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Computer-Assisted Post-prandial SMBG Can Dramatically Reduce the Frequency of Hypoglycemia in the Intensive Management of IDDM

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Intensive (basal/bolus) therapy can afford Type 1 patients flexible meal times, composition, and quantity, *but* reputedly leads to an increase in the frequency of hypoglycemia. In this feasibility study we attacked this tendency as follows:

First, basal insulin is adjusted so as to just maintain euglycemia while fasting all day long; a "true basal" regimen. This not only precludes basal insulin from contributing to hypoglycemia, but moreover enables straightforward calculation of the needed quantity of bolus insulin *and* its effect on BG over time.

Next, the well-known time course of the fast acting bolus insulin, in conjunction with the patient's insulin sensitivity, is used to predict the amount BG can fall, as a function of time, at any point after the bolus injection(s). From a few hours after eating, when most of the meal is absorbed, BG will have peaked and this function can be used to predict how far BG can fall thereafter as the bolus insulin runs its course.

Then, with post-prandial SMBG, a palm-sized computer (PDA) enables immediate prediction of hypoglycemia should the bolus have been too large for the meal. It also enables prediction of just when BG will fall to any given level, and what the ultimate BG deficit will be, so that a carbohydrate supplement may be calculated and eaten any time before then. It similarly enables calculation of the insulin deficit should the bolus have been too small, enabling an insulin supplement to be taken immediately, without waiting to learn BG is high at the next meal/bed time. Calculated bedtime supplements can ensure normal fasting BG whatever bedtime BG may have been.

Because the time course of insulin action is more predictable than the effect of food on BG, any errors in BG prediction will tend to be on the low side, and thereby effectively "fail-safe". Since the PDA is also used to log BG and insulin, the model parameters that influence the BG prediction are adaptively refined over time with "learning" algorithms to further minimize predictive error and even track the patient over time.

In our study over a 5 year period, hypoglycemic events were reduced by more than 90%, while HbA_{1c} was simultaneously reduced by almost 1 percent. Lower average BG and HbA1c does not *necessarily* imply an increased frequency of hypoglycemia.

Background

- Hypoglycemia is said to be the result of such things as "missed or delayed meals", "infrequent monitoring", or "failure to follow a meal plan", *but* these are merely the context of the mechanical cause in IDDM: too much insulin for conditions.

- The key to avoiding hypoglycemia is to not take too much insulin, and to learn about it in time if you do.

- The key to insulin administration is the regimen. Only one regimen enables omission of meals and the possibility of precluding at least one source of too much insulin: Basal/Bolus.

- The Basal/Bolus regimen is capable of accomodating missed meals, even all day long (e.g. during the Ramadan fast), because basal needs are managed separately from prandial needs. By adjusting basal insulin to match basal metabolic need this insulin cannot contribute to hypoglycemia, leaving too much prandial insulin the only remaining concern in patients where bouts of intense sports or other exercise activity are not an issue.

- Mathematically, basal and prandial insulin needs may be considered to be independent glycemia influencing "factors", which simplifies their calculation when basal insulin is adjusted to ensure euglycemia absent any food or exercise perturbations.

- With basal insulin need "factored out", the effect of prandial insulin is easily calculated, knowing its time course of action.

- This is done by integrating the insulin action profile over time, obtaining a fractional action over time curve, which is then converted into a "percent insulin action remaining" as a function of time curve.

(see attached Medical Informatics article, p. 14)

System Models

- All control systems require at least two components: a model of system behavior, and a strategy for using that model to determine appropriate system inputs to achieve the desired results.

- Traditional do-and-eat-the-same-thing-every-day regimens use the past as a model of the future, and adapt the insulin to match strategy using that model. This model and strategy can work, even work well, but since the domain of definition of the model is limited to the agreed upon regimen, it is inherently inflexible.

- Moreover, if the agreed upon regimen is *not* followed, there is nothing on which to base a strategy to recover from the indiscretion. Any supplemental food or insulin must be taken without benefit of calculation, because there is no model on which to base it.

- With a "true" Basal / Bolus regimen, the glucose response to food and insulin may be estimated from models of their effect. The most pressing research need for achieving good glucose control without unwanted hyper- or hypo-glycemia is therefore suitable models of food absorption in the gut and insulin absorption and action, and for the latter the additional effect of exercise.

- There is only one published model, each, of food and insulin absorption. They are both physiological compartmental "minimal models". The food model needs parameters for each food to be modeled, and these do not exist apart from the two example foods published. The insulin model is limited to absorption, and needs to be combined with insulin action to be usable for this purpose. Fortunately, an empirical model of insulin action over time has been published for Regular and Lispro, but it omits the standard deviation data needed for estimating the potential error of a prediction made using it.

Control Strategy

- Since both the effect of both food and insulin are known as a function of time using these models, glucose can be predicted into the future from any point after eating and injecting, starting from the resulting glucose at that time.

- The precise effect of food is less well known than that of insulin, but in general food is absorbed and has its effect to a given extent faster than bolus insulin does.

- Thus we have this strategy of measuring BG 2-3 hours after eating, as the glucose response of the meal is peaking and most of the food has been absorbed, but the bolus insulin has yet to completely run its course.

- From that point, between meals (or bedtime), BG can be expected to fall, but knowing the insulin dose and quantity remaining "on board", future BG may be predicted over time, providing the critical information needed to make use of this BG measurement.

- If too much bolus insulin was taken, the prediction will indicate when BG will fall to any given level, and what the ultimate BG deficit will be, enabling calculation of the requisite carbohydrate supplement and how long until the patient must eat it.

- If too little bolus insulin was taken, the predicted ultimate BG excess enables calculation of the requisite insulin supplement, which may be taken immediately rather than waiting until the next meal.

- At the next mealtime BG need not be measured, because the previous post-prandial BG reading and possible calculated supplements have ensured that it will be close enough to normal that the bolus insulin dose may simply be based on the meal being covered. This strategy thus requires no more testing than do strategies utilizing pre-prandial SMBG.

- At or before bedtime the same strategy may be employed to ensure no nighttime hypoglycemia and that the subsequent fasting glucose is close to normal. Insulin supplements at bedtime are not ordinarily recommended, because of concern for nighttime hypoglycemia, but that's because they lack a precictive model that can take into account the residual effect of previously injected insulin. Since there is no danger of unanticipated food or exercise overnight, this BG predicton is even less subject to error, and the patient can enjoy normal fasting BG no matter what it was at bedtime.

Split and Mixed Regimen

While convenient, this regimen suffers from several fundamental flaws that can lead to hypoglycemia:

- Taking NPH before dinner places its peak of activity in the middle of the night, when the patient is not in a position to notice impending hypoglycemia, much less take appropriate action should this occur.

- Taking NPH before breakfast in order to accomodate lunch places a broad peak of activity from before to well after lunch. The pre-lunch activity in particular is responsible for the hypoglycemia commonly seen at that time with this regimen.

- Taking NPH before breakfast in order to accomocate lunch commits the patient to the quantity and timing of lunch, making this regimen paticularly inflexible. This is the source of the notion that hypoglycemia can be caused by "missed or delayed meals", which is only true of this regimen.

- Basal *and* Prandial insulin requirements are both met by the fast and intermediate acting insulin used in this regimen. This confounding of insulin action makes it difficult to impossible to analyze mathematically.

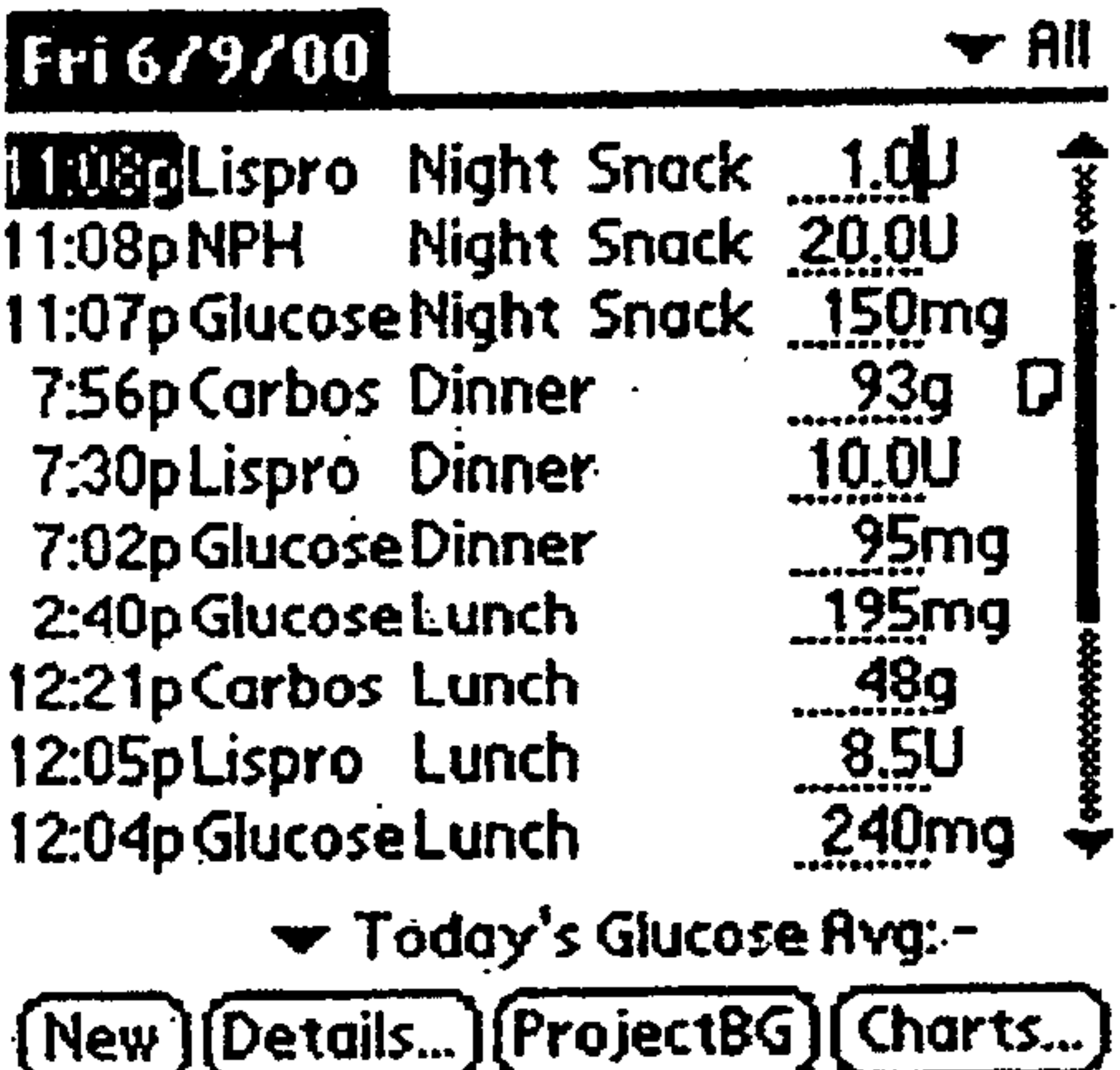
This regimen should be <u>contra</u>indicated for any patient with adequate self-management skills, as it is a sure prescription for frustration and hypoglycemia.

Implementation

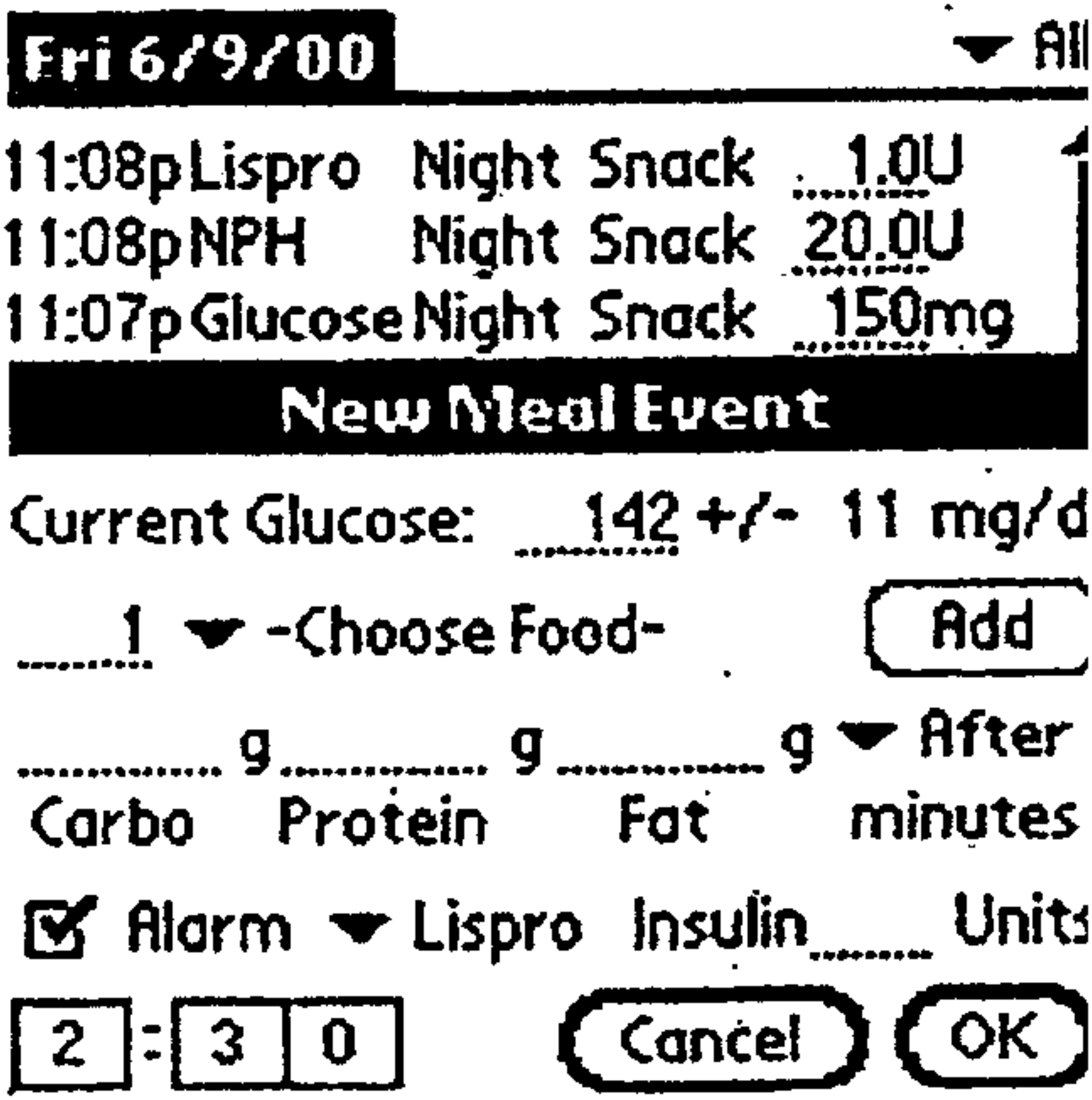
- Personal Digital Assistant running the Palm OS, available from Palm, Handspring, IBM and others for $100 - up, comparable in cost to many SMBG meters.

- PDA program provides an electronic logbook for BG readings, insulin taken, and food eaten, with the time and date automatically added, and with provision for appended notes and category labels.

- Example screen shot:



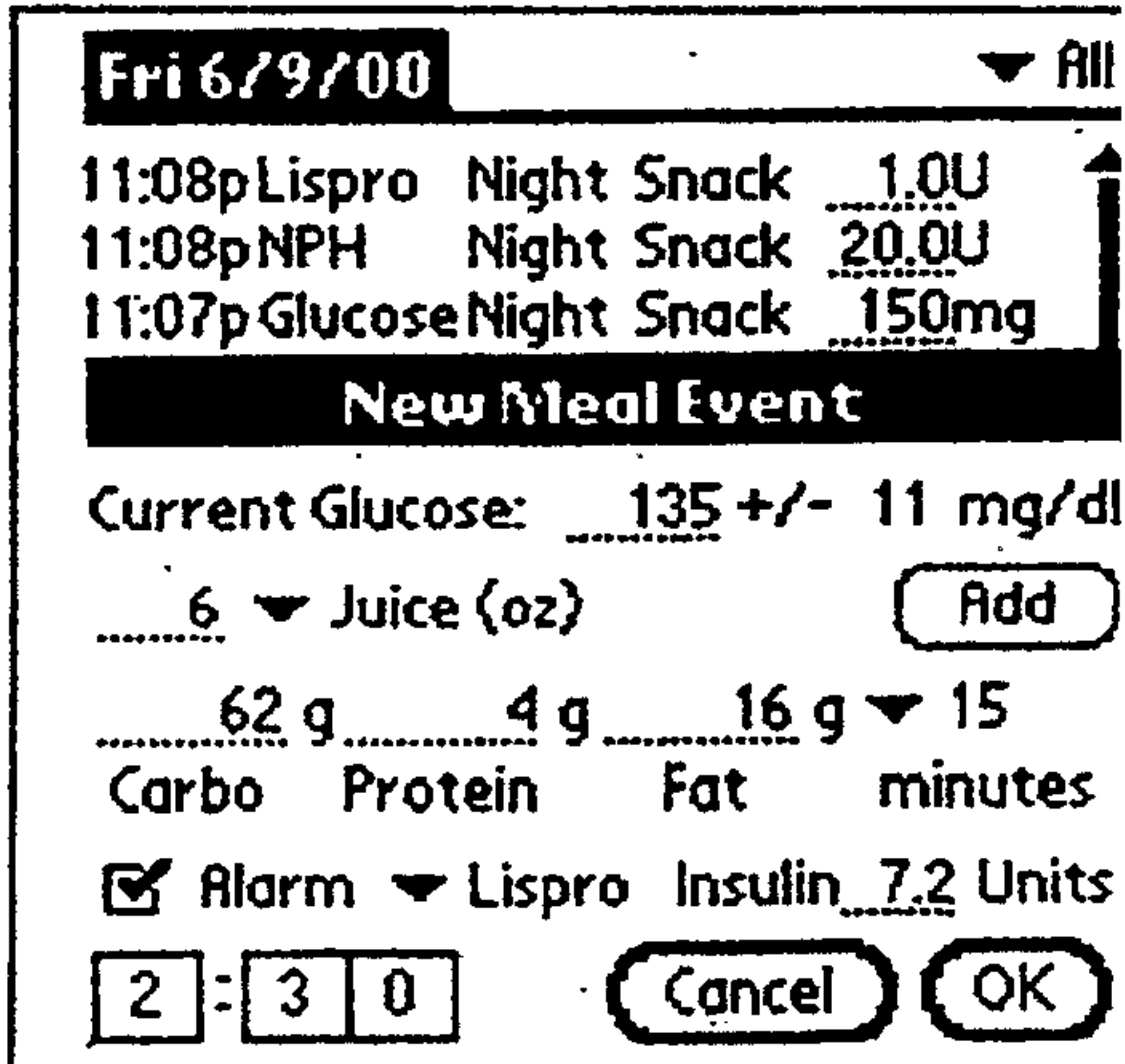
- Pressing "New" brings up a New Meal Event dialog:



- Current BG is estimated, along with the remaining "on board" insulin from before. This may be taken as is, or if desired the actual BG reading may be substituted.

- Food to be eaten is entered by quantity and item, or by entering the component Carbo, Protein and Fat directly. The Add button adds the components of the selected food to the total.

- When Add is pressed, the needed insulin is calculated from the BG and Food components, and displayed at the lower right above the OK button.



- The estimated "After minutes" time delay until the meal begins enables the insulin and meal quantity to be automatically entered into the electronic journal when OK is pressed. Here, "15 minutes" has been selected.

- An alarm reminder for post-prandial SMBG may be set for any later time at the lower left. By de-selecting the Alarm checkbox, this reminder alarm will not be set.

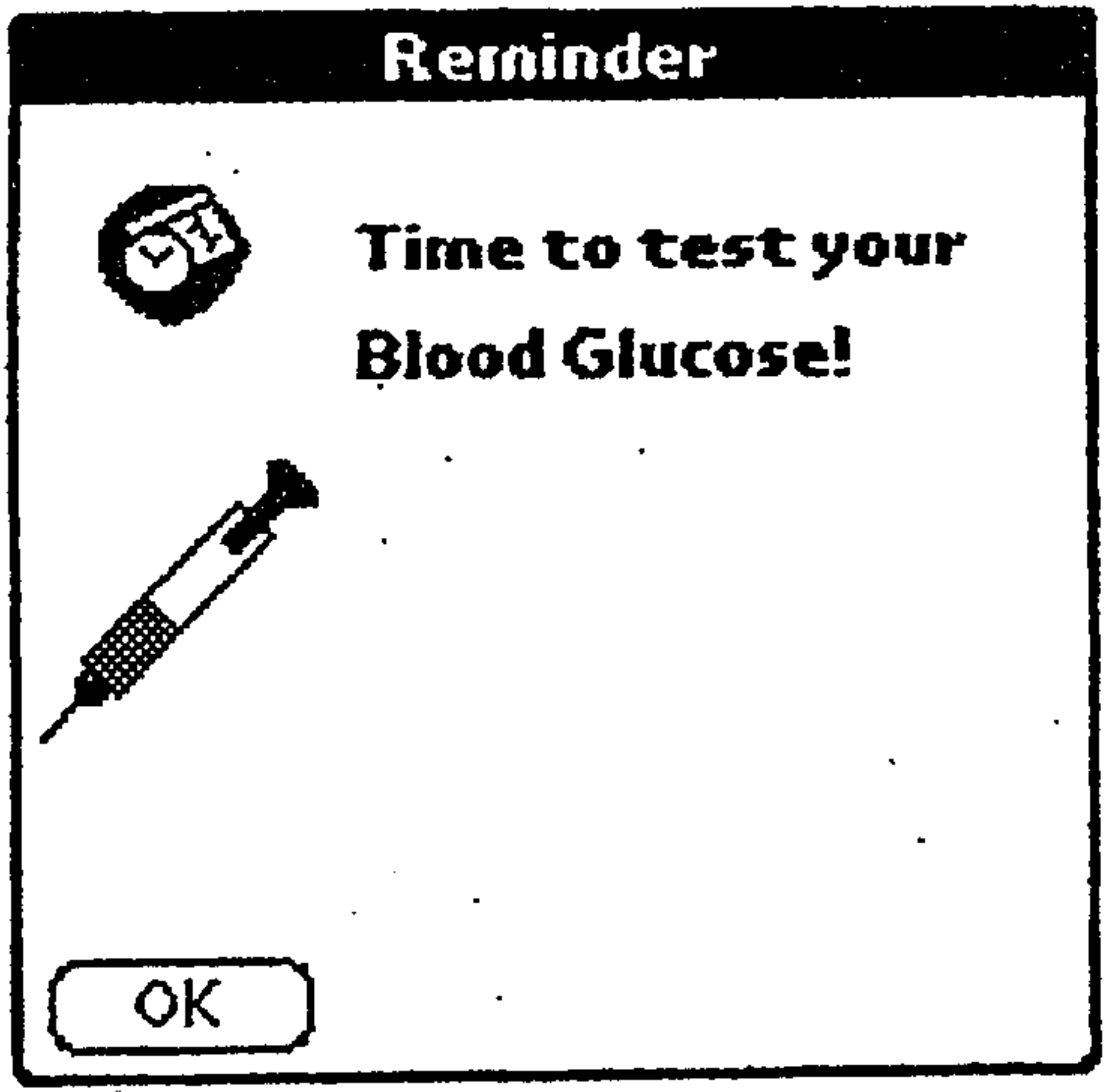
- The amount of time until the alarm is set here to 2 hours 30 minutes, but may be changed by selecting the hour and minutes boxes, which reveals up and down controls which may be used to adjust the time.

- After pressing the OK button, the Food and Insulin quantities are transferred to the electronic logbook, as illustrated above.

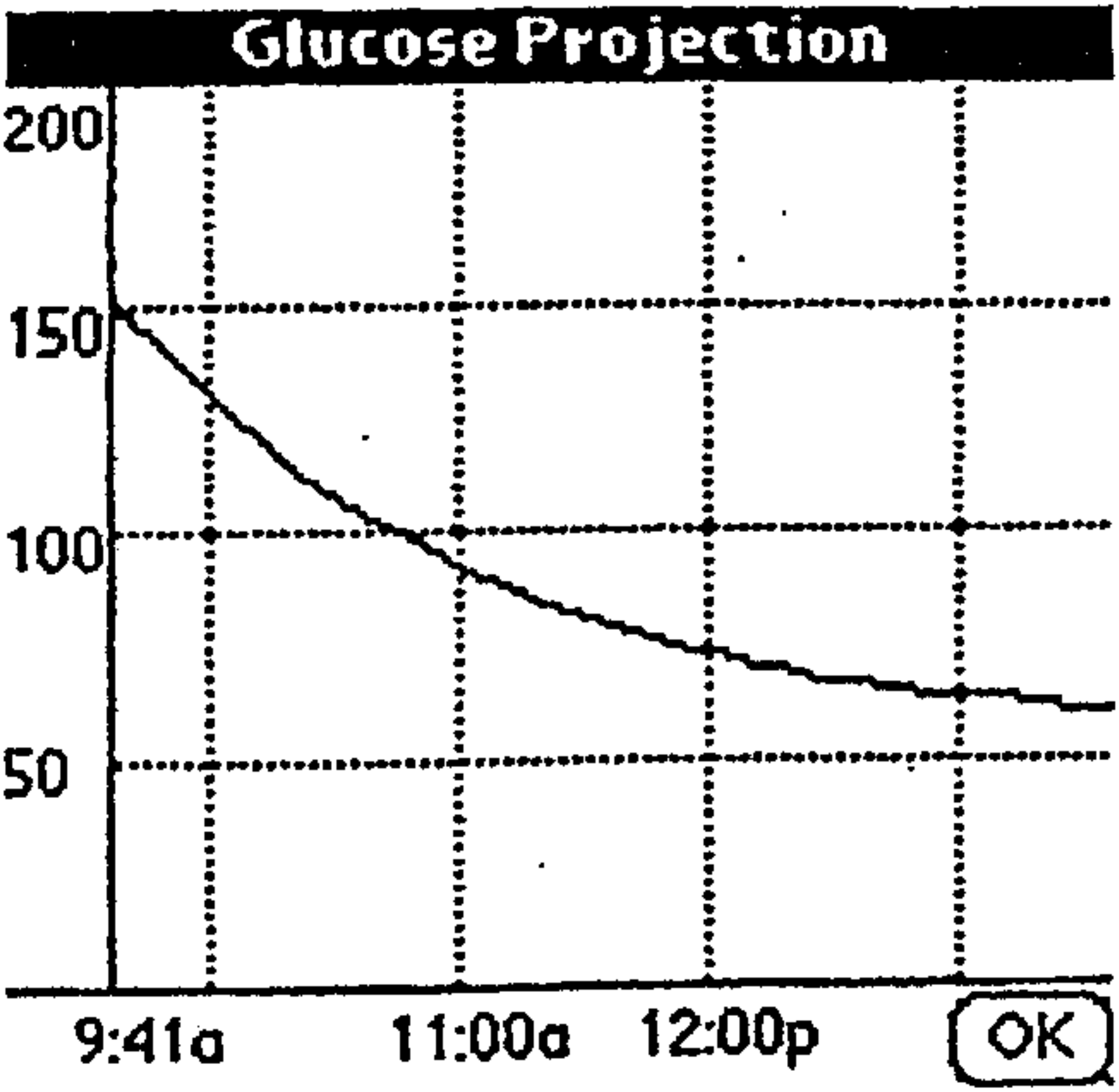
- If the BG quantity is modified from the original Current Glucose estimate, it is taken to be a new BG measurement, and is inserted into the electronic logbook as well.

- The times are taken from the PDA's built-in clock, with the Carbos entry adjusted by the 15 minutes specified in the New Meal dialog.

- After the 2 and a half hour alarm interval has passed, at 9:39 AM in this case, a Reminder alarm is generated by the Palm Operating System. It consists of an audable alarm and a visual display:



- The audable alarm repeats every 4-5 minutes for up to a half hour, or until the OK button is pressed.
- After testing, the measured BG is entered into the PDA, at which point the Project button may be pressed, which brings up a Glucose Projection.
- This projection starts with the measured BG, here 150 mg/dl, and utilizes the known BG lowering effect of the residual pre-breakfast insulin: 7.4 Units of Lispro.
- It indicates BG will fall to no less than 75 mg/dl by Noon. Actual BG will likely be higher, due to the residual effect of the Food eaten at breakfast (which is not explicitly modeled here).



- A larger prandial dose at breakfast, leading to the same 150 mg/dl BG at 9:41 am, would show a BG projection falling faster than this example.
- The ultimate projected BG level gives an indication of how much carbohydrate must be eaten to raise this ultimate BG level, if needed, to avoid hypoglycemia.
- If the ultimate projected BG level is higher than normal, the excess gives an indication of how much insulin is yet needed to bring BG down.
- These supplements may be taken immediately, even at bedtime, so that BG may be normalized as soon as possible.

Results

Knowing what to expect, and when to expect it, provides significant advantages for managing BG in practice:

- Without a 'true basal' NPH regimen, and without a model-based estimate of 'on board' residual insulin, high BG that was destined to fall was corrected with a larger supplement than needed, leading to hypoglycemia.
- Mild 40-50 mg/dl hypoglycemia occurred one to two times/month. Serious 30-40 mg/dl hypoglycemia requiring assistance occurred one to two times/year. Severe 20-30 mg/dl hypoglycemia occurred one to two times/decade. This despite responsible behavior.
- Since adopting a 'true basal' NPH regimen, and having a rough estimate of 'on board' residual insulin action from recent doses, these frequencies have improved by over an order of magnitude:
- Mild hypoglycemia occurs about once a year. Serious hypoglycemia hasn't happened in over 5 years. Analysis of these events revealed that the strategy did not fail, but rather was not followed. [the model was implemented mentally prior to programming the PDA]
- The difference between these two treatment groups is so significant it goes far beyond the usual 5% or 1% levels. The null hypothesis can thus be rejected with absolute certainty despite the N=1 sample size. It is only a question of which patients are capable of understanding and properly utilizing the predictions of the PDA.
- HbA1c has declined under this strategy as well, but not as dramatically as hypoglycemia has been reduced. The recent implementation of a post-prandial alarm may catch high BG more consistently and sooner than before, resulting in the significantly lower HbA1c theory would predict.