mias, was not included in the original screening panel for the selection of a monoclonal anti-methadone antibody. With the feedback from users such as Lichtenwalner (DrugScan, Inc.), we confirmed that verapamil and its metabolites did cause false-positive responses in our methadone enzyme immunoassay (EIA). Verapamil was then included in our immediate selection effort of a new monoclonal anti-methadone antibody. We are happy to report that a new antibody without the interference by verapamil and its metabolites has been identified and used in the formulation of the methadone EIA assay since June 1997. With the methadone reagents manufactured before June 1997, verapamil parent drug at a concentration of 15 mg/L can give a positive response in the assay, whereas verapamil as high as 1 g/L will still give a negative response in the subsequent lots of reagent.

We agree with Lichtenwalner et al. (1) that immunological urine drug screen assays provide only a preliminary analytical result and should be used for excluding the presence of a particular drug in the sample. A more specific alternative analytical method such as HPLC or gas chromatography–mass spectrometry should be used for confirmation of positive results. We would like to thank our users who have constantly provided us with valuable feedback to assist us in improving the test devices.

References

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Three of the authors of the Technical

Brief cited above respond:

To the Editor:
We are pleased to find that the interferences mentioned in our publication (1) have been eliminated. Utilization of monoclonal antibodies has substantially increased the specificity of immunoassays in recent years. The fact that a 60-fold increase in the amount of verapamil still shows no cross-reactivity to the newly formulated methadone antibody should completely eliminate any further false-positive responses caused by verapamil.

References

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Diagnostic Criteria for Diabetes Mellitus

To the Editor:
In his editorial article (1), Dr. Sacks welcomes the new guidelines for diagnosis of diabetes published recently by the American Diabetes Association (ADA) (2). Replacement of the oral glucose tolerance test (OGTT) by measurement of fasting plasma glucose (FPG) on more than one occasion certainly simplifies the diagnostic procedure, and the chosen FPG cutoff of ≥7.0 mmol/L (≥126 mg/dL) appears to be almost as sensitive for diabetes detection as the OGTT 2-h plasma glucose (2hPG). Unfortunately, the situation is not quite as simple as that.

We recently conducted a survey of 401 nonpregnant subjects having OGTT because of suspected diabetes mellitus (3). The OGTT was performed according to WHO protocol and interpreted on the basis of the 2hPG value. The prevalence of diabetes in this population according to the results of the OGTT was 44.4%, compared with 41.4% by the ADA FPG criterion. This is in line with the ADA’s data on the different sensitivities of the two tests and suggests that they are giving approximately the same answers. However, when we compared results by the two methods for individual patients, the agreement was not always so good. Of 178 patients positive for diabetes by 2hPG, only 139 were positive by the ADA FPG criterion, which means the latter gave 39 (22%) false negatives if the OGTT 2hPG is regarded as the reference method. This discrepancy was not immediately apparent in the prevalence figures because 27 other subjects were falsely positive by the ADA criterion, and these partially balanced the false negatives. In its overall view of the situation, the ADA seems to have omitted considering in any detail the possibility of a substantial number of individual discrepancies within the population. Furthermore, subjects whose FPG is lower than 6.1 mmol/L (110 mg/dL) are regarded by the ADA criteria as normal; available evidence, however, suggests that an appreciable proportion of diabetics have FPG below this (4, 5), and our recent survey confirms it. Eighteen out of 178 subjects with a diabetic OGTT 2hPG had FPG below 6.1 mmol/L (110 mg/dL).

Owing to the change from the OGTT to FPG, the term impaired glucose tolerance (IGT) has had to be replaced by impaired fasting glucose (IFG), the latter being FPG in the range 6.1–6.9 mmol/L (110–125 mg/dL) inclusive. In our survey, 94 subjects fell into the IGT category, but only 27 of these met the criteria for IFG. Therefore, the two categories cannot really be regarded as equivalent.

Similar discrepancies between the two methods of classification were recently reported by Harris et al. (6). In an assessment of the prevalence of undiagnosed diabetes in a population, the ADA criteria detected 4.4% compared with 6.4% by WHO crite-
ria; however, 1.0% of the ADA figure were subjects classified by WHO as IGT or normal, and 3.0% of the WHO “diabetics” were classified as IFG or normal by the ADA method. This means that in their study almost one-half of those diagnosed as diabetic by WHO were considered nondiabetic by ADA.

Although we welcome attempts to simplify diagnostic testing for diabetics, it should be realized that although the proposed ADA changes may not greatly affect population prevalence figures for diabetes, the identities of the subjects constituting the various categories may show some differences, and some patients classified as diabetic by one method may not be by the other procedure. We fully accept that in many cases it is unnecessary to perform an OGTT to make a diagnosis, but we believe that comparison of the new ADA and WHO 1985 systems would reveal considerable numbers of diagnostic discrepancies at the lower levels of glucose intolerance. The argument that the new criterion should increase the number of diagnosed patients is only valid if one assumes that hitherto they would have been assessed solely on the higher FPG cutoff. Although there may be valid arguments for changing the protocol for diagnosing diabetes, clinical chemists should not fall into the trap of thinking that the new ADA criteria are a straightforward substitute for the OGTT and will produce the same results for individual patients. An epidemiologist wanting to ascertain the diabetes prevalence in a population might be forgiven for taking this view, but try convincing the patient who might now be told he is no longer diabetic based on ADA criteria after being diagnosed as such by the OGTT and perhaps having had restrictions placed on his life insurance or even his driving license!

References

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Dr. Sacks responds:

To the Editor:

It is widely recognized that diagnosis of diabetes mellitus by fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT) are not equivalent. This disparity was one of the two primary motivations for revising the diagnostic criteria and lowering the FPG threshold [the other was to encourage use of the FPG instead of the OGTT (see below)] (1). Despite this change, the Expert Committee recognized the lack of correlation between the two tests and conceded that simultaneous measurement of FPG and 2-h postload glucose would lead to some diagnostic discrepancies. Two large studies (2, 3) published after the editorial was written, one by a member of the Expert Committee (2), clearly demonstrate this predicament.

Furthermore, it was acknowledged that diagnosing diabetes by the FPG alone would yield a prevalence lower than that obtained by the OGTT [see Table 4 in the report by the American Diabetes Association (1)]. The OGTT is more sensitive than the FPG because, as previously indicated (4), impaired release of insulin in response to glucose develops early in the course of type 2 diabetes; increased fasting glucose is a later manifestation. Thus, the observation by Wiener and Roberts that 18 of the 178 subjects with a “diabetic” OGTT had FPG <6.1 mmol/L (110 mg/dL) is not unexpected and corroborates the findings by Tanaka et al. in 2121 individuals (3).

An element of fundamental importance that confounds interpretation of their data was omitted from the letter by Wiener and Roberts; namely, the lack of reproducibility of the OGTT. This finding has been documented by multiple studies. For example, a group of 334 apparently healthy volunteers underwent six OGTTs over a period of 1 year. Using US Public Health Service criteria (the study antedated the recommendations of the 1979 National Diabetes Data Group), 29 subjects (9%) had abnormal results on at least one test, but none had all six tests abnormal (5). Moreover, of the seven individuals who were classified with diabetes, six were diagnostic on only one of the OGTTs. Another evaluation in 26 healthy subjects and 32 offspring of conjugal diabetic parents demonstrated that only about 50% of two OGTTs were reproducible (6). More recently, 524 subjects without a history of diabetes mellitus were evaluated with two OGTTs performed 2–6 weeks apart (7). Of the 198 patients classified with impaired glucose tolerance by the first OGTT using WHO criteria, 78 (39%) and 25 (13%) were classified with normal glucose tolerance and diabetes, respectively, by the second OGTT. Thus, if the initial OGTT is used as the gold standard, a repeat OGTT will “misclassify” ~50% of subjects with initial values near the cutoff. For this reason, the National Diabetes Data Group emphasized that it was imperative (emphasis added) that the OGTT be abnormal on more than one occasion for a diagnosis of diabetes to be established (8).

These factors were recognized in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes (1). The principal reason
to diagnose and treat diabetes is to decrease the risk of complications. Accordingly, the revised cutoff for FPG was established on the basis of the risk for the development of complications of diabetes. Analysis of several studies revealed that the approximate thresholds for increased risk of retinopathy and microvascular and macrovascular disease were 6.9 mmol/L (125 mg/dL) and 11.1 mmol/L (200 mg/dL) for fasting and 2-h postload glucose concentrations, respectively (1). Thus, FPG and the OGTT have approximately equal predictive value for the most pertinent and practical clinical outcome of diabetes, namely the development of long-term complications. Since it is less complex, less expensive, more reproducible, more readily obtained, and more acceptable to patients than the OGTT, the FPG should be the primary strategy for the assessment of glycemia.

Notwithstanding this recommendation, measurement of blood glucose concentrations is an imperfect method for identifying individuals with diabetes mellitus (4). Blood glucose concentrations are a continuum, and there is no absolute threshold for the development of complications, necessitating a somewhat arbitrary choice of cutoff. The advent of molecular and immunological assays that are capable of accurately diagnosing diabetes is eagerly awaited.

Effect of Antiresorptive Therapy on Day-to-Day Variation of Urinary Free Deoxypyridinoline Excretion

To the Editor:

Measurement of bone markers provides information about bone resorption and formation. One of the proposed clinical applications is to monitor antiresorptive therapy (1); however, this could be precluded because bone markers show day-to-day and circadian variation (2–6). High intradividual variation might be the principal cause of limited utility in the individual patient. Most of the studies on variability were done in untreated individuals. Therefore we decided to evaluate the effect of antiresorptive therapy on day-to-day variation of urinary free deoxypyridinoline (DPD).

Eight postmenopausal women (mean age, 62.5 ± 3.9 years) were studied. They all had osteoporosis (defined according WHO densitometric criteria) and pretherapy baseline DPD values above the upper limit of the reference interval (3–8 μmol/mol creatinine) with a mean ± SD of 10.83 ± 2.81 μmol/mol creatinine. Women were placed on therapy (10 mg of alendronate plus evening supplementation of 1000 mg calcium) for at least 6 months. Day-to-day variability was studied after 6 months to avoid the period of very dynamic changes in DPD as it responds to treatment. Five second void morning urine samples were collected with 2-day intervals for each patient. Samples were all collected between 0800 and 1000 because untimed urine collections would potentiate intradividual variability. DPD was measured by ELISA (Pyrilinks-D, Metra Biosystems) following the manufacturer’s instructions. All 40 samples were measured in duplicate in one batch, and results are expressed as μmol DPD/mol creatinine. The within-run analytical imprecision (CV) was <4%. The mean day-to-day CV was 12%, with a range of 5–15%. These values were considerably lower than those reported for untreated premenopausal women (mean CV, 16%; range, 7–25%) (4). To our knowledge, these are the first data on day-to-day variation of bone resorption markers under treatment. The lower variation observed herein would be explained by changes in the diurnal rhythm induced by treatment. Sarainen et al. (7), in a short-term treatment with clodronate, observed a nonsignificant trend in suppression of the diurnal rhythm of cross-linked N-telopeptides of type I collagen (NTx) excretion and no indication of such suppression in two other markers of bone resorption. Greenspan et al. (8) found no effect of 5 mg/day alendronate in a short-term treatment with clodronate, observed a nonsignificant trend in suppression of the diurnal rhythm of cross-linked N-telopeptides of type I collagen (NTx) excretion and no indication of such suppression in two other markers of bone resorption. Greenspan et al. (8) found no effect of 5 mg/day alendronate on the day-night difference in NTx excretion. Thus, although our patients received a different dose (10 mg/day), an alendronate-induced alteration of the diurnal rhythm in DPD excretion seems unlikely. On the other hand, Blumsohn et al. (9) reported that evening supplementation with 1000 mg of calcium completely abolished the diurnal rhythm of total DPD. Therefore, in our patients calcium supplementation may have reduced day-to-day variability by a reduction of diurnal variation of DPD excretion. Additional studies are needed to completely clarify this issue.

After 6 months of antiresorptive therapy, DPD concentrations in all women decreased to within the ref-