Characteristics of Glycemic Stability

F. JOHN SERVICE AND ROGER L. NELSON

Glucose homeostasis in healthy subjects is characterized by postmeal glucose increases of about 40 mg/dl, peaks at about 45 min, decreases close to antecibal levels 1 h after the peak, and no spontaneous oscillations until the next meal. Diabetes is characterized by progressive loss of glucose homeostasis from stable to unstable, which is directly proportional to loss of insulin secretory reserve. Degree of instability of diabetes in ambulatory subjects within a 24-h period can be expressed as mean amplitude of glycemic excursion or M-value and between two successive 24-h periods as mean of daily differences of blood glucose. Stable diabetic persons have lower values, which are closest to those of nondiabetic persons, and unstable diabetic persons have higher values. The mean diurnal blood glucose level is a measure of glycemic control. The failure to restore glycemic patterns of diabetic to those of nondiabetic persons is largely due to the failure of subcutaneously administered insulin to mimic the pattern of insulinemia of healthy subjects. DIABETES CARE 3: 58–62, JANUARY–FEBRUARY 1980.

Webster's dictionary defines stability as the property of a body that causes it, when disturbed from a condition of equilibrium, to develop forces that restore the original condition.[1] A synonym for stability in physiologic systems is homeostasis. The control of glycemia in healthy man is a prime example of stability. When undisturbed by outside influences, the most important of which is food ingestion, plasma glucose shows no spontaneous oscillations, and with prolonged fasting there is a gradual decrement of glycemia within a range that is compatible with health (Figure 1).

The major perturbation of glycemia is that resulting from ingestion of food (Figure 2). After a mixed meal, plasma glucose begins to increase within 15 min from an antecibal level of 80–90 mg/dl and reaches peak levels at about 45 min (Figure 3). The glycemic increase averages 40 mg/dl. Usually the glycemia is restored to the antecibal level within 1 h after the peak, unless, as is occasionally observed, a second glycemic peak of lesser magnitude occurs (Figure 2). Once the normal antecibal level of glycemia has been restored, it remains there until perturbed again by ingestion of food. Glucose appearance and disappearance rates are similar preprandially at about 2.5 mg/kg/min, and increase after meal ingestion to about 5 mg/kg/min (Figure 3). The peak in glucose appearance coincides in time with the glycemic peak; the peak in glucose disappearance coincides in time with the postpeak glucose decline.

The primary determinant of glucose homeostasis is the secretion of insulin. After a mixed meal, secretion of insulin is stimulated both by the nutrient-stimulated increase in gastrointestinal insulinogenic factor, gastric inhibitory polypeptide (GIP), and by increasing glycemia (Figure 2). In the postabsorptive state, glycemia is restored to basal levels *pari passu* with the reduction of serum insulin and plasma GIP levels. Although plasma glucagon contributes to the maintenance of basal glycemia,[2] it may not play a major role in disposition of nutrients after a mixed meal (Figure 2). Another feature of glucose stability is the small difference in glycemia between two successive days of similar meals and activities.[3]

Diabetes is characterized by loss of glucose homeostasis—that is, impairment in glucose stability. There is a spectrum of this impairment of glucose stability (diabetes) from the least unstable to the most unstable, which manifests itself clinically in varying degrees of difficulty in controlling glycemia from least difficult to most difficult, respectively. By convention, diabetes in which the glycemia is easiest to control is referred to as stable diabetes. Although this terminology appears to contravene the equation of stability to normality, it does not; stable diabetes is that form of an unstable physiologic system (diabetes) that most closely approximates glucose stability (normality). The glycemic pattern of stable diabetes is characterized by later and higher-than-normal postprandial peaks and failure both to return to antecibal levels within 1 to 2 h and to maintain that level until the

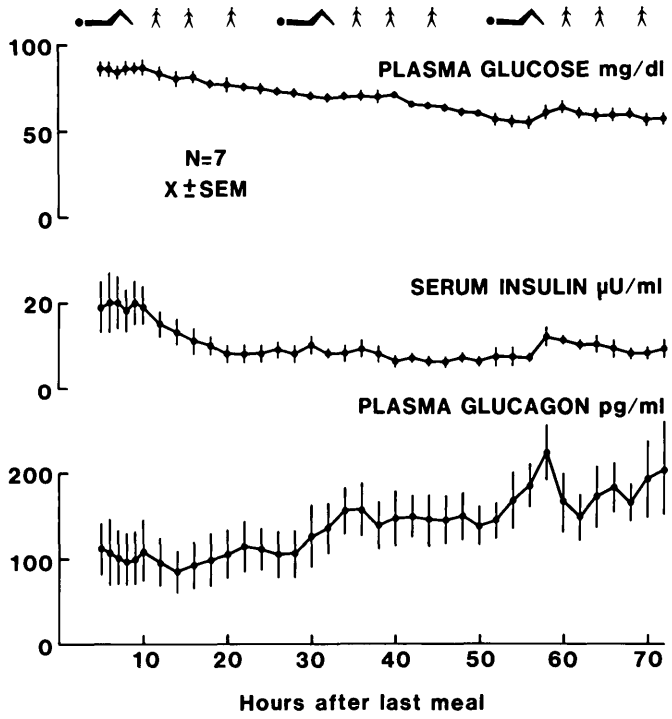

FIG. 1. Circulating glucose, insulin, and glucagon levels in seven healthy subjects during 72 h of food deprivation. The striding figure represents exercise for 1 h on a bicycle ergometer; the reclining figure represents the period of sleep. Note that there are no oscillations in glycemia in the absence of food ingestion.

next meal (Figure 4). The glycemic pattern of unstable diabetes does not even remotely resemble the pattern in nondiabetic persons who show high peaks and often hypoglycemic nadirs (Figure 4).

The pathogenesis of diabetes instability has been ascribed in the past to a number of mechanisms. Hyperglycemic rebound as a result of the release of hyperglycemic hormones secondary to unrecognized hypoglycemia has been touted as one mechanism of the instability of diabetes.[4] However, the existence of this mechanism is in doubt. Chester et al.[5] could not demonstrate a hyperglycemic rebound after the induction of hypoglycemia. Using continuous blood glucose monitoring of unstable diabetic patients, Molnar et al. did not observe hyperglycemic rebound after hypoglycemia in studies of ambulatory, fed patients[6] or after induction of hypoglycemia with an infusion of insulin.[7] Secretion of counterregulatory hormones during hypoglycemia is often impaired in unstable diabetes.[6–8] Recently, Gale et al.[9] have observed that post-hypoglycemic glycemia can be accounted for entirely by circulating levels of free insulin.

Depot insulins have been incriminated in the etiology of diabetes instability.[10] To some extent, this contention is correct, for such types of insulin do not mimic normal beta cell function. However, the corollary—that multiple injections of short-acting insulin daily can stabilize diabetes—has not been substantiated.[11]

The view that "labile diabetics are made and not born"[12] emphasizes the importance of therapeutic errors in the genesis of apparent diabetes instability. Even when such errors are corrected, there remains a group of patients whose diabetes is unstable despite the best efforts of experienced diabetologists administering treatment in a research ward. Molnar[13] has speculated on the existence of a wide range of theoretic possibilities as causes of unstable diabetes. In subsequent studies, he and his associates have demonstrated that diabetes instability parallels degrees of insulin deficiency:[14] stable diabetes is characterized by insulin secretory reserve and unstable diabetes by its absence (Figures 4 and 5). This observation has been confirmed by others.[15] The ability to augment insulinemia in response to meals despite receiving a single injection of insulin daily in patients with stable diabetes undoubtedly contributes to the glycemic stability. In contrast, in those with unstable diabetes, whether treated with intermediate-acting insulin or multiple injections of short-

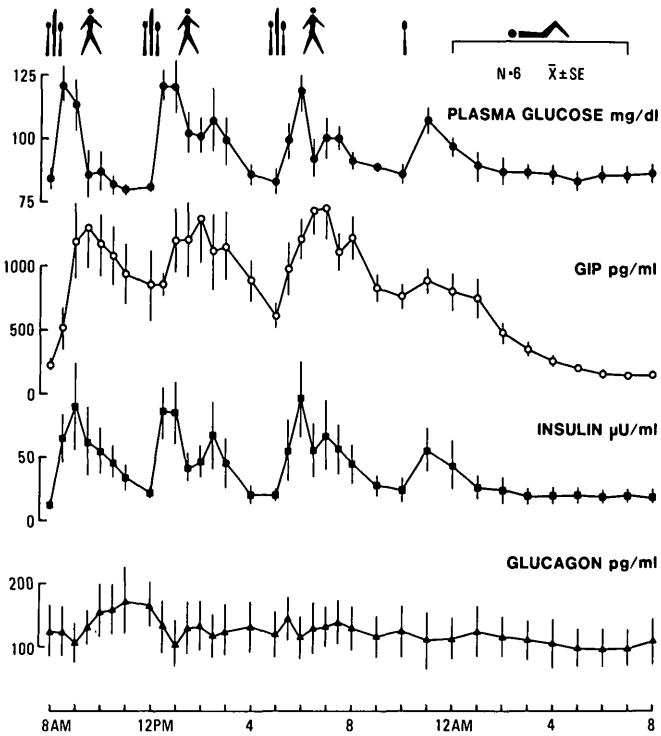

FIG. 2. Circulating glucose, insulin, gastric inhibitory polypeptide (GIP), and glucagon levels are shown for six healthy subjects under ambulatory conditions for 24 h. Fork-spoon-knife represents a mixed meal; the solitary spoon is a snack. Glucose, GIP, and insulin are perturbed from the basal state only with food ingestion. With overnight fasting, the basal levels are restored.

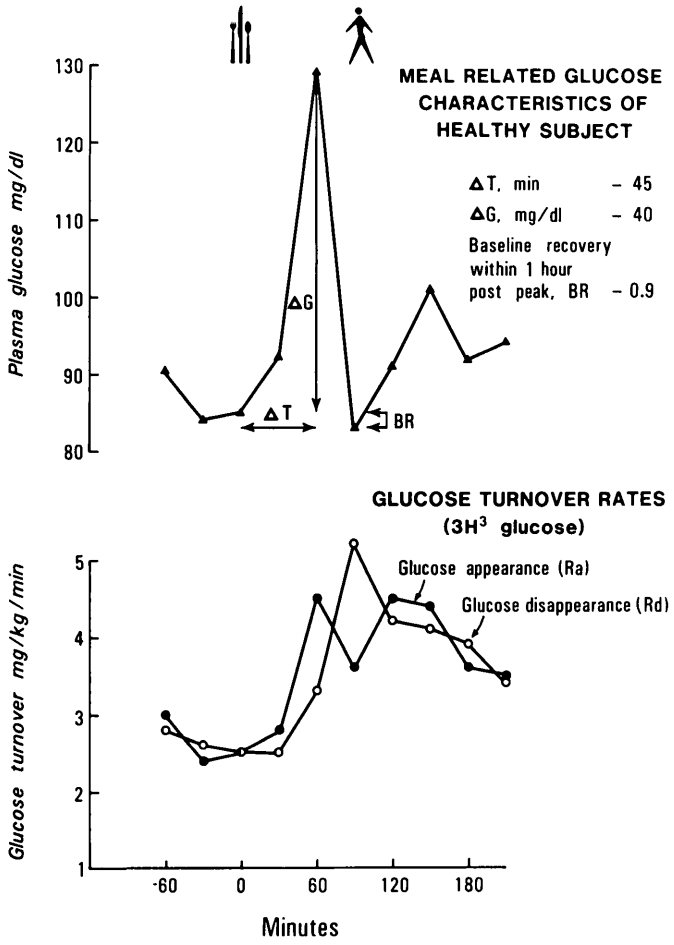

FIG. 3. Meal-related glucose responses and glucose turnover are shown for a healthy subject. The parameters ΔT (time), ΔG (glucose), and BR (baseline recovery) can be used as goals for therapy with open-loop or closed-loop devices for glucose control.

acting insulin daily, there is an inverse correlation between glycemia and insulinemia that is indicative of the dependency of the former on the latter. The patterns of insulinemia and glycemia do not approach those of stable diabetes and normality (Figure 4). These data indict our current modes of insulin administration for their failure to restore glycemia to normal. This is most glaringly seen in the unstable diabetic patient. What is needed is a technique to get insulin into the circulation in sufficient concentration at the time of meals and to reduce its concentration to low levels in the postabsorptive state.

Systems have been developed—both closed-loop (glucose sensor, computer, and insulin pump)[16,17] and open-loop (insulin pump with or without computer)—which, by providing insulin in the manner described above, result in restoration to normal of the glycemic pattern in the ambulatory, fed state in patients with even the most unstable diabetes.[18]

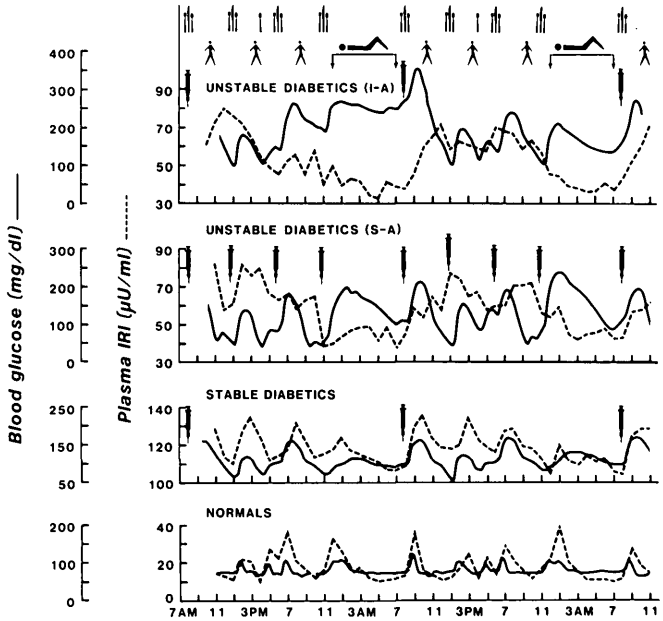

FIG. 4. Blood glucose and plasma insulin in normal, stable diabetic, and unstable diabetic subjects under ambulatory, fed conditions for 48 h. Blood glucose was analyzed continuously. I-A refers to treatment with once-daily injections of intermediate-acting insulin; S-A refers to injection of short-acting insulin before each meal. The syringe is the symbol for the timing of insulin administration. Note the progressive loss of glucose homeostasis from normal subjects to patients with unstable diabetes, the meal-related insulin responses in the stable diabetic group, and the inverse correlation between glycemia and insulinemia in unstable diabetic patients.

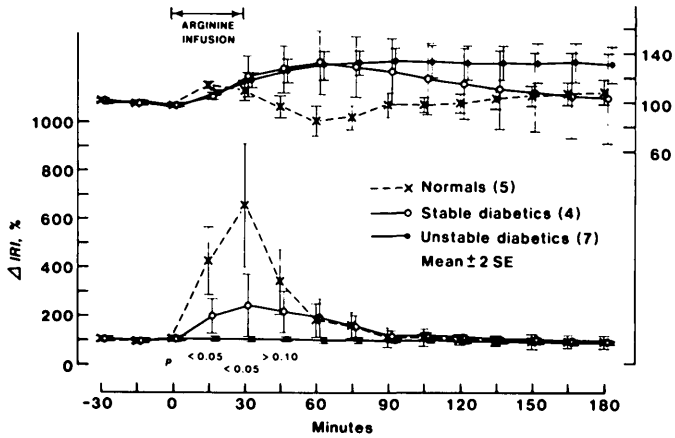

FIG. 5. Insulin response to arginine infusion is blunted in patients with stable diabetes compared with normal control subjects and is absent in unstable diabetic patients. ΔIRI, change in immunoreactive insulin; ΔBG, change in blood glucose. (Modified from Cremer, G. M., Molnar, G. D., Taylor, W. F., Moxness, K. E., Service, F. J., Gatewood, L. C., Ackerman, E., and Rosevear, J. W.: Studies of diabetic instability. II. Tests of insulinogenic reserve with infusions of arginine, glucagon, epinephrine, and saline. Metabolism 20: 1083–98, 1971. By permission of Grune & Stratton.)

Efforts to quantitate diabetes instability have relied on intermittent blood glucose determinations and either semiquantitative or quantitative urine glucose measurements.[19–25] With the development of continuous blood glucose monitoring and its application to the study of diabetes instability of patients under ambulatory and fed conditions, complete quantitative characterization of blood glucose dynamics was possible[11] (Figure 6). The mean diurnal blood glucose is a measure of glycemic "control" or the degree to which overall glycemia approximates, or deviates from, normal. Mean glycemia in healthy subjects is a blood glucose level of 80 mg/dl for whole blood and 90 mg/dl for plasma. Patients with diabetes have higher values, those with stable diabetes having the smallest deviation from normal and those with unstable diabetes the greatest when treated with conventional therapy. A measure of within-day glucose instability—that is, the variability of glycemia under ambulatory, fed conditions within 24 h—is the mean amplitude of glycemic excursion (MAGE). In the development of this quantification, the decision was made not to use the standard deviation of glycemic measurements for the quantification of glucose variability, because that parameter gives a dispersion of all glycemic measurements and can have the same numerical value for glycemic patterns of differing configurations. In order to emphasize the major glucose swings and eliminate minor ones, glucose excursions that exceed one standard deviation are used for the calculation of MAGE. In nondiabetic subjects, the meal-related glucose swings also exceed one standard deviation of glycemia. MAGE for nondiabetic persons varies from 20 to 60, and the values are higher for diabetic patients, the highest occurring in those with unstable diabetes.

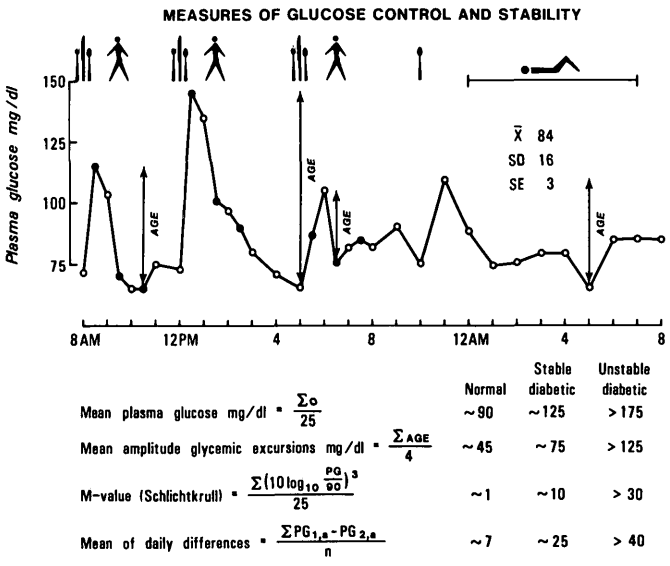

FIG. 6. Derivation of measures of glucose control and stability. The glycemic profile of a healthy subject is used, and typical values for normal, stable diabetic, and unstable diabetic subjects are given. For the example shown, the mean 24-h plasma glucose value is 84 mg/dl, standard deviation 16, and standard error 3. AGE, amplitude of glycemic excursions.

The M-value of Schlichtkrull[26] as modified by Mirouze et al.[27] and by us[11] is a quantitative index of the deviations of several blood glucose determinations in a 24-h period from an arbitrarily selected standard (mean 24-h blood/plasma glucose). The mathematical formula is designed to give proportionately greater emphasis to hypoglycemia than to hyperglycemia. The M-value results in a single numerical expression—a combination of glycemic control and stability.

Not only is glycemic instability characterized by within-day variability—that is, MAGE—but there is also between-day variability (Figure 7). Healthy subjects show small differences in glycemia from day to day. Diabetic patients show greater differences, with the greatest being seen in those with unstable diabetes.

The evaluation of any new mode of therapy for diabetes is

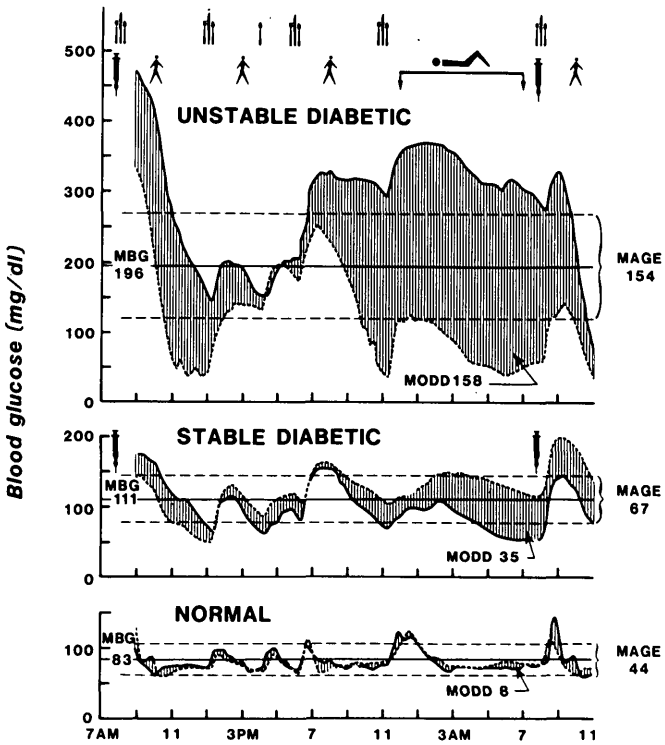

FIG. 7. Three quantitative measurements—MBG, mean blood glucose; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences of blood glucose—of normal, stable diabetic, and unstable diabetic subjects studied with continuous blood glucose analysis while subjects pursued normal activities. (Modified from Molnar, G. D., Taylor, W. F., and Langworthy, A.: On measuring the adequacy of diabetes regulation: comparison of continuously monitored blood glucose patterns with values at selected time points. Diabetologia 10: 139–43, 1974. By permission of Springer-Verlag, Berlin.)

best accomplished by complete characterization of glycemia either by continuous glucose monitoring or by frequent intermittent sampling for plasma glucose. This should be done no less frequently than hourly in the postabsorptive and fasting states, and more often at meal times. To determine whether a new mode of therapy achieves better results than established treatment programs, control studies using the latter should be included in the investigation. In addition, if the new treatment has the likelihood of restoring glycemia to the pattern observed in healthy subjects, the control studies using healthy subjects should also be part of the protocol design. The standard means of quantifying glycemic control and stability, or new ones, should be applied for analysis. Furthermore, if normalization of glycemia is attempted, detailed analyses of meal-related glycemia should be included.

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901.

Address reprint requests to F. J. Service.

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