From the Editor:

As part of our mission to provide a forum in which important issues in Diabetes Care *can be raised and discussed, the editors have invited two leading experts to address the issue of screening for NIDDM. We are delighted to publish below the resulting, thoughtful, viewpoints of Drs. Maureen Harris, Michaela Modan, and William Knowler. Please let us know whether you feel this new format is helpful and what issues you would like addressed in a similar manner by writing to Allan L. Drash, M.D., Editor,* Diabetes Care *(Personal Views), Children's Hospital of Pittsburgh, 3705 Fifth Avenue, Rangos Research Center, Pittsburgh, PA 15213.*

Screening for NIDDM

Why is there no national program?

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Non-insulin-dependent diabetes mellitus (NIDDM) is a major clinical and public health problem in the U.S. The prevalence of NIDDM is 7% among all adults and reaches over 20% among those 65–74 years of age (1–3). NIDDM and insulin-dependent diabetes mellitus (IDDM) combined account for 50% of all nontraumatic amputations in the U.S., 15% of all blindness, and 35% of all end-stage renal disease (4). At least 50% of these events occur in NIDDM patients (5–7). Prevalence of neuropathy and ischemic heart disease in NIDDM and risk of death from cardiovascular disease is two to three times that of those without diabetes even after adjusting for other risk factors (8–13). Diabetes is estimated to cost the nation over $100 billion annually (14). Despite this profound impact, it is estimated that half of all NIDDM remains undiagnosed and, consequently, untreated (15). A concerted national effort to screen for undiagnosed NIDDM does not exist. This situation is in marked contrast to that of undiagnosed hypertension, undiagnosed hyperlipidemia, and undiagnosed breast cancer, for which major national programs have been instituted.

Diagnosis of NIDDM defines a group at high risk for micro- and macrovascular disease. The diagnostic criteria were established by the U.S. National Diabetes Data Group (NDDG) and the World Health Organization (WHO) in 1979–1980 (16,17). They were developed from long-term population-based studies in which individuals were administered a 2-h oral glucose tolerance test (OGTT) at baseline and were followed prospectively for deterioration of glucose tolerance and development of diabetes complications. The sentinel findings from these studies were that populations with high prevalence of NIDDM had a bimodal distribution of 2-h postchallenge plasma glucose, with the antimode at ~11.1 mM. In addition, microvascular complications specific to diabetes did not develop or were rare in subjects whose fasting plasma glucose (FPG) was <7.8 mM or whose 2-h postchallenge glucose was <11.1 mM. Subjects with fasting values ≥7.8 mM or 2-h postchallenge values ≥11.1 mM were at high risk for diabetic retinopathy and nephropathy. Based on this risk for microvascular complications, the NDDG and WHO established the criteria of FPG ≥7.8 mM or 2-h postchallenge glucose ≥11.1 mM after a 75-g OGTT as the diagnostic criteria for diabetes in asymptomatic subjects. Both the NDDG and WHO criteria require a repeat determination of FPG or postchallenge plasma glucose for a definitive diagnosis of diabetes; that is, in an asymptomatic patient the diagnosis cannot be made with a single glucose result. (For patients with symptoms of diabetes, a single elevated blood glucose value was considered sufficient for confirmation of the diagnosis.) The NDDG suggested that a mid-test OGTT value be ≥11.1 mM, but essentially all people meeting the 2-h criteria also meet this mid-test requirement (1). The recommendations of the NDDG and WHO have been accepted and endorsed by the American Diabetes Association and other national diabetes organizations representing the scientific bodies most concerned with diabetes.

Subsequent studies using these criteria have found that NIDDM onset occurs ~10 years before clinical diagnosis in populations that are not screened for diabetes (18). Micro- and macrovascular

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; NDDG, National Diabetes Data Group; WHO, World Health Organization.

complications begin to develop before diagnosis, and considerable morbidity exists in individuals with undiagnosed NIDDM. For example, diabetic retinopathy is estimated to become evident ~7 years before diagnosis of NIDDM (18), during which time no therapy is offered for the hyperglycemia that is the major risk factor for retinopathy and other microvascular complications. Retinopathy is present in 10–29% of patients at clinical diagnosis of NIDDM (18–22). Proteinuria has been found in 10–37% of newly diagnosed patients (23–25). Macrovascular disease risk factors and macrovascular disease are present even earlier, at the stage of impaired glucose tolerance (26,27). Synergism has been documented between diabetes and macrovascular disease risk factors, such that the adverse effect of diabetes on coronary heart disease is increased disproportionately in the presence of other risk factors (28,29). In adults with undiagnosed NIDDM in the U.S., prevalence of abnormal heart findings (22%), coronary heart disease (19%), peripheral vascular disease (10%), and neuropathy (9%) were similar to that found in established diabetes (15,26). Among newly diagnosed NIDDM cases in Finland, peripheral arterial disease was present in 20% and coronary heart disease in 59%, both of which were considerably more frequent than in nondiabetic control subjects (30,31). Risk factors for these complications are very common and are often found as frequently as in diagnosed NIDDM (15,26,30–36). Among adults with undiagnosed NIDDM in the U.S., prevalence of hypertension is 61%, hypercholesterolemia is 49%, low-density lipoprotein cholesterol >160 mg/dl is 40%, hypertriglyceridemia is 28%, obesity is 50% for males and 82% for females, and cigarette smoking is 32% (15). Clearly, NIDDM is being detected late in the natural history of the disease, when metabolic derangements are already established and clinical management is more difficult.

Despite the development of diagnostic criteria for NIDDM based on risk of complications, the worldwide endorsement of these recommendations by the diabetes community, and the high morbidity rates in patients with undiagnosed NIDDM, it appears that clinicians are not actively screening for the disease, because ~7 million adults may have undiagnosed NIDDM in the U.S. (2,15).

Screening for a disease implies identification, for the purpose of intervention, of individuals who are unaware of having the disease. Three major questions must be considered for NIDDM screening: *1*) Is undiagnosed NIDDM clinically important, conveying increased risk for morbidity and mortality?; 2) Is screening beneficial for patients at risk of diabetes?; and 3) What is the most effective screening method?

We have presented evidence above, garnered from numerous studies, that undiagnosed NIDDM probably has its onset ~10 years before clinical diagnosis, that individuals with undiagnosed NIDDM have a substantial prevalence of micro- and macrovascular complications, and that risk factors for these complications are very frequent in these individuals.

It has been argued that screening for asymptomatic NIDDM is unnecessary, because there is no proven benefit in its early detection (37,38), although others have refuted this argument (15,39). This opposition to screening is based primarily on the fact that controlled intervention studies demonstrating the effectiveness of treatment for hyperglycemia in reducing or preventing complications in NIDDM have not yet been conducted. However, such conclusive evidence for IDDM has been presented recently. The Diabetes Control and Complications Trial showed substantial reductions in retinopathy, nephropathy, neuropathy, and macrovascular disease events with intensive therapy to control blood glucose (40). Importantly, the rate of progression of retinopathy decreased continuously with decreasing glycemia, which suggests that any improvement in glycemic control will be beneficial (41). A similar reduction of complications through control of hyperglycemia can likely occur in NIDDM. A large body of evidence has established that hyperglycemia is the proximate cause of the microvascular and neuropathic complications of diabetes, regardless of the type of diabetes. Substantial hyperglycemia is found in subjects screened by OGTT and discovered to have NIDDM. The mean FPG level is 7.6 mM, and the mean 2-h postchallenge glucose level is 14.6 mM. Over 31% have FPG >7.8 mM, and 45% have postchallenge glucose >13.9 mM (15). If such values were found in a patient with known diabetes, the clinician would surely institute hypoglycemic treatment, either by dietary therapy or oral agents.

Substantial additional evidence indicates that intervention and treatment will improve the prognosis of individuals who are screened and found to have NIDDM. Weight reduction, appropriate diet composition, and increased physical activity will improve glucose tolerance (42–50), reduce blood pressure (47,51-53), and correct lipoprotein abnormalities (42,54–57). Dietary management and treatment of hypertension may prevent or even reverse diabetic nephropathy (58–60), and blood pressure control can prevent cerebrovascular complications (61,62). Cessation of cigarette smoking is accompanied by improved lipoprotein profile and cardiovascular risk (63,64). Thus, the evidence strongly indicates that early detection and intervention with diet, weight control, exercise, and medication to reduce blood glucose, blood pressure, and hyperlipidemia will improve prognosis in NIDDM. Most importantly, if the clinician is aware that the patient has diabetes, it is likely that a more aggressive program for treatment and reduction of micro- and macrovascular risk factors will be pursued.

The OGTT is the internationally recognized standard for diagnosing asymptomatic diabetes (16,17), but the perceived complexity of the OGTT seems to make it an unpopular test, and fasting or casual glucose is preferred. These latter

are unsatisfactory tests for screening. Only ~31% of diabetes cases are detected when FPG ≥7.8 mM is used; screening using lower fasting cutoff values results in undesirably low specificity and positive predictive value (this issue, M. Modan, M.I. Harris, p. 436–439). Casual blood glucose cannot be standardized with respect to detecting diabetes because of the considerable fluctuations of plasma glucose levels according to time since the previous meal and the unstandardized content of the meal, and thus it provides potentially misleading information to the clinician about the patient's glycemia. Glycosylated hemoglobin has the same advantage as fasting glucose in that it requires minimal patient cooperation and is not affected by time of day or recent food intake; however, it is unsatisfactory for screening because of the considerable overlap between diabetic and nondiabetic groups in its distribution (65–69). We believe the OGTT should be endorsed as the primary screening method because the complexity of this test is more than balanced by its sensitivity, specificity, and positive predictive value. This complexity may be merely a perception, because only a single 2-h postchallenge glucose measurement is needed for screening purposes. FPG, however, may detect a group of NIDDM patients at higher risk for complications than those with postchallenge hyperglycemia alone.

We believe that screening for NIDDM is an important health promoting measure. This is particularly true for obese and hypertensive patients who are at high risk for NIDDM. Moreover, patients with both diabetes and hypertension are at the highest risk for developing micro- and macrovascular complications, and early follow-up and treatment of these individuals is essential. In community screening programs where considerations of cost and efficiency are important, restricting screening to individuals who are obese and/or hypertensive might be considered. In the clinical setting, it is important to incorporate periodic screening for diabetes into routine follow-up of at-risk patients.

Treatment for newly diagnosed patients should include a program of diet, physical activity, weight maintenance/reduction, and hypoglycemic medication to address the patient's hyperglycemia and insulin resistance. Vigorous attention should be paid to the treatment of risk factors for micro- and macrovascular disease including hyperglycemia, hypertension, dyslipidemia, obesity, and cigarette smoking.

References

1. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population. *Diabetes* 36:523–534, 1987
2. National Center for Health Statistics: *Current Estimates From the National Health Interview Survey, 1990*. Vital and Health Statistics, 1991 (Tech. Rep. Ser. 10, no. 181)
3. Harris MI: The epidemiology of diabetes mellitus among the elderly in the United States. *Clinics in Geriatric Medicine* 6:703–719, 1990
4. Harris M, Hamman R (Eds): *Diabetes in America*. Washington, DC, U.S. Govt. Printing Office, 1985 (NIH publ. no. 85–1468)
5. Moss SE, Klein R, Klein BE: The prevalence and incidence of lower extremity amputation in a diabetic population. *Arch Intern Med* 152:610–616, 1992
6. Moss SE, Klein R, Klein BE: The incidence of vision loss in a diabetic population. *Ophthalmology* 95:1340–1348, 1988
7. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM: Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–1079, 1989
8. Harris MI, Cowie CC, Eastman RC: Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population. *Diabetes Care* 11:1446–1152, 1993
9. Kleinman JS, Donahue RP, Harris MI, Finucane FF, Madans JH, Brock DB: Mortality among diabetics in a national sample. *Am J Epidemiol* 128:389–401, 1988
10. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men. *JAMA* 265:627–631, 1991
11. Abbott RD, Donahue RP, Kannel WB, Wilson PWF: The impact of diabetes on survival following myocardial infarction in men vs. women: the Framingham study. *JAMA* 260:3456–3460, 1988
12. Eschwege E, Richard JL, Thibult N, Ducimetiere P, Warnet JM, Claude JR, Rossselin GE: Coronary heart disease mortality in relation with diabetes, blood glucose, and plasma insulin levels: the Paris Prospective Study ten years later. *Horm Metab Res* 15 (Suppl.):41–46, 1985
13. Mitchel BD, Hazuda HP, Haffner SM, Patterson JK, Stern MP: Myocardial infarction in Mexican Americans and non-Hispanic whites. *Circulation* 83:45–51, 1991
14. American Diabetes Association: *Direct and Indirect Costs of Diabetes in the United States in 1993*. Alexandria, VA, American Diabetes Association, 1993
15. Harris MI: Kelly West Lecture: Undiagnosed NIDDM, clinical, and public health issues. *Diabetes Care* 16:642–652, 1993
16. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
17. World Health Organization: *WHO Expert Committee on Diabetes Mellitus*. Geneva, World Health Org., 1980 (Tech. Rep. Ser., no. 646)
18. Harris MI, Klein RE, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 years before clinical diagnosis. *Diabetes Care* 15:816–822, 1992
19. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol* 102:527–532, 1984
20. Dolben J, Owens DR, Young S, Vora J, Atiea J, Dean J, Luzio S: Retinopathy at presentation in type II (non-insulin-dependent) diabetic patients. *Diabetic Med* 5 (Suppl. 2):20, 1988
21. Aldington SJ, Kohner EM, Nugent A: Retinopathy at entry in the United Kingdom

Prospective Diabetes Study (UKPDS) of maturity-onset diabetes. *Diabetic Med* 4:355, 1987
22. Haffner SM, Fong D, Stern MP, Pugh JA, Hazuda HP, Patterson JK, Van Heuven WAJ, Klein R: Diabetic retinopathy in Mexican Americans and non-Hispanic whites. *Diabetes* 37:878–884, 1988
23. Fabre J, Balant LP, Dayer PG, Fox HM, Vernet AT: The kidney in maturity-onset diabetes mellitus: a clinical study of 510 patients. *Kidney Int* 21:730–738, 1982
24. Haffner SM, Mitchell BD, Pugh JA, Stern MP, Kozlowski MK, Hazuda HP, Patterson JK, Klein R: Proteinuria in Mexican Americans and Non-Hispanic whites with NIDDM. *Diabetes Care* 12:530–536, 1989
25. Uusitupa M, Siitonen O, Penttila I, Aro A, Pyorala K: Proteinuria in newly diagnosed type II diabetic patients. *Diabetes Care* 10: 191–194, 1987
26. Harris MI: Impaired glucose tolerance in the U.S. population. *Diabetes Care* 12: 464–474, 1989
27. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
28. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, Arky RA, Speizer FE, Hennekens CH: A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 151:1141–1147, 1991
29. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the multiple risk factor intervention trial. *Diabetes Care* 16:434–444, 1993
30. Uusitupa M, Siitonen O, Aro A, Pyorala K: Prevalence of coronary heart disease, left ventricular failure, and hypertension in middle aged newly diagnosed type II (non-insulin-dependent) diabetic subjects. *Diabetologia* 28:22–27, 1985
31. Siitonen O, Uusitupa M, Pyorala K, Voutilainen E, Lansimies E: Peripheral arterial disease and its relationship to cardiovascular risk factors and coronary heart disease in newly diagnosed non-insulin-dependent diabetics. *Acta Med Scand* 220: 205–212, 1986
32. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, Chetrit A, Fuchs Z: Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 75:809–817, 1985
33. Harris MI: Hypercholesterolemia and glucose intolerance in the U.S. population. *Diabetes Care* 14:366–374, 1991
34. Howard BV, Knowler WC, Vasquez B, Kennedy AL, Pettitt DJ, Bennett PH: Plasma and lipoprotein cholesterol and triglyceride in the Pima Indian population: comparison of diabetics and nondiabetics. *Arteriosclerosis* 4:462–471, 1984
35. Modan M, Halkin H, Lusky A, Segal P, Fuchs Z, Chetrit A: Hyperinsulinemia is characterized by jointly disturbed plasma VLDL, LDL, and HDL levels. *Arteriosclerosis* 8:227–236, 1988
36. Laaksu M, Barrett-Connor E: Asymptomatic hyperglycemia is associated with lipid and lipoprotein changes favoring atherosclerosis. *Arteriosclerosis* 9:665–672, 1988
37. Singer DE, Samet JH, Coley CM, Nathan DM: Screening for diabetes mellitus. *Ann Intern Med* 109:639–649, 1988
38. Singer DE, Nathan DM: Screening for diabetes mellitus. *Guide to Clinical Preventive Services*. U.S. DHHS, 1989
39. Harris MI: Screening for undiagnosed non-insulin-dependent diabetes. In *Proceedings of the Symposium on Research and Clinical Frontiers in Diabetes*. KGGM Alberti, Ed. New York, Elsevier, 1989, p. 119–131
40. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
41. Eastman RC, Siebert CW, Harris M, Gorden P: Implications of the Diabetes Control and Complications Trial. *J Clin Endocrinol Metab* 77:1105–1107, 1993
42. Olefsky JM, Reaven GM, Farquhar JW: Effects of weight reduction on obesity: studies of lipid and carbohydrate metabolism in normal and hyperinsulinemic subjects. *J Clin Invest* 53:64–76, 1974
43. Doar JWH, Thompson ME, Wilde CE, Sewel CE: Influence of treatment with diet alone on oral glucose tolerance test and plasma sugar and insulin levels in patients with maturity onset diabetes mellitus. *Lancet* 1:1263- 1266, 1975
44. Snowdon DA, Phillips RL: Does a vegetarian diet reduce the occurence of diabetes? *Am J Public Health* 75:507–512, 1985
45. Marshall JA, Hamman RF, Baxter J: High-fat, low-carbohydrate diet and the etiology of non-insulin-dependent diabetes mellitus: The San Luis Valley Diabetes Study. *Am J Epidemiol* 134:590–603, 1991
46. Feskens EJM, Bowles CH, Kromhout D: Carbohydrate intake and body mass index in relation to the risk of glucose intolerance in an elderly population. *Am J Clin Nutr* 54:136–140, 1991
47. Krotkiewsky M, Mandroukas M, Sjostrom L, Sullivan L, Witterquist H, Bjorntorp P: Effects of long-term physical training on body fat, metabolism, and blood pressure in obesity. *Metabolism* 28:650–658, 1979
48. Modan M, Lubin F, Lusky A, Chetrit A, Fuchs Z, Halkin H: Interrelationships of obesity, habitual diet, physical activity, and glucose intolerance in the four main Israeli Jewish ethnic groups: the Israel Glucose Intolerance, Obesity, and Hypertension (GOH) Study. In *Recent Advances in Obesity Research*. Berry EM, Blondheim SH, Eliahou EH, Shafrir E, Eds. London, Libbey, 1987, p. 46–59
49. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
50. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325: 147–152, 1991
51. Tuck ML, Sowers J, Dornfeld L, Kledzik G, Maxwell M: The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *N Engl J Med* 304:930–933, 1981
52. Langford HG: Non-pharmacological ther-

apy of hypertension. *Hypertension* 13 (Suppl. 1):98–102, 1989
53. Urata H, Tanabe Y, Kiyonaga A: Antihypertensive and volume depleting effects of mild exercise on essential hypertension. *Hypertension* 9:245–252, 1987
54. Shonfeld G, Patsch W, Rudell LL, Nelson C, Epstein M, Olson RE: Effects of dietary cholesterol and fatty acids on plasma lipoproteins. *J Clin Invest* 69:1072–1080, 1982
55. Howard BV, Abbott WGH, Swinburn BA: Evaluation of metabolic effects of substitution of complex carbohybrates for saturated fat in individuals with obesity and NIDDM. *Diabetes Care* 14:786–795, 1991
56. William PT, Krauss RM, Vranizan KM, Albers JJ, Terry RB, Wood PDS: Effect of exercise-induced weight loss on low-density lipoprotein subfractions in healthy men. *Arteriosclerosis* 9:623–632, 1989
57. Blumenthal JA, Matthews K, Fredrikson M, Rifai N, Schniebolk S, German D, Steege J, Rodin J: Effect of exercise training on cardiovascular function and plasma lipids, lipoprotein and apolioprotein concentrations in premenopausal and postmenopausal women. *Arteriosclerosis* 11:912–917, 1991
58. Parving H-H, Andersen AR, Smidt UM, Svendsen PA: Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1:1175–1179, 1983
59. Vasquez B, Flock EV, Savage PJ, Nagulesparam M, Bennion LJ, Baird HR, Bennett PH: Sustained reduction of proteinuria in type II (non-insulin-dependent) diabetes, following diet induced reduction of hyperglycemia. *Diabetologia* 26:127–133, 1984
60. Aubia J, Hojman L, Chine M, Lloveras J, Masramon J, Llorach I, Cuevas X, Puig JM: Hypertension and nephrotoxicity in the rate of decline in kidney function in diabetic nephropathy. *Clin Nephrol* 27:15–20, 1987
61. Herbert PR, Fiebach NH, Eberlein KA, Taylor JO, Hennekens CH: The community based randomized trials of pharmacologic treatment of mild to moderate hypertension. *Am J Epidemiol* 127:581–590, 1988
62. Bonita R, Beaglehole R: Does treatment of hypertension explain the decline in mortality from stroke. *Br Med J* 292:141–142, 1986
63. Halkin H, Or J, Fuchs Z, Lusky A, Chetrit A, Modan M: Smoking accounts for adverse effect of antihypertensive medications on plasma lipids: a population-based study. *Hypertension* 14:210–217, 1989
64. Heyden S, Heiss G, Manegold C, Tyroler HA, Hames CG, Bartel AG, Cooper G: The combined effect of smoking and coffee drinking on LDL and HDL cholesterol. *Circulation* 60:22–25, 1979
65. Modan M, Halkin H, Karasik A, Lusky A: Effectiveness of glycosylated hemoglobin, fasting plasma glucose, and a single post load plasma glucose level in population screening for glucose intolerance. *Am J Epidemiol* 119:431–444, 1984
66. Orchard TJ, Daneman B, Becker DJ, Kuller LH, LaPorte RE, Drash AL, Wagener D: Glycosylated hemoglobin: a screening test for diabetes mellitus? *Prev Med* 11:595–601, 1982
67. Lester E, Frazer AD, Shepherd CA: Glycosylated hemoglobin as an alternative to the glucose tolerance test for the diagnosis of diabetes mellitus. *Ann Clin Biochem* 22: 74–78, 1985
68. Little RR, England JD, Wiedmeyer HM, McKenzie EM, Pettitt DJ, Knowler WC, Goldstein DE: Relationship of glycosylated hemoglobin to oral glucose tolerance. *Diabetes* 37:60–64, 1988
69. Guillausseau PJ, Charles MA, Paolaggi F, Timsit J, Chanson P, Peynet J, Godard V, Eschwege E, Rousselet F, Lubetzki J: Comparison of HbA_1 and fructosamine in diagnosis of glucose-tolerance abnormalities. *Diabetes Care* 13:898–900, 1990