Letters and Comments

Which Reference Method for Comparing Blood Glucose Reagent Strips

Blood or Serum?

The recent study by Barreau and Buttery (1) concluded that interpretation of results from reagent strip methods was affected substantially by the hematocrit value. This is hardly surprising because the reference method was a whole-blood glucose rather than plasma glucose estimation. When questioned on the validity of the reference method in a similar study (2), the authors replied that the manufacturers have stated that a blood glucose reference method is preferred in a comparative study of this type (3).

Over the years, *Diabetes Care* has published several articles on the precision and accuracy of blood glucose monitoring with reagent strips with or without a meter. The latest of these studies used whole-blood glucose samples analyzed by the YSI analyzer (4). It was stated that

> This technique eliminated the need for cumbersome and imprecise conversion factors required in converting serum glucose determinations to equivalent whole blood glucose values as displayed by the HMBG (Home Monitor Blood Glucose).

At first it would appear that, because a drop of whole blood is placed on the reagent strip, a whole blood estimation should be an appropriate reference measurement. However, it is only the plasma that permeates the reagent pad, leaving the cellular components behind to a variable extent depending on the type of strip. What is actually being measured in reagent strips is closer to plasma than whole-blood glucose.

The Symposium on Blood Glucose Monitoring reported in *Diabetes Care* contained four similar articles evaluating early glucose meter models (5–8). The first of these used a formula (which made allowances for the hematocrit to convert the reagent strip reading to an apparent serum reading) and used a serum reference method. The second and fourth articles used a whole-blood reference method. The third article looked at both blood and plasma as reference methods. They found that the plasma method showed a closer correlation, and suggested that "the strip serves to create an ultrafiltrate which results in only plasma actually coming to contact with the glucose-oxidase reagent."

This matter is of some importance because many studies have compared one manufacturer's meter with another and have often come to conclusions that may not be valid. In an unpublished study we performed in 1983, our finding that one brand of meter was more accurate than a competitor could be reversed by use of a plasma rather than a blood glucose reference method.

Perhaps readers of *Diabetes Care* or the strip manufacturers could shed some light on this matter to assist in the more appropriate evaluation of meters in the future.

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Reply

We agree with Dr. Cohen that glucose reagent-strip manufacturers should state how strips are calibrated to avoid the confusion and uncertainty over the use of plasma or whole blood in the reference method.

For the glucose reagent-strip test, it is a fallacy to assume that because plasma permeates the reagent pad and reacts with the reagent strip, plasma should be used in the reference method. The color formed on the reagent strip is correlated to a glucose value, and this value could be obtained by any glucose method with either plasma or blood. Ames appears to use whole blood in their reference method because they have stated that Glucostix results should only be compared with the results of other whole-blood methods. It would therefore be wrong for investigators to do otherwise in their studies. We have used whole blood in our study and further report on the divergence in the glucose-concentration results at extremes of hematocrit concentrations. When plasma was used in the reference method, the same divergence in the results was seen. However, overestimation at 20% hematocrit was reduced slightly, but the underestimation at 60% hematocrit was increased. We also found that a second blot to remove blood from the test pad lowered the final result.

Earlier and unpublished studies on blood glucose monitoring have no place in our discussion because we are dealing with a newly formulated reagent strip.

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Acute Painful Diabetic Neuropathy

The article by Allen and MacDonald (1) illustrated a phenomenon that is increasingly recognized, i.e., the precipitation of painful neuropathy in diabetic patients after improved glycemic control. We have previously reported such an occurrence in an 18-yr-old brittle diabetic girl 6 wk after commencement of continous subcutaneous insulin infusion (CSII) with good control of glycemia (2). Persistent burning pain and paresthesias in both feet with severe cutaneous hyperesthesia developed acutely and worsened at night, initially requiring opiate analgesics for control. Other measures, including the use of a cooling fan, carbamazepine, and the combination of phenothiazine and tricyclic antidepressant drugs, provided only marginal benefit. With continued tight glycemic control, her symptoms improved after 14 wk and have remained reasonably well controlled since then. Sural nerve biopsy performed shortly after the onset of pain showed evidence of a chronic neuropathy with predominant small-fiber loss and prominent regenerative activity. Since we reported this case, we have observed an acute painful neuropathy in two other patients after the institution of insulin therapy and strict diabetic control. One of these was a 50-yr-old diabetic patient who developed a painful neuropathy with burning paresthesias within 6 wk of starting insulin; his HbA_1 was 7.2% (normal 5.5–8.5%), and sural nerve biopsy again showed marked regenerative activity.

A relationship between the onset of painful neuropathy and precipitous weight loss was observed by Archer et al. (3). Weight loss could be relevant in this context because it may result in a significant improvement in the quality of diabetic control. However, in the cases reported by Archer et al., stricter diabetic control and weight gain were followed by amelioration of symptoms. More recently, Steel et al. (4) documented four female cases with poorly controlled insulin-dependent diabetes and anorexia nervosa in whom the onset of painful neuropathy coincided with maximal weight loss. They stated that there was no change in glycosylated hemoglobin levels during the development of the acute neuropathy. This group is probably distinct from those whose symptoms follow the initiation of diabetic treatment or improvement of existing control.

Uncertainty as to the nature of the underlying pathophysiology of painful diabetic neuropathy makes rational treatment difficult (5). Steel et al. (4) suggested that nutritional factors could be important in their group of anorexic women. Whether this is due to a deficiency of specific vitamins or minerals is not known. A preliminary study with γ-linolenic acid treatment in diabetic neuropathy showed improvement in physiological parameters (6). A deficiency of certain essential fatty acids could contribute to the development of painful diabetic neuropathy. Continuous good glycemic control is important, perhaps with CSII (7). Aldose reductase inhibitors have only been shown to be of possible benefit in chronic painful diabetic neuropathy (8,9), and their long-term efficacy has not been proven.

It is relevant that the introduction of strict diabetic control after a protracted period of badly controlled diabetes can also result in deterioration of a preexisting retinopathy (10) and the occurrence of retinopathy de