Counterpoint: Appreciating Homeostasis Model Assessment

More useful earlier rather than later

The insulin-deficient mechanism for diabetes, discovered around a century ago, was questioned by observations on the human response to intravenous insulin (1). Later, it was more severely challenged by the raised plasma insulin values usually found by radioimmunoassay in type 2 diabetic subjects (2), then and since rapidly increasing in number, and often with accompanying adiposity (3). At this time, the pathogenesis of type 2 diabetes was unknown, and it seemed crucial to determine whether it was essentially based on increased resistance to the hypoglycemic action of insulin or on failing β-cells with secondary gluco- and lipotoxicities. Could this be determined from the glucose and insulin levels of single or duplicate basal blood samples? If so, epidemiological logistics might be transformed, without the need for stimulated tests or tests as sophisticated as measurement of the basal endogenous glucose production rate with tritiated glucose, and the calculation of postabsorptive hepatic insulin resistance to the hypoglycemic effect of insulin as the product of this and the overnight fasting insulin concentration (4).

Basal and stimulated tests measure two different phenomena, rather than two different aspects of the same thing. In theory, the two islet cell states do not need to be closer than are muscular activity in movement and in posture. There will always be common features (e.g., muscle bulk), and, indeed, there are consistent positive relationships between basal and poststimulation insulin. However, there are also many different properties with altered membrane potentials (e.g., in the basal state, there is no influence on β-cell activity from recent glucose variation [5], which presumably leaves β-cells aware of changes in glucose). Additionally, the various clamp tests do not measure basal function, for while they involve steady states, clamp tests follow considerable interference. In these tests, insulin action in muscle is the major determinant of glucose disposal, whereas basally 50% is in the brain without the benefit of insulin, whose main targets are the liver (which restricts glucose release) and adipose tissue (the main source of oxidized substrates and the relatively low respiratory quotient).

Action

The homeostasis model assessment (HOMA) system (6) seeks numerical statements of resistance to the hypoglycemic effect of insulin and of β-cell function from the two basal measures, in comparison with a standard group of normal weight, normoglycemic, healthy young adults. The small size of this group is immaterial, as it merely serves to provide fixed points against which to compare the calculated values (always as comparative ratios). Other indices based on basal glucose and insulin values have been developed (7,8), but we comment on HOMA in its two models (6,9) because we view it as the most sophisticated, widely used, and widely appreciated method. In addition, we use the original resistance to the hypoglycemic effect of insulin, although later (9), HOMA-S was substituted to show sensitivity (rather than resistance) to insulin's hypoglycemic action. However, such terms should always raise three questions: what is the resistance to which action of insulin, on what tissue, and in what metabolic state?

Reaction

Two developments gradually changed the picture. First, the results from groups that were likely to develop type 2 diabetes swung between an increased resistance to the hypoglycemic effect of insulin and a reduced mass of pancreatic β-cells functionally active in insulin secretion as the key forerunner of developing hyperglycemia, and neither predominated. For example, increasing weight (and no doubt resistance to the hypoglycemic effect of insulin) and decreasing acute insulin secretion were coassociated with increasing glycemia in initially normoglycemic Pima Indians (10). Very likely, both processes were intertwined, at least once hyperglycemia had developed, and very possibly even while future type 2 diabetic subjects were still normoglycemic.

Second, confusion silently developed between what was delivered by the system and what some people wanted. They hoped it would record inherent entities, even if these varied from time to time in a particular person. Thus, the resistance to the hypoglycemic effect of insulin should be widespread through tissues and have a substantial metabolic effect. Instead, the calculated factors were always what they are: overall results on the day of all the processes that interact to determine the basal glucose and insulin concentrations and are capable of change within a few days (11).

For example, the resistance index "reveals" how easily insulin ushers glucose into insulin-sensitive (in the glycemic sense) tissues, but does this resultant value reflect a cellular property common to liver, muscle, and adipose tissue (or even the latter two)? Does it describe some property universal to an important membrane of such tissues? The latter would be in ill accord with the increasingly detailed knowledge that has developed from genomics and proteomics, showing modifications of the particular enzymes, genes, and/or the proteins that act on them. Other difficulties with the HOMA system arise from the huge simplifications necessary to achieve it.

General simplifications. Initially, the basic assumption was that both plasma glucose and insulin were determined by just two processes: the responsiveness of β-cells to glucose stimulus and the effectiveness of insulin's hypoglycemic action via the liver and other insulin-responsive tissues, such as muscle and adipose tissue (12). However, the system was steadily refined and expanded (8) to include urinary loss and all peripheral glucose uptake, although the latter was complicated, despite much consideration (13).

But, reality remained much more complicated. Basal insulin secretion, for

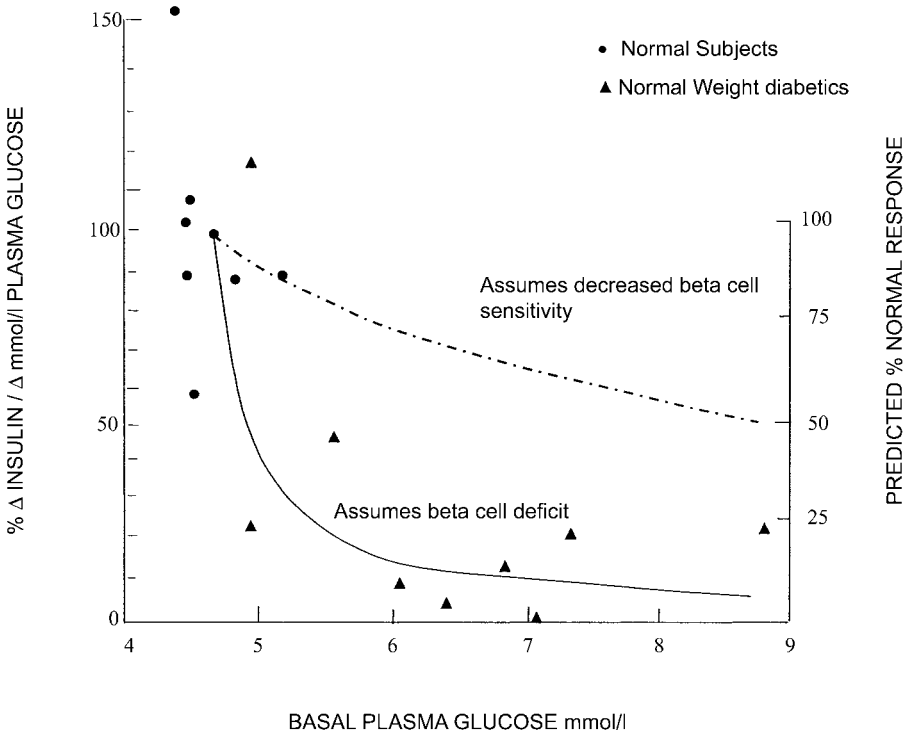

Figure 1—*Insulin response to changes of ~1 mmol/l FPG concentration for 90 min in six normal subjects (●) and nine normal-weight maturity-onset diabetic patients (▲). An increase was obtained by a glucose infusion and a decrease by fish insulin infusion. The change in insulin secretion was similar in each patient to both an increment and decrement of the plasma glucose. The β-cell function of each patient was expressed as the slope of the overall insulin-glucose response. (This may be a more appropriate estimate than the usually measured first-phase insulin response to an acute intravenous glucose load, which appears to be secondarily attenuated by only moderate fasting hyperglycemia.) The full line represents the β-cell response predicted from Fig. 2, assuming β-cell depletion causes diabetes, and is in accordance with the observed data. The dotted line, which represents the predicted response assuming the β-cells have decreased sensitivity to glucose, does not fit the data. References to the individual statements can be obtained elsewhere (12). Reprinted with permission from ref. 12.*

example, is affected by many factors beyond the active β-cell mass (*V*), its glucose sensitivity (K_m), and glucose concentration, including *1*) concentrations of other metabolites, such as some amino acids and perhaps nonesterified fatty acids; *2*) influence of neurotransmitters, activators, and modulators in the pancreas (14) and paracrine substances (such as pancreatic glucagon and somatostatin); *3*) plasma concentrations of other hormones, such as cortisol, growth hormone, and the adrenalines; *4*) the rate of destruction and elimination of insulin, primarily involving the liver and kidneys; and *5*) plasma volume or, more accurately, "insulin space" (i.e., the volume in which secreted insulin is distributed). The latter is obvious but rarely stressed. HOMA factors are ratios without any units with the underlying assumption that if you have a larger pancreas, you will have a larger body with the same ratio of β-cell secretory mass–to–insulin space as if you had a smaller body. We have little knowledge of how far this is true in those with muscles unduly developed by exercise, as in Polynesian subjects compared with subjects from South Asia or in those whose early development was affected by poor nutrition.

There are likewise complications with fasting plasma glucose (FPG), e.g. of its uptake by non–insulin-sensitive tissues other than the brain. In all of these, as with insulin-sensitive tissue, such uptake increases with increasing glucose concentrations. Also, circulating nonesterified fatty acid competes with glucose for cellular entry and mitochondrial oxidation (15), and this must be influenced by intracellular lipid concentrations. The intracellular cortisol metabolism (16), determining the balance between active cortisol and inactive cortisone, and their passage between the cells' compartments will also affect substrate handling. We feel that it is not uncommon for a type 2 diabetic patient to show a "touch of Cushing's disease," with a suggestive appearance, reduced body calcium levels, and increased skin capillary fragility.

For HOMA-R and HOMA-B indices to have values that can be used constructively to solve type 2 diabetes' pathogenesis, it is necessary to assume that all these complexities differ so little between subjects that such differences can be neglected in subsequent considerations. It is also important to realize that the differences have been quietly buried within HOMA-R and HOMA-B indices.

A particular simplification. It should be recognized that with HOMA, changes in the mass of pancreatic β-cells functionally active in insulin secretion are completely attributed to changes in the V_{max} (maximal secretory capacity) of the basal insulin-glucose relationship. Effects from the change in its K_m (glycemic sensitivity) were excluded (12) and never restored. This can be criticized on two grounds. First, the key diagram (Fig. 1) where this decision was based is wide open to review. The results from eight of the nine type 2 diabetic subjects (comparative rarities with their normal weights) could well be thought to lie along a straight line. Representing all the subjects by a hyperbolic curve assumes they are a homogenous group. Second, its rationale is compressed in the figure's legend and never spelled out. This simplification had to be made if there was to be any understanding of the nature of changes in the mass of pancreatic β-cells functionally active in insulin secretion. Otherwise, two measured "knowns" were going to have to solve equations for three "unknowns" (the resistance to the hypoglycemic effect of insulin, the mass of pancreatic β-cells functionally active in insulin secretion, and the β-cells' glycemic sensitivity).

The quandary in practice. This is not purely academic, as illustrated by reanalysis of a previous study (17). Figure 2 shows the changes in FPG, overnight fasting insulin concentration, and BMI over 10 years in 141 normoglycemic, middle-aged, Indian subjects (a population with a high incidence of type 2 diabetes) subdivided into three groups according to their increase in FPG. The three groups, respectively, show *1*) little change during the 10 years, *2*) a "healthy" rise in overnight fasting insulin concentrations in response to hyperglycemia accompanying an increasing resistance to the hypoglyce-

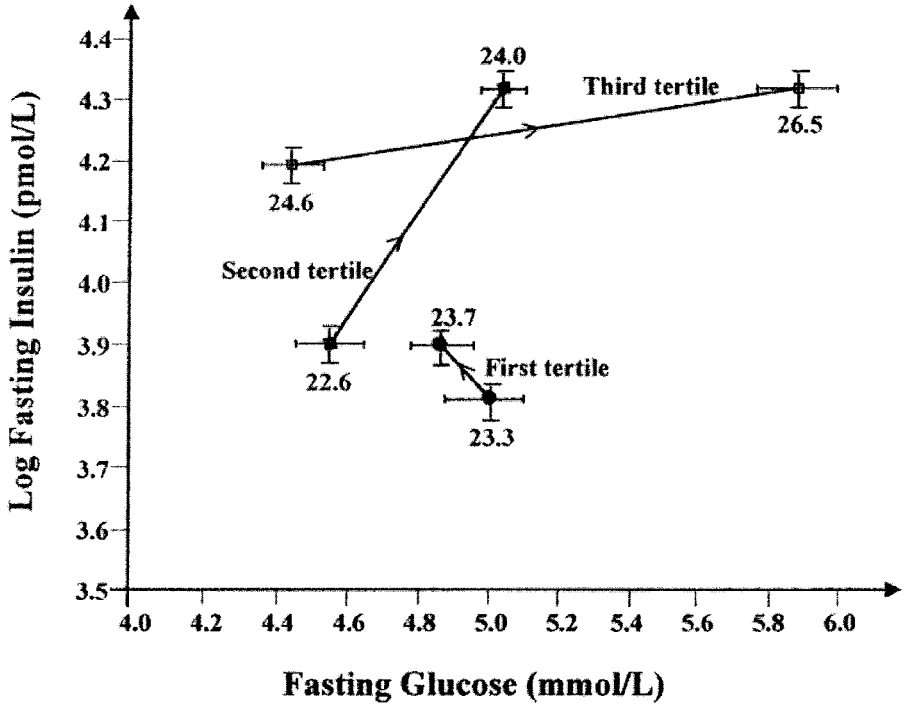

Figure 2—*Vectors over 10 years of the FPG/overnight fasting insulin concentration coordinates for 141 subjects for the three groups of 10 years increase in FPG (with the first group having the smallest rise). The horizontal bars indicate the SEM of each FPG mean value, and vertical bars indicate the SEM of each log overnight fasting insulin concentration median value. Arrows on the vectors indicate the direction of change. The numbers close to each point are the mean BMI (as the weight in kilograms divided by the square of height in meters) of the nearby group at that time.*

mic effect of insulin, and *3*) virtually no change in the overnight fasting insulin concentration, even though this group showed the biggest glycemic rise and had the highest initial insulin value; it suggests that the β-cells have lost normal responsiveness and are beginning to fail.

The 10-year measure of overnight FPG concentrations (5.3 ± 0.9 mmol/l) was positively correlated with the initial overnight FPG concetration ($P < 0.05$), but the change in FPG over the 10 years was negatively correlated to that initial value ($P < 0.001$), as would be expected from the law of initial values (18). However, the negative relationship persists ($b = -0.67 \pm 0.29$, $P < 0.05$) after applying a correction for regression toward the mean (19,20). The inverse relationship was even stronger among the 113 who remained normoglycemic throughout (corrected $b = -0.63 \pm 0.10$, $P < 0.001$).

Regression toward the mean is an important but not completely predictable phenomenon. Nonetheless, a negative correlation between an initial value and its change over time can also arise from measurements around the inflection of a hyperbolic curve, and an icon of type 2 diabetes pathogenesis is the "bell-shaped" or "inverted U" curve that shows changes in basal insulin with change in glucose (21).

An explanatory hypothesis for results from the Indians could be that long-standing enhanced glucose sensitivity of basal insulin secretion, with accompanying β-cell overactivity, is associated with increased liability to β-cell failure, especially under the further provocation of "middle-aged spread" or "second adiposity rebound." This may seem paradoxical, as later failure is often presaged by early underactivity; however, the possibility is in accordance with a generalization from type 2 diabetes epidemiology that β-cell failure is associated with greater unit-hours of insulin secretion, as shown by increasing age (22) and several causes of increased resistance to the hypoglycemic effect of insulin (e.g., from adiposity [3], chronic inflammation [23], and smoking [24]).

The K_m exclusion. Whatever the final interpretation of this data, exclusion of K_m change perverts and restricts the conclusions to be drawn, e.g., from a "high" overnight fasting insulin concentration for a given FPG, which already points to increases in both HOMA-R and HOMA-B indices (as in ref. 17). Less directly, exclusion of K_m change from such a widely used system may have led to its general neglect among type 2 diabetes pathogenetic factors.

How likely is K_m to vary appreciably from person to person? We know little of this, apart from studies on glucokinase abnormalities (25,26); however, there are possible mechanisms. First, fetal or infantile malnutrition might produce epigenetic changes in either the affinity or functional response of a protein to a ligand. Second, variations in the amount of a hypothetical bodily molecule that binds to the β-cells' sulfonylurea receptor (27) could correspondingly alter the K_m of glucose-stimulated insulin secretion. Additionally, HOMA hardly seems to be the proper agent with which to examine, without disclaimer, the actions of sulfonylurea drugs (28), which certainly alter the K_m of insulin secretion, or even thiazolidines (29), which may have such an action.

HOMA in practice

Reproducibility. The coefficients of variation (CVs) for HOMA-R and HOMA-B indices were first reported as 31 and 32%, respectively (9). Later studies, using many more subjects, report much lower values (with CVs ~10%) when using specific insulin assays (30,31). The "basal state " must be clearly defined. Overnight fasted subjects were either *1*) admitted at least the previous evening and sampled either between 0300 and 0500 h (overnight basal) or between 0630 and 0730 h (morning basal) or *2*) they traveled from home that morning and rested for 30 min before sampling (stressed fasting) (32). HOMA-B values differed significantly in the latter, at 101% for nondiabetic individuals and 45% for diabetic individuals, from the values for the two insignificantly different basal states (150 and 162% for normal subjects and 117 and 101% for the diabetic subjects). HOMA-R values did not differ significantly among the three states, which is notable in view of the absolute variation, for the median values were 1.3, 2.0, and 2.0 times the arbitrary standard for normal subjects and 2.5, 2.8, and 2.4 times the standard for diabetic subjects.

Fluctuation in the basal overnight fasting insulin concentration is a major source of this variability, but its cause remains uncertain, although possibly based on pancreatic nerve activity. The mean of

three samples was recommended (6), although just a single sample is often acceptable (8). In view of the cyclical oscillations in insulin levels (33), an even number of samples would seem preferable for normoglycemic subjects, or those nearly so, especially if spaced 6.5 min apart rather than the customary 5 or 10 min. The insulin variability is so important because its value dominates that calculated for resistance to the hypoglycemic effect of insulin. Indeed, very often the correlation of some studied factor with resistance to the hypoglycemic effect of insulin differs immaterially from that with overnight fasting insulin concentration.

Practical use

How has the HOMA system influenced therapeutic targets and agents and diabetes pathogenesis? Crudely, all therapeutic targets center on the glucose level because of the crucial importance of this in the development of tissue damage, along with other mainly vascular factors. None target HOMA-R and HOMA-B values in themselves, although diet is known to be important for resistance to the hypoglycemic effect of insulin, just as it is for overnight fasting insulin concentrations.

When deciding what agent should be prescribed, resistance to the hypoglycemic effect of insulin is crudely judged from the adiposity (though too often this is derived from weight and height alone, instead of from palpation and lateral silhouette of the patient), as well as the chances of obtaining weight reduction by diet and exercise.

What about the role for which the HOMA indices were introduced, discovering the pathogenesis of type 2 diabetes? Despite much effort, not enough is known for certain to refute the crude deduction from the basic method's first application (12) that the condition was due to β-cell failure in approximately one-quarter of the patients, to excessive resistance to the hypoglycemic effect of insulin in another quarter and to these factors combined in the remaining one-half, although no one now would investigate newly clinically diagnosed type 2 diabetes rather than normoglycemic subjects moving toward greater glycemia.

In this quest, fine quantification provides little advantage over the qualitative information that can be gained from the basal glucose-insulin coordinate, plotted directly, with either a basal insulin (Y-axis) versus basal glucose (X-axis) curve (12,34,35) or the inverted U curve (21) as a background reference. The former is preferable, as it helps visualize the pitfall in interpretation once any summit plateau has been reached. Including changes with time must improve understanding (as in our Fig. 2), and the disposition index, a nonbasal formulation, is often so displayed. Considering the influence of birth weight (38), long-running studies that start early (39,40) seem sensible.

We are still essentially ignorant as to whether, of 100 type 2 diabetic patients, 90 have the same basic abnormality, whereas 10 each have a different genetic abnormality or whether 10 sets of 10 patients each acquire a different fundamental genetic, epigenetic, or environmental pathogenesis. The answer probably lies in between; certainly, detailed knowledge of proteins and nucleo-proteins reveals increasing plurality. Another unsolved conundrum is whether obesity is an essential part of the type 2 diabetes process(es) or whether it is merely, though importantly, an exacerbating factor.

Derek Hockaday, phd, frcp[1]
Mehmood Sayyad, msc[2]
Chattaranjan Yajnik, md, frcp[2]

From the [1]Oxford Centre for Diabetes and Metabolism, Churchill Hospital, Oxford, U.K.; and the [2]Diabetes Unit, King Edward VII Memorial Hospital and Research Centre, Pune, India.

Address correspondence and reprint requests to Derek Hockaday, Oxford Centre for Diabetes and Metabolism, Churchill Hospital, Oxford, U.K., OX3 7LJ. E-mail: derekhock@btinternet.com.

Received for publication 8 June 2007 and accepted in revised form 13 June 2007.

DOI: 10.2337/dc07-1093

Acknowledgments— We thank the subjects studied (17) and the Wellcome Trust for financial support.

References

1. Himsworth HP: Mechanism of diabetes mellitus: the Goulstonian Lectures III. *Lancet* 2:171–176, 1939
2. Yalow YS, Berson SA: Immunoassay of endogenous insulin in plasma in man. *J Clin Invest* 39:1157–1175, 1960
3. Medalie JH, HermanJB, Goldbourt U, Papier CM: Variations in the incidence of diabetes among 10,000 adult Israeli males and the factors related to their development. In *Advances in Metabolic Disorders*. Levine R, Luft R, Eds. New York, Academic Press, 1978, p. 93–110
4. Abdul-Ghani MA, Balas B, Matsuda M, DeFronzo RA: Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care* 30:89–94, 2007
5. Jenkins DJ, Wolever TM, Sarson DL, Bloom SR, Ahern J, Alberti KGMM, Hockaday TDR: Improved glucose tolerance 4 hours after taking guar with glucose. *Diabetologia* 19:21–24, 1980
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
7. Matsuda M, DeFronzo RA: Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic glucose clamp. *Diabetes Care* 22: 1462–1470, 1999
8. Wallace TM, Levy JC, Matthews DR: Use and abuse of HOMA modelling. *Diabetes Care* 27:1487–1495, 2004
9. Levy JC, Matthews DR, Hermans MP: Correct homeostasis model assessment (HOMA) evaluation uses the computer program (Letter). *Diabetes Care* 21:2191–2192, 1998
10. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
11. Wall JR, Pyke DA, Oakley WG: Effect of carbohydrate restriction in obese diabetics: relationship of control to weight loss. *BMJ* 1:577–578, 1973
12. Turner RC, Holman RR, Matthews D, Hockaday TDR, Peto J: Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. *Metabolism* 28:1086–1096, 1979
13. Rudenski AS, Matthews DR, Levy JC, Turner RC: Understanding "insulin resistance": both glucose resistance and insulin resistance are required to model human diabetes. *Metabolism* 40:908–917, 1991
14. Ahren B, Lundquist I: Modulation of basal insulin secretion in the obese, hyperglycaemic mouse. *Metabolism* 31:172–179, 1982
15. Randle P: Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. *Diabet Metab Rev* 14:263–283, 1998
16. Arlt W, Stewart PM: Adrenal corticosteroid biosynthesis, metabolism and action. *Endocrinol Metab Clin North Am* 34:293–313, 2005
17. Yajnik CS, Shelgikar KM, Naik SS, Sayyad MG, Raut KN, Bhat DS, Deshpande JA, Kale SD, Hockaday TDR: Impairment of glucose tolerance over 10 years in normal glucose tolerant Indians. *Diabetes Care* 26:2212–2213, 2003
18. Thorndike EL: The influence of the

chance imperfections of measures upon the relation of the initial score to gain or loss. *J Exp Psychol* 7:225–232, 1924
19. Blomqvist N: On the relation between change and initial value. *J Am Stat Assoc* 72:746–749, 1977
20. Svardsudd K, Blomqvist N: A new method for investigating the relation between change and initial value in longditudinal blood pressure data. I. Description and application of the method. *Scand J Soc Med* 6:85–95, 1978
21. DeFronzo RA: The triumvirate: β-cell, muscle, liver. *Diabetes* 37:667–687, 1988
22. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in U.S. population aged 20–74 years. *Diabetes* 36:523–534, 1987
23. Laaksonen DE, Niskanen K, Nyyssonen K, Punnonen K, Tuomainen T-P, Valkonen V-P, Salonen JT: Resistance to the hypoglycemic effect of insulin, C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia* 47:1403–1410, 2004
24. Carlsson S, Midthjell K, Grill V: Smoking is associated with an increased risk of type 2 diabetes but a decreased risk of autoimmune diabetes in adults: an 11-year follow-up of incidence of diabetes in the Nord-Trondlag study. *Diabetologia* 47: 1953–1956, 2004
25. Froguel PH, Vaxillaire M, Sun M, Velho G, Zouali H, Butel MO, Lesage S, Vionnet N, Clement K, Fougerousse F, Tanizawa Y, Weissenbach J, Beckmann JS, Lathrop GM, Passa PH, Permutt MA, Cohen D: Close linkage of glucokinase locus on chromosome 7p to early-onset non-insulin-dependent diabetes mellitus. *Nature* 356:162–164, 1992
26. Hattersley AT, Turner RC, Permutt MA, Patel P, Tanizawa Y, Chiu KC, O'Rahilly S, Watkins PJ, Wainscoat JS: Linkage of type 2 diabetes to the glucokinase gene. *Lancet* 339:1307–1310, 1992
27. Sturgess NC, Ashford MJL, Cook DL, Hales CN: The sulphonylurea receptor may be an ATP-sensitive potassium channel. *Lancet* 2:474–475, 1985
28. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type 2 diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
29. Wallace TM, Levy JC, Matthews DR: An increase in insulin sensitivity and basal beta-cell function in diabetic subjects treated with pioglitazone in a placebo-controlled randomised study. *Diabet Med* 21:568–576, 2004
30. Bonora E, Targher G, Alberichie M, Bonadonna RC, Saggianni F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity. *Diabetes Care* 23:57–63, 2000
31. Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagishi T, Shoji T, Okuno Y, Morii H: Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulphonylureas. *Diabetes Care* 22:818–822, 1999
32. Holman RR, Turner RC: Maintenance of basal plasma glucose and insulin concentrations in maturity-onset diabetes. *Diabetes* 28:227–230, 1979
33. Matthews DR, Lang DA, Burnett MA, Turner RC: Control of pulsatile insulin secretion in man. *Diabetologia* 24:231–237, 1983
34. Turner RC, Oakley NW, Nabarro JD: Control of basal insulin secretion, with special reference to the diagnosis of insulinomas. *BMJ* 2:132–135, 1971
35. Turner RC, Grayburn JA, Newman GB, Nabarro JD: Measurement of the insulin delivery rate in man. *J Clin Endocrinol Metab* 33:279–286, 1971
36. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwarz MW, Neifing JL, Ward WK, Beard JC, Palmer P, Porte D Jr: Quantification of the relationship between insulin sensitivity and B-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 42:1663–1672, 1993
37. Stumvoll M, Tataranni PA, Stefan N, Vozarova B, Bogardus C: Glucose allostasis. *Diabetes* 52:903–909, 2003
38. Hales CN, Barker DJP, Clark PMS, Cox LJ, Falls C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303:1019–1022, 1991
39. Yajnik CS: Interactions of perturbations in intrauterine growth and growth during childhood on the risk of adult onset disease. *Proc Nutr Soc* 59:257–265, 2000
40. Ong KK, Petry CJ, Emmett PM, Sandhu MS, Keiss W, Hales CN, Ness AR, Dunger DB, the ALSPAC team: Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-1 levels. *Diabetologia* 47:1064–1070, 2004