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Keep an eye on diabetes

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Diabetes has been with us throughout recorded history but recently knowledge of this disease has increased dramatically, which has brought good news and bad. On the minus side, diabetes prevalence is rising virtually everywhere in the world as a result of population aging (and, happily, prolonged survival of affected people). The true incidence of diabetes is also increasing—mostly, it seems, as a consequence of obesity and physical inactivity—and age of onset is decreasing. We have learned that no major gene locus can explain its distribution in the population, and the candidate-gene approach has borne little fruit. We are, therefore, (reluctantly) considering a scenario in which a group of genes spread throughout the genome—in variable combinations and in complex interaction with acquired factors—drive the onset of diabetes in numerous disease subsets, each with a slightly different clinical phenotype. Finally, the classical distinction between type 1 and type 2 diabetes—already diluted by the recognition of type 1.5 diabetes (i.e. latent autoimmune diabetes of adulthood)—is becoming blurred: we diagnose increasing numbers of cases of maturity-onset diabetes of youth (MODY; these patients have a specific genetic defect); identify pedigrees that exhibit all types of diabetes (type 1, 1.5 and 2, MODY and unclassified forms of glucose intolerance); and witness the emergence of classical type 2 diabetes among obese adolescents. Minor degrees of glucose intolerance are detected wherever one cares to look: in gestation, polycystic ovary syndrome, nonalcoholic fatty liver disease and the general population.

On the plus side, we now understand the pathophysiology of hyperglycemia almost to the point of being able to account for every milligram of glucose in the bloodstream. We understand the cellular basis of the insulin resistance that predicts, precedes and characterizes diabetes (and glucose intolerance). We have gained deep insights into the endocrine role of the pancreas in the natural history of diabetes: loss of β-cell function; structural disarray of pancreatic islets; and eventually loss of islets. The contribution of gastrointestinal hormones to islet function is increasingly recognized, and the effect of obesity and the mechanisms of islet hypertrophy (neogenesis vs replication of β-cells) are being investigated.

The possibility of literally normalizing glycemia around the clock might soon be achievable

This new body of knowledge, and market analyses (Smyth S and Heron A [2006] *Nat Med* 12: 75–80), have stimulated intense pharmacologic research. For half a century, insulin, sulfonylureas (and, in Europe, metformin) have been the only tools for treating hyperglycemia. Now, new drugs target multiple sites of glucose metabolism, insulin action and β-cell function. Today we can try to slow down glucose entry into the system (using α-glucosidase inhibitors), sensitize tissues to insulin (using thiazolidenediones), potentiate meal-induced insulin release (using glucagon-like peptide 1 analogs, dipeptidyl peptidase IV inhibitors) or combine drugs to target the insulin resistance and the β-cell dysfunction simultaneously. Exciting novel strategies include activating glucokinase, blocking glucagon action, impeding renal glucose reabsorption, delaying gastric emptying, and inhaling or ingesting insulin. The possibility of literally normalizing glycemia around the clock might soon be achievable; a feat that would be comparable to what statins do for serum cholesterol.

Chronic hyperglycemia, however mild and asymptomatic, causes damage to small and large vessels, to peripheral nerves and, it is suspected, to the central nervous system: in the near future we should be able to treat and prevent chronic hyperglycemia and its effects. Keep an eye on diabetes—you will see a lot more about it in the near future.

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