SUMMARY Glycosylated hemoglobin concentration (GHb), which is considered an indication of glycemia over the preceding several months, was examined in 50 patients hospitalized for recent stroke or transient ischemic attacks (TIA), and compared to that in several reference populations. Patients with stroke or TIA had GHb (mean % A1c ± SD, 10.2 ± 2.3) higher than in hospital controls without cerebrovascular disease (8.3 ± 0.9, p < 0.005), and equivalent to values for ambulatory diabetic patients treated with diet or diet plus oral agents (9.5 ± 2.4) or with insulin (10.7 ± 2.9). Twenty percent (10/50) of the stroke/TIA group were previously known to have abnormal glucose tolerance or diabetes; when this subgroup was excluded, there remained 42% of the original group (21/50) with abnormal GHb (> 10% A1c) not previously known to have hyperglycemia, and the difference between GHb values for the stroke/TIA patients not known to have glycemic abnormality and for the hospital control group remained significant (p < 0.005). Sixty-two percent of stroke/TIA patients (31/50) were under treatment for glycemic abnormality, or had high GHb, or both. The high prevalence of elevated GHb in this population could not be attributed to a relationship to age, sex, smoking history, hypercholesterolemia, or hypertension. We conclude that hyperglycemia commonly precedes stroke and TIA, is usually unrecognized, and has been under-appreciated as a risk factor for cerebrovascular disease.

EPIDEMILOGIC DATA SHOW an increased risk of stroke associated with hyperglycemia. For example, in the Framingham Study the incidence of thrombotic stroke was 2.5 times higher in diabetic men and 3.6 times higher in diabetic women than in those without diabetes. However, the prevalence of hyperglycemia preceding cerebrovascular events is poorly defined, so the relative importance of hyperglycemia as a risk factor is uncertain. In particular, the importance of mild hyperglycemia, as opposed to symptomatic diabetes, as a precursor of stroke is unclear. Measurement of glycosylated hemoglobin (GHb), which reflects glycemic levels for the preceding 1–3 months, in patients with recent stroke or transient ischemic attacks (TIA) has allowed us to address this question.

Patients and Methods

Patients

Fifty patients hospitalized on the Neurology service because of recent stroke or TIA were studied. Blood samples for GHb assay were collected within 7 days after admission. Patients with stroke were all hospitalized within several days after the event, so the interval between stroke and GHb sample collection was never more than 10 days, and usually less than a week. Hospital records were subsequently reviewed to verify the diagnosis and record admission blood pressure and serum cholesterol, history of smoking, hypertension or carbohydrate intolerance, and use of antihypertensive drugs. Patients with hemorrhagic stroke, tumors, and other disorders initially simulating thrombotic stroke or TIA were excluded, as were patients in whom the diagnosis was considered in doubt. Blood samples for GHb were also collected from four reference populations: (1) well ambulatory persons without known major illness, including diabetes mellitus and cerebrovascular disease, recruited from laboratory staff, a Dermatology clinic, and persons entering a fitness program (64 subjects; 34 men, 30 women; mean age ± SD, 37 ± 15 years); (2) patients hospitalized on the Neurology service for disorders other than cerebrovascular disease, excluding patients with known previous stroke but not excluding those with diabetes or glucose intolerance (30 subjects; 19 men, 11 women; age 54 ± 18 years); (3) diabetic outpatients treated with diet alone or diet plus oral hypoglycemic drugs (27 subjects; 6 men, 21 women; age 62 ± 11 years); and (4) diabetic outpatients taking insulin (71 subjects; 23 men, 48 women; age 56 ± 15 years).

Glycosylated Hemoglobin Assay

Glycosylated hemoglobin was determined by a modification of the Fluckiger-Winterhalter method. Five ml blood samples were collected in tubes containing 7.5 mg EDTA. Red cell hemolysates were prepared by hemolyzing the packed, washed red cells with 2.5 ml distilled water and freeze/thawing once. Membranes were spun down and discarded. One half ml of 0.3N oxalic acid was added to 1.0 ml lysate and incubated 1 hour at 100°C. After cooling, 0.5 ml of 40% TCA was added to the tubes and the precipitate spun down. Six-tenths ml of supernatant was incubated with 0.3 ml of 0.05 N 2-thiobarbituric acid at 40°C for 40 min. OD was read at 443 nm. Comparison of results by this method yielded excellent correlation (r = 0.90) with those by a standard column chromatographic method for separation of "fast" hemoglobins, allowing expression of glycosylated hemoglobin as percent
A1. Our normal range for persons with proven normal glucose tolerance (2 hr. plasma glucose < 140 mg/dl) is 4–10% A1 (mean ± SD, 7.0 ± 1.5).

Results

Stroke versus transient ischemic attack

Twenty-eight (20 men, 8 women) of the study patients had stroke while 22 (13 men, 9 women) had TIA. The two groups were very similar. Mean age ± SD was 63 ± 13 for stroke and 63 ± 8 for TIA. Of stroke patients 16 of 28 were treated for hypertension, and of TIA patients 14 of 22. Mean diastolic blood pressures on admission were 88 ± 11 and 88 ± 12 mmHg, respectively. Of stroke patients 18 of 28 had smoked at least 15 pack-years, and of TIA patients 12 of 22. Serum cholesterol was over 225 mg/dl in 4 of 24 stroke patients, and 5 of 21 TIA patients. Glycosylated hemoglobin was 10.5 ± 2.2 in stroke and 9.8 ± 2.3 in TIA patients; this difference was not statistically significant. For comparison with the reference groups, stroke and TIA patients were considered a single group.

GHB in Stroke/TIA and Reference Groups

The figure compares GHB values for the stroke/TIA group, well ambulatory controls, hospitalized controls, and diabetic outpatients. Mean GHB ± SD for the stroke/TIA patients was 10.2 ± 2.3, which was higher than for ambulatory controls without known hyperglycemia (7.7 ± 1.5, p < 0.001) and hospitalized controls without known cerebrovascular disease (8.3 ± 0.9, p < 0.005), and similar to the values for diet/oral (9.5 ± 2.4) and insulin-treated (10.7 ± 2.9) diabetic outpatients. Because of selection, none of the ambulatory controls was known to have abnormal carbohydrate tolerance. Nevertheless, 12% (8/64) had GHB values over 10% A1, which was 2 SD above the normal control mean. Patients with abnormal glucose tolerance were not excluded from the hospital control group, but none with known glucose intolerance appeared in the group collected. Of this group 7% (2/30) had GHB over 10% A1. Corresponding figures for the diabetic groups were 41% (11/27) for diet/oral patients and 54% (38/71) for insulin-treated patients. Fifty-six % (28/50) of the stroke/TIA patients, of whom only 20% (10/50) were previously known to have diabetes or impaired glucose tolerance, had GHB over 10% A1. Of the 10 persons with known glycemic abnormality, four were taking insulin, three took oral agents, and three were treated with diet alone. Three had GHB values below 10% A1, and seven values above 10% A1. When these 10 persons were excluded from the stroke/TIA population, the mean GHB decreased only slightly (from 10.2 ± 2.3 to 9.9 ± 1.8% A1), and 21 (42% of the original 50) had GHB over 10% A1. Mean GHB for the 40 stroke/TIA patients without previously known glycemic abnormality (9.9 ± 1.8% A1) remained significantly higher (p < 0.005) than that for the hospital control group (8.3 ± 0.9% A1) when compared by analysis of variance using a pooled error term. Finally, adding to the 28 persons with high GHB the three with GHB under 10% who were under treatment for diabetes, 62% of stroke/TIA patients (31/50) had evidence of glycemic abnormality.

Effect of age and sex on GHB in Stroke/TIA and Reference Groups

The relationship between age and GHB in the same five groups is shown in table 1. No definite effect of age was apparent in any group, when subgroups of persons under 50 years of age, 40 to 64, and over 64 were compared. In addition, linear regression analysis of data for all persons 40 years of age or older in all five groups yielded no significant correlations. When the age 40–64 and over 64 subgroups of hospital control and stroke/TIA populations were compared the differences observed when the whole groups were compared persisted. Mean GHB in stroke/TIA patients was clear-
Evidence of neither hypertension nor hyperglycemia (5/50) had neither. The ages of the five patients with evidence of hypertensive disease or of glycemic abnormality. The great majority of this population (90%, 45/50) had either one or the other of these indications. Similarly, 62% (31/50) had either one or the other of these indications, 60% (30/50) were taking antihypertensive drugs, and 72% (36/50) had either one or the other of these indications on hospital admission. The colorimetric assay for GHb has advantages over column methods for separation of "fast" hemoglobins, while the colorimetric assay for GHb may lead to continued glucose intolerance. Thus, glucose intolerance in a stroke patient may or may not reflect glycemia prior to the event.

Discussion

Evidence suggesting a greatly increased prevalence of glucose intolerance among persons with cerebrovascular disease has long been available.①② Jakobsen studied patients with cerebrovascular disease but without overt diabetes, finding 21% with abnormal glucose tolerance (Fajans and Conn criteria) and 50% with abnormal Prednisone-augmented glucose tolerance tests. Gertler and his colleagues④⑤ in a population with thrombostic stroke, found overt diabetes in 30% and abnormal glucose tolerance (Fajans and Conn criteria) in 50% of the rest. They concluded that over 70% of their stroke population had overt or covert diabetes mellitus. However striking, these figures have attracted little attention. The difficulties inherent in interpreting plasma glucose behavior in ill persons may in part account for this. Glucose intolerance or even fasting hyperglycemia may follow an acute vascular event, and ensuing physical inactivity and poor food intake may lead to continued glucose intolerance. Thus, glucose intolerance in a stroke patient may or may not reflect glycemia prior to the event.

Measurement of GHb rather than glucose as an indicator of prior glycemia offers a new perspective. The rate of non-enzymic glycosylation of hemoglobin is believed to depend largely or solely on plasma glucose concentration.①② Since the erythrocyte survives about 3 months, GHb measurements in patients with normal erythrocyte survival reflect plasma glucose concentrations during that period. The colorimetric assay for GHb has advantages over column methods for separation of "fast" hemoglobins. Column separations are confounded by variant hemoglobins, while the colorimetric assay for GHb is not.

### Table 1. GHb (mean % A1 ± SD) in the Stroke/TIA Population and Reference Populations, Divided into Subgroups by Age. The Number in Each Subgroup is Shown in Parentheses

<table>
<thead>
<tr>
<th></th>
<th>Under 40 yrs</th>
<th>40–64 yrs</th>
<th>Over 64 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambulatory controls</td>
<td>7.6 ± 1.4 (40)</td>
<td>8.1 ± 1.6 (20)</td>
<td>6.8 ± 0.8 (4)</td>
</tr>
<tr>
<td>Hospital controls</td>
<td>8.5 ± 1.0 (6)</td>
<td>8.5 ± 0.9 (14)</td>
<td>8.0 ± 0.8 (10)</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>10.3 (1)</td>
<td>10.3 ± 2.3 (25)</td>
<td>10.1 ± 2.2 (24)</td>
</tr>
<tr>
<td>Diabetics (diet/oral)</td>
<td>9.2 (1)</td>
<td>9.5 ± 2.5 (15)</td>
<td>9.5 ± 2.2 (11)</td>
</tr>
<tr>
<td>Diabetics (insulin)</td>
<td>10.8 ± 2.7 (12)</td>
<td>11.1 ± 3.0 (38)</td>
<td>10.0 ± 2.7 (21)</td>
</tr>
</tbody>
</table>

### Table 2. Clinical Features Related to Vascular Risk in Stroke/TIA Population, Divided into Subgroups with Normal or High GHb Values. Means ± SD are Shown for the Continuous Variables. Statistical Comparison of Continuous Variables is by Student’s t-test, of Remaining Variables by Chi-square

<table>
<thead>
<tr>
<th></th>
<th>GHb &lt; 10% A1</th>
<th>GHb &gt; 10% A1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 9</td>
<td>61 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>16M, 6F</td>
<td>17M, 11F</td>
<td>—</td>
</tr>
<tr>
<td>BP systolic (mm Hg)</td>
<td>154 ± 17</td>
<td>151 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>BP diastolic (mm Hg)</td>
<td>92 ± 10</td>
<td>84 ± 11</td>
<td>0.01</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>14/22 (64%)</td>
<td>16/28 (57%)</td>
<td>NS</td>
</tr>
<tr>
<td>Over 15 pack-yrs smoking</td>
<td>12/22 (55%)</td>
<td>18/28 (64%)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol over 225 mg/dl</td>
<td>4/20 (20%)</td>
<td>5/25 (20%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
was, if anything, relatively lacking in stroke/TIA patients with high GHB. This negative relation between GHB and hypertension suggests the two operate as separate risk factors. The scarcity of patients with stroke or TIA who had evidence of neither hypertension nor hyperglycemia strengthens the impression that hyperglycemia and hypertension are separate, leading risk factors for cerebrovascular disease. Only one patient of 38 under 70 years of age in this study had no evidence of either hyperglycemia or hypertension.

These findings pose several questions. What mechanisms might link mild as well as severe hyperglycemia to cerebrovascular injury? Should asymptomatic persons without diabetes but with slightly elevated GHB (12% of our well ambulatory group) be considered at risk, as are persons with mild diastolic hypertension? If so, will treatment designed to lower plasma glucose alter this risk? Because of the large numbers of persons involved, and the high morbidity and mortality of the disorder, these questions deserve attention.

References
Hyperglycemia, recognized and unrecognized, as a risk factor for stroke and transient ischemic attacks.
M C Riddle and J Hart

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