These two conditions are considered variants of the same defect of the stimulatory guanine nucleotide-binding (Gs) protein of adenylate cyclase, which is necessary for parathyroid hormone and other hormones such as gonadotropin, beta-adrenergic agonist, and thyrotropin to use cAMP as an intracellular second messenger.

We described two related women with apparent AHO and late-onset diabetes. Both patients had normal serum calcium levels, normal parathyroid hormone levels, and the characteristic somatic features of short stature, round face, obesity, and shortened fourth and fifth metacarpals and metatarsals, consistent with pseudo-PHP.

Both disorders, PHP and pseudo-PHP, can occur within the same family, and there is accumulating evidence that genomic imprinting is involved in the disease (1). Full phenotypic expression (AHO and parathyroid hormone resistance, as in PHP type Ia) occurs in maternally transmitted cases, whereas partial expression (AHO without parathyroid hormone resistance, as in pseudo-PHP) occurs when the gene is paternally transmitted. The pedigree of our patients showed genetic transmission from their father.

Patients with type 2 diabetes have defects in insulin action, abnormal insulin secretion, and increased hepatic glucose production. Although precise pathways responsible for these defects have not been thoroughly identified, they are likely to be genetically heterogenous with mutations in several different genes that are able to cause hyperglycemia. Some reported genetic loci for type 2 diabetes have been mapped on chromosome 20q, chromosome 7p, chromosome 12q, chromosome 2, and so forth (2,3).

In most cases of AHO, reduced levels of Gs protein α subunit (Gsα protein) have been found. A number of deactivating mutations in the gene for Gsα protein located on chromosome 20q13 have been described for this disorder (1), but del(2)(q37) has also been described in some AHO patients (4) and thus explains the heterogeneity observed in this AHO disorder.

PHP type Ia or pseudo-PHP is assumed to be a Gsα protein problem and this protein is encoded by chromosome 20q13. 2–3. Occasionally, these disorders may be associated with resistance of diverse target tissues to hormones and neurotransmitters whose actions require stimulation of adenylate cyclase and thus open calcium channels. It should be considered whether this Gsα protein problem will lead to diabetes with insulin resistance. Certainly, either these pseudo-PHP women with type 2 diabetes have a mutation in the Gsα protein or nearby genome for its susceptibility to type 2 diabetes, or they represent just a phenomenon of coincidence. Further evaluation and collection of cases are necessary to define the possible role and interrelationship of pseudo-PHP and type 2 diabetes.

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High Prevalence of Albuminuria Among African-Americans With Short Duration of Diabetes

There is controversy regarding the prevalence of albuminuria in urban African-American patients with newly diagnosed type 2 diabetes. In Atlanta, we found significant albuminuria in 30–36% of patients with diabetes of <1 year's duration (1), while the New York sample described by Chaiken et al. (2) had a prevalence of only 3%. To resolve this issue, we examined albumin excretion in a large group of patients with type 2 diabetes.

Between October 1992 and January 1998, 3,091 African-American patients with type 2 diabetes presented to the Grady Diabetes Clinic for a first visit and had measurements of urine albumin excretion. As described previously (1), albumin-to-creatinine ratios were measured in untimed urine specimens; such determinations correlate well with measurements of 24-h urine albumin (1,2). Patients were divided into those with diabetes diagnosed either <1 year (n = 1,533) or ≥1 year previously (n = 1,558).

Patients with diabetes duration ≥1 year, compared with those with duration <1 year, had significantly higher age (53.9 years vs. 51.0 years), HbA_{1c} (9.5 vs. 9.2%), mean blood pressure (96 vs. 93 mmHg), and serum creatinine (97 vs. 88 μmol/l) ($P < 0.01$ for each comparison). Of patients with duration <1 year, 20% had microalbuminuria (30–300 mg/g creatinine) and 4% had nephropathy (>300 mg/g). Corresponding prevalences for those with duration ≥1 year were significantly higher, at 26 and 13%, respectively ($P < 0.05$). Even normotensive patients with diabetes duration <1 year had a 17% rate of microalbuminuria and a 2% rate of nephropathy. Hypertensive patients with diabetes of any duration had a significantly increased rate of microalbuminuria and nephropathy compared with normotensives ($P < 0.05$). Thus, both hypertension and longer duration of diabetes increased the prevalence of significant albuminuria.

To determine contributing factors, we performed stepwise regression. In patients with known duration of diabetes <1 year, the quantity of albuminuria correlated positively with higher levels of systolic blood pressure, serum creatinine, fasting plasma glucose, BMI, male sex, and fasting plasma C-peptide. Other parameters, such as age, diastolic blood pressure, and HbA_{1c}, did not contribute significantly. When patients with diabetes of any duration were considered, albuminuria correlated positively with systolic blood pressure, fasting C-peptide, fasting serum glucose, HbA_{1c}, serum creatinine, age, and duration of diabetes.

We conclude that renal damage is common in African-Americans with diabetes, even in recently diagnosed patients without hypertension. Our criteria for albuminuria are standard, but even a cutoff of 50 mg/g would identify an 11% prevalence of microalbuminuria among normotensive patients with duration of diabetes <1 year. The presence of renal damage in our analysis is comparable to that in a European population with type 2 diabetes (3). However, the basis for the discrepancy between these results and those of Chaiken et al. remains unclear. Harris et al. (4) estimate that diabetes may begin 9–12 years before diagnosis; the observations by Chaiken et al. could reflect earlier diagnosis in New York than in Atlanta or Denmark. The discrepancy could also reflect genetic differences in susceptibility to diabetic nephropathy. Clearly, aggressive screening is needed to permit early detection and appropriate treatment.

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COMMENTS AND RESPONSES

Use of HbA_{1c} in Screening for Diabetes

We wish to comment on the report by Kilpatrick et al. that appeared in the February 1998 issue of *Diabetes Care* (1).

The concepts of screening and cutoff levels are being used in clinical medicine for the purpose of detecting individuals with a particular risk, present or future, of having or developing a certain disease. In the case of diabetes, the risk to search for is the development of long-term complications. The threshold or cutoff value is fixed arbitrarily according to the purpose of the study: to identify all or almost all subjects at risk, or only those whose risk is great. Feasibility and economic factors are also taken into account. The cutoff levels for HbA_{1c} used in various studies were based on the undisputed fact that above a certain level, the risk of developing chronic diabetic complications increases markedly (2–4). In the hypothetical example given by Kilpatrick et al. of two people whose intraindividual HbA_{1c} levels occupy both extremes of the normal population distribution curve, what really matters is not whether they are more or less close to the threshold. The relevant issue is that if they reach or cross the threshold, their risks for developing complications will become comparably high. While it is true that the subject whose HbA_{1c} levels were closer to the cutoff point has a greater probability for this occurring than the one with the lower HbA_{1c} values, what screening means is to find those individuals who already have that risk at the time the test is made to offer them the appropriate counseling on further diagnostic testing or preventive measures.

We wonder if the authors of the report have done a similar evaluation with the fasting plasma glucose values taken simultaneously with the HbA_{1c} measurements, since the fasting glucose has been recommended for screening purposes in the recent report of the American Diabetes Association Expert Committee on Diagnosis and Classification of Diabetes Mellitus (5). We suspect that the variation and indexes of individuality might be quite similar to those of HbA_{1c}. If that was not the case, it is remarkable that it was not mentioned in the paper.

Finally, we ask ourselves whether, with the authors' reasoning, we would have to question most screening methods that use threshold values to pinpoint individuals at risk for various diseases, such as serum cholesterol levels (there are normal subjects with mean levels of 150 mg/dl and others with 195 mg/dl) or blood pressure (normal subjects with 90/50 and others with 135/85).

We feel that despite the theoretical data presented by Kilpatrick et al., the idea of determining a particular threshold value of HbA_{1c} for screening purposes is valid, as has been shown in practice by several field studies (3,6). Efforts should continue to reach a consensus about the best methods and cutoff levels to be recommended for high-risk populations.

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