite obvious heterogeneity, present methods do not permit type 2 diabetes to be subdivided into more sharply defined clinical entities. As a result, we are trapped in a mental loop; we tell medical students that type 2 diabetes arises because of a combination of insulin deficiency and insulin resistance. This amounts to telling them that glucose rises because we do not have enough insulin, and that we do not have enough insulin because we do not have enough insulin.

In my youth, we solemnly advised one another not to adjust our minds; there was a fault in reality. With age, we acquired more respect for reality. When a century of scientific endeavour brings us round to the conclusion that we cannot define what we are talking about, it might be time to consider adjusting our minds. It is widely appreciated that type 2 diabetes is not a uniform disease entity with a definable cause, mechanism, and treatment, so why are these terms always used? The explanation can be given in the words of Carl Wunderlich (1815–77), “A view which takes abstract concepts as things, implying their actual existence and at once treating them as entities, is a logical blunder that has
frequently crept into medicine and flourished there.”? Type 2 diabetes is not only a category error; it is reinforced by cognitive dissonance, the remarkable ability we have to entertain irreconcilable beliefs in different compartments of the brain.

Some might argue that these explorations of the pathology of thought should have no place in the mind of the practical investigator or clinician, but this omission has caused the work of generations of young investigators to be wasted in pursuit of indefinable entities.

In practical terms, the unitary disease concept has failed to achieve satisfactory management of type 2 diabetes and its associated risks. This failure has been reinforced by the introduction of one-size-fits-all guidelines for disease management. These have been based on the utilitarian rule of the greatest benefit for the greatest number, but ignore the large variation between the risks and benefits of different interventions in different clinical situations. Uncritical implementation of formal guidelines assigns many people, especially elderly people, to inappropriate or useless interventions, backed by financial incentives for the provider. Ironically, awareness of the shortcomings of inflexible guidelines has led to recognition of the need for individualised treatment—ie, treatment based on the needs of the patient. This type of treatment was what we were trying to offer before the introduction of guidelines. Truly individualised approaches to treatment based on real evidence will need clear understanding of the heterogeneity of type 2 diabetes.

Problems are easier to identify than solutions. Technology moves fast, habits of thought move slowly; familiar problems are easier to pursue with familiar methods than the pursuit of new problems with unknown solutions. Ruling paradigms become entrenched around the sources of money and influence, and new thinking must wait for the present generation of power brokers to move into the rose garden. The ghostly entity of type 2 diabetes is likely to haunt us for years to come, although we might for the interim avoid a terminological loop by referring to it as idiopathic hyperglycaemia.

What does the future hold? Certain avenues can be suggested. Present biomedical thinking is reductionist: it resolves complex problems into simpler questions that can be answered one by one. Future thinking will be constructionist, rebuilding complex systems from their component elements. Present thinking examines glucose or lipids; future thinking will abandon the sectarian boundaries of academic specialties to achieve a more integrated view of phenotypic development. Idiopathic hyperglycaemia will no longer be considered as a disease in its own right, but as an outcome of networked processes contributing to the affluent phenotype of adiposity, hypertension, hyperglycaemia, hyperlipidaemia, and cancer. The affluent phenotype will be viewed in dynamic rather than static terms, and as adaptation rather than disease. The analogy will no longer be with a faulty machine, but with complex interactive systems of the type studied by ecologists and economists. The fundamental issue will be phenotypic plasticity in response to environmental challenge, and medicine might eventually find its rightful place in evolutionary biology.

Conflicts of interest
I declare that I have no conflicts of interest.

References