The ADA has recently revised its guidelines to include the category of "impaired glucose tolerance" (FPG 6.1–6.9 mmol/l [110–125 mg/dl]) and has lowered the threshold for clinical diabetes from 7.8 to 6.9 mmol/l (140 to 126 mg/dl) (9). The implications of these new guidelines, as well as recent findings on tight control of diabetes (4–6) and the recommendations that beta-blockers be used in diabetic patients at risk of myocardial infarction for secondary prevention (10), raise the concern that there may be more cases like the one reported.

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Glycosylated Hemoglobin Levels and New Diagnostic Criteria

The recent American Diabetes Association (ADA) expert committee report (1) has revised the diagnostic criteria for diabetes by lowering the fasting plasma glucose (FPG) level from 140 mg/dl (7.77 mmol/l) to 126 mg/dl (7.0 mmol/l). The ADA report has also introduced a new statistical risk group called "impaired fasting glucose" (IFG), which is based on an FPG value of 110–125 mg/dl. There are no data on HbA_{1c} levels in relation to the new diagnostic criteria.

The present study is based on an analysis of 2,635 oral glucose tolerance tests (OGTTs) and HbA_{1c} measurements done during a 3-year period from 1 April 1994 to 31 March 1997. All OGTTs were done using a 75-g oral glucose load, with World Health Organization study group recommendations (2). Pregnant women were not included in the analysis. Fasting and half-hourly venous plasma (EDTA) samples up to 2 h were used for glucose estimations, which were done within 15 min of sample collection by the glucose oxidase method, using kits provided by Boehringer Mannheim (Mannheim, Germany) on a Ciba Corning Express Plus Auto Analyzer (Medfield, MA). Quality control was done on a daily basis, and the coefficient of variation for glucose was <3.0%. HbA_{1c} was measured using a dedicated high-performance liquid chromatography system (Variant; BioRad, Hercules, CA). Our center is certified by the unity quality control program of BioRad for precision in HbA_{1c} estimation.

The new categories of glucose intolerance were based on the FPG of the individuals (1). Impaired glucose tolerance (IGT) was diagnosed based on the 2-h plasma glucose (2). Nondiabetic healthy control subjects were selected from an ongoing epidemiology study.

Table 1 presents the HbA_{1c} levels for the different categories of glucose intolerance. HbA_{1c} levels of the IFG and IGT patients were significantly different from those of control subjects and type 2 diabetic patients. The HbA_{1c} levels and the 2-h plasma glucose levels of the subjects with IFG were significantly higher than those of the subjects with IGT ($P < 0.001$).

To our knowledge, there are no data available on the HbA_{1c} levels in different categories of glucose intolerance. We report that the levels of HbA_{1c} are higher in the statistical risk classes of diabetes, namely IGT and IFG, compared with those in healthy control subjects. This suggests that even at this stage of prediabetes, hemoglobin undergoes glycosylation, though it is below the value seen in subjects with type 2 diabetes (3). Our data also suggest that in those patients with IFG, the HbA_{1c} levels and 2-h plasma glucose values are higher than in those with IGT. These data could have significance for future epidemiological studies on diabetes.

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Table 1—*HbA_{1c} levels in patients from different categories of glucose intolerance*

	Control subjects	IFG patients	IGT patients	Type 2 diabetic patients
n	303	419	509	1,053
FPG (mg/dl)*	70 ± 12	117 ± 5	105 ± 14	142 ± 27
HbA_{1c} (%)*	5.3 ± 0.49	6.8 ± 0.9	6.3 ± 0.8	7.8 ± 1.4
2-h plasma glucose (mg/dl)*	94 ± 42	199 ± 58	168 ± 17	277 ± 59

*Groups are significantly different from each other ($P < 0.001$).

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COMMENTS AND RESPONSES

Response to Allen et al. and Holl et al.

I read with interest the recent article by Allen et al. and the letter by Holl et al. regarding the diagnosis of cystic fibrosis–related diabetes (CFRD) (1,2). CFRD has become increasingly common as cystic fibrosis (CF) patients survive longer. CFRD has distinctive clinical and pathological features compared with type 1 and type 2 diabetes (3), and this condition should be considered as a separate clinical entity. Allen et al. found that random blood glucose (RBG) was the most common method used in the diagnosis of CFRD in the centers studied. It is important to note that RBG has not been found to be sufficiently sensitive or specific in the diagnosis of CFRD. My colleagues and I had previously reported that even in CF patients with normal glucose tolerance, as defined by an oral glucose tolerance test (OGTT), the RBG can exceed 180 mg/dl, provided that a large enough glucose load is taken before blood sampling (4). This finding may be related to a more rapid gut absorption of glucose in patients with CF. Lanng et al. had also reported that whereas OGTT is the "gold standard" diagnostic method in the diagnosis of CFRD, fasting blood glucose and glycosylated hemoglobin are not sufficiently sensitive in the diagnosis of CFRD (5).

Between August 1996 and May 1997, 91 clinically stable adult CF patients (aged ≥16 years) who were not known to be diabetic and who were attending the adult CF clinic at the Royal Brompton Hospital in London (a national CF center) underwent OGTTs according to the standard protocol (6). All patients had RBG measured within 1 month before their OGTTs. The mean age of the studied patients was 27 years (range, 16–60), and the ratio of male to female subjects was 58:33. Of the 91 patients studied, 12 were found to have OGTT-defined diabetes; of these 12 patients, 3 had abnormal fasting blood glucose (>110 mg/dl) and 4 had abnormal RBG (>180 mg/dl). Thus, the sensitivities of the above-mentioned two methods in the diagnosis of CFRD (using OGTT as the "gold standard") were found to be only 25% (95% CI, 1–50) and 33% (7–60), respectively. These data confirm the point made by Holl et al. that OGTTs should be used in preference to other methods in the diagnosis of CFRD. Because there is evidence that the development of CFRD may be associated with a deterioration in patients' clinical status that may be reversed by prompt treatment (7), CF patients should be screened for diabetes regularly using OGTTs.

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Response to Yung

Should the oral glucose tolerance test be performed as a routine screening test for diabetes in cystic fibrosis patients?

Dr. Yung makes several valid and important points regarding screening for cystic fibrosis–related diabetes (CFRD). The purpose of our study surveying physicians' attitudes and practices for patients with CFRD was not to imply that these attitudes or practices are correct or well informed, but simply to report that this is what the U.S. physicians surveyed are doing. Dr. Yung's observation that random blood glucose (RBG) correlates poorly with glucose tolerance testing in adult British cystic fibrosis (CF) patients is important because there is no literature on the sensitivity or specificity of RBG or urine glucose measurements. Poor correlations between fasting blood glucose or HbA_{1c} and the oral glucose tolerance test (OGTT) have been described by several investigators (1–5), but not by all (6,7). Lanng et al. (3) found in a prospective study that only 16% of CF patients had abnormal elevations of HbA_{1c} on the day of a diabetic glucose response to the OGTT.

If CFRD is defined as diabetic glucose response to OGTT, then by definition the OGTT is 100% sensitive and specific for the diagnosis of CFRD. Defining diabetes in the general population has proved to be a challenge, and recently an Expert Committee on the Diagnosis and Classification has revised blood glucose criteria and de-emphasized the OGTT (8). It is not known whether these criteria are appropriate for the CF population. A factor that is important in determining a meaningful definition of diabetes in any population is whether identification of the disease allows for an intervention that improves outcome. Although some investigators describe a deterioration in clinical status that occurs