of course increases 250% if U100 insulin is used. Using syringes with fixed needles (small dead space) and injecting the insulin surplus back into the bottle, a daily loss of 1–2 U will occur.

In addition, we have now carried out an anonymous inquiry in a group of 53 insulin-dependent patients. When asked about how often they changed their insulin doses and the magnitude of the dose change, 70% admitted deviations from the habitual dose (a term that we prefer to "recommended," since we encourage rather than discourage our patients to adjust insulin doses before extra meals, sports activities, or according to the results of self-monitoring of blood glucose). Eight percent of the patients changed doses daily and 50% one day weekly or monthly. The daily dosage adjustments averaged 3.4 U. Furthermore, there was a slight predominance of those who lowered the dose over those who took extra insulin.

The results of the inquiry thus demonstrate that extra insulin could have had no or only a minor influence on our calculated wastage of insulin. Neither is it reasonable to assume that a significant upward trend in the insulin doses could have infuenced the results, since the "recommended" doses were reevaluated every third month during the 2-yr period of investigation.

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# Which Patients Might Benefit from Combining a Sulfonylurea with Insulin?

Combining a sulfonylurea with insulin is an obvious but little-tested therapeutic option for type II diabetes. While published experience is scanty,[1–5] we believe empirical use of combination therapy is common. Available data suggest that responses to this approach are highly variable between individual patients. Therefore, information regarding which patients are the best candidates is needed.

A number of our patients, in efforts to improve on prior suboptimal glycemic control, have used a regimen combining bedtime intermediate-acting insulin with daytime sulfonylurea (BIDS). This approach is designed to control fasting glycemia, including the "dawn phenomenon," with bedtime insulin, while enhancing daytime glycemic control with tolazamide. We have reviewed the outcome for 22 patients (5 men, 17 women; age 53–73 yr; relative body weight by 1983 Metropolitan Life tables 100–180%; duration of diabetes 1–25 yr) with enough follow-up data, including a 4-mo period on prior therapy and between 4 and 8 mo on BIDS. Prior therapies included tolazamide (500–1000 mg/day, N = 4), a single insulin injection (14–48 U/day, N = 5), and multiple injections (22–100 U/day, N = 13). On BIDS, patients took 250–500 mg tolazamide in one (acB) or two (acB, acL) doses, and lente or NPH insulin at bedtime, the doses at last follow-up ranging from 12 to 90 U/day, mean ± SD 32 ± 21 U/day. Insulin doses were adjusted according to clinical judgment and, for the patients previously using insulin, averaged 79% of the original dose at last follow-up. Glycosylated hemoglobin (GHb, colorimetric, normal mean ± SD = 7.0 ± 1.5 $\%A_1$) was unchanged from baseline (10.7 ± 0.4 $\%A_1$, mean N of samples = 2.7/patient) to follow-up (10.4 ± 1.1 $\%A_1$, mean N of samples = 2.7/patient). However, the change of GHb (ΔGHb) from baseline to follow-up showed, by multiple correlation analysis, significant correlations with relative body weight ($P < 0.01$) and duration of diabetes ($P < 0.05$), a decline of GHb on BIDS being associated with leanness and short duration. These relationships are shown another way in Figure 1. A significant correlation between relative body weight and GHb was apparent ($r = 0.424$, $P < 0.05$). When patients with diabetes >12 yr (open circles) were excluded, a stronger correlation ($N = 13$, $r = 0.819$, $P < 0.001$) was evident.

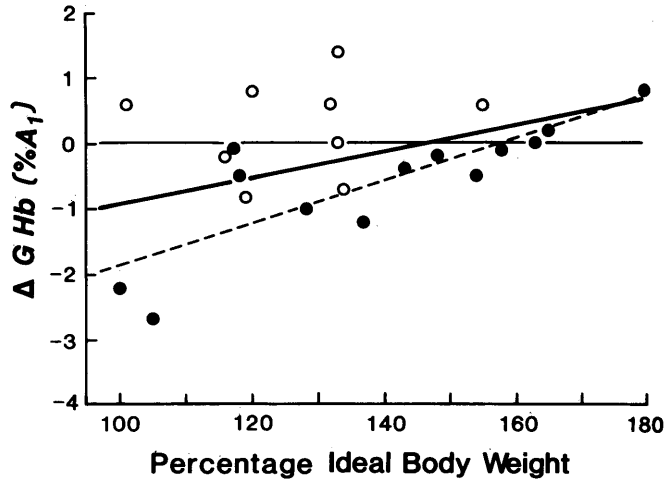


*FIG. 1. The relationship between glycemic outcome on BIDS (ΔGHb) and relative body weight for 22 patients with type II diabetes. Improved mean plasma glucose is suggested by a negative ΔGHb. Closed circles represent 13 patients with diabetes ≤12 yr; open circles represent 9 patients with diabetes of longer duration. The solid line represents the linear regression for all patients ($y = -2.76 \pm 0.019x$, $r = 0.424$, $P < 0.05$); the interrupted line represents that for the patients with diabetes ≤12 yr ($y = -5.07 \pm 0.032x$, $r = 0.819$, $P < 0.001$). In each case there is a significant relationship between leanness and favorable glycemic outcome on BIDS.*

These preliminary findings suggest relatively nonobese persons with short duration of type II diabetes are the best can-

didates for BIDS, despite the supposition that a major benefit of adding a sulfonylurea to insulin lies in improving the insulin responsiveness of tissues of obese persons. In a prospective trial of BIDS now underway we are limiting entry to persons weighing <150% of ideal and with diabetes ≤12 yr. We propose that, for properly selected persons incompletely responsive to a sulfonylurea alone, this regimen may prove a simple, safe, and effective therapeutic alternative.

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REFERENCES

[1] Lotz, N., Lacher, F., and Bachmann, W.: Combination of sulfonylureas and insulin in the treatment of type II diabetes with secondary failure of sulfonylurea therapy. Diabetes 1984; 33 (Suppl. 1):24A.

[2] Dornhurst, A., Powell, S., and Pensky, J.: Tolazamide therapy in insulin treated type II diabetics reduces insulin dosage and improves glycemic control. Diabetes 1984; 33 (Suppl. 1):103A.

[3] Groop, L., Harno, K., Nousianinen, R., and Karonen, S.-L.: The combination of insulin with sulfonylurea in the treatment of maturity-onset diabetes. Acta Endocrinol. 1980; 94 (Suppl. 237):28.

[4] Fabrykant, M.: Use of Orinase as a basic adjuvant in management of insulin-dependent diabetes. Metabolism 1958; 7:213–21.

[5] Volk, B. W., and Lazarus, S. S.: Significance of effectiveness of combined insulin-Orinase treatment in maturity-onset diabetes. Am. J. Med. Sci. 1959; 237:1–7.

# Empirical Determination of Diabetes Clinical Type

Clinical subtypes of diabetes mellitus have been promulgated by the National Diabetes Data Group,[1] namely, insulin-dependent diabetes mellitus (IDDM); non-insulin-dependent diabetes mellitus (NIDDM), with patients further divided into obese (obese NIDDM) and not obese (nonobese NIDDM) subgroups; and diabetes secondary to some other disease process or to the use of drugs that impair glucose metabolism (secondary diabetes mellitus). This categorization appears to represent a substantial improvement over the traditional "juvenile onset" and "maturity onset" dichotomy.[2] There are, however, important practical problems with using the new criteria in retrospective epidemiologic studies, especially those based on medical records. To obviate this difficulty, we proposed an empirical approach to the determination of clinical type through existing medical records.[2]

In our original report, we neglected to show how well this ad hoc classification performed in predicting the subsequent risk of ketoacidosis. These data are shown in Figure 1. By 20 yr after the initial diagnosis of diabetes, an actuarially estimated 35% of the patients classified as IDDM had experienced at least one episode of ketoacidosis. Comparable figures for obese and nonobese NIDDM patients were 2.7% and 4.4%, respectively. One of 29 patients with secondary diabetes (3.4%) developed ketoacidosis, but the experience of this group could not be estimated beyond 6 yr due to the small number of subjects being followed.

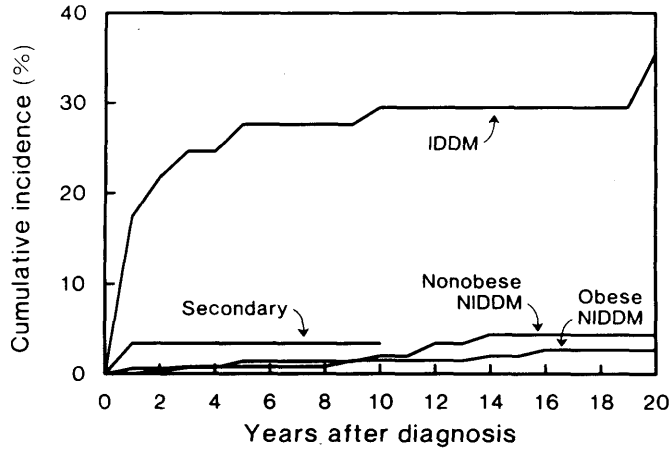


*FIG. 1. Actuarially estimated cumulative incidence of ketoacidosis following the initial diagnosis of diabetes mellitus among Rochester, Minnesota residents with different clinical types of disease.*

While the individuals classified as IDDM were at substantially increased risk of subsequent ketoacidosis, it must be noted that some patients not classified as IDDM also experienced ketoacidosis.

This may be due in part to misclassification. However, it also seems to result from non-insulin-dependent patients later developing insulin dependence, a phenomenon recognized by the National Diabetes Data Group.[1] This suggestion is supported by observations from earlier studies in this population, which revealed that patients not using insulin were placed on insulin therapy at the rate of over 2% per yr,[3] and that the initial episode of ketoacidosis often appeared only after diabetes of many years duration.[4]

Modern laboratory methods may permit more definitive determination of insulin dependence in prospective clinical studies. However, relatively arbitrary criteria are needed for investigations employing existing medical records, especially if older records must be used, as in the case of retrospective cohort studies. We suggest that investigators using medical records restrict insulin dependence at the time of diagnosis to the situation where a patient is started on insulin within 1 wk of diagnosis of diabetes and remains on that therapy for an extended period (arbitrarily defined here as 1 yr or until death), that the patient not be obese (relative weight less than 1.2), and that he or she display some evidence of ketosis or ketonuria.[2] The IDDM patients so restricted represent only one-third of all insulin users in the diabetic population. This approach identifies patients with the characteristics tradi-