Plasma Homocysteine Concentrations in the Acute and Convalescent Periods of Atherothrombotic Stroke

D.J. Meiklejohn, MBChB; M.A. Vickers, MD; R. Dijkhuisen, MD; M. Greaves, PhD

**Background and Purpose**—Homocysteine is a proposed causal risk factor for atherosclerosis, but this remains controversial. We measured fasting plasma homocysteine concentrations immediately after atherothrombotic stroke and in the convalescent period to investigate this controversy.

**Methods**—One hundred six patients (59 men and 47 women, mean age 57.2 [25 to 70] and 56.5 [26 to 69] years, respectively) were recruited within 24 hours of admission, and 82 patients were resampled at least 3 months later. Fasting total plasma homocysteine (tHcy) concentrations were measured by high-performance liquid chromatography.

**Results**—Median tHcy in the acute phase of stroke was not significantly higher than in matched control subjects (men 9.2 [range 4.4 to 22.8] versus 8.7 [4.9 to 20] μmol/L, P=0.09, Mann-Whitney U test; women 8.1 [4.8 to 32.3] versus 7.6 [3.3 to 14.4] μmol/L, P=0.58). Median plasma concentrations increased significantly in the convalescent period (from 8.5 [4.8 to 19.2] to 10.1 [4.3 to 31.5] μmol/L, P<0.001, Wilcoxon signed rank test) and were then significantly higher than in control subjects in both men and women (P=0.03 and 0.05, respectively, Mann-Whitney U test). This did not appear to be explained by alteration in the known covariates red-cell folate, serum B₁₂, or creatinine concentrations.

**Conclusions**—Homocysteine concentrations are not elevated after recent atherothrombotic stroke but rise in the convalescent period. These data do not support the hypothesis that raised plasma homocysteine concentrations predate atherothrombotic stroke. Instead, they offer an explanation for the discrepancies between prospective and retrospective studies and suggest that elevated tHcy levels may be caused by the disease process itself. (*Stroke. 2001;32:57-62.)*

**Key Words:** atherothrombotic stroke ■ homocysteine

Homocysteine is a thiol-containing amino acid derived from the metabolism of methionine that circulates in plasma in 3 forms: as a single free amino acid (1%), as homocysteine or cysteine-homocysteine disulfides (20% to 30%), or bound to plasma proteins (70% to 80%). Together, these account for total plasma homocysteine (tHcy). Inborn errors of metabolism arising from a deficiency of Hcy-metabolizing enzymes result in extremely high tHcy concentrations (severe hyperhomocysteinemia) and are associated with arterial and venous thrombosis, possibly as a result of oxidative damage mediated by the sulfhydryl group of free single-chain homocysteine. Mild hyperhomocysteinemia results from both nutritional and more subtle genetic influences. Subclinical deficiencies of folate, vitamins B₁₂ and B₆, and inheritance of the thermolabile variant of methylenetetrahydrofolate reductase are associated with modest elevations above the 90th percentile of the normal range. Other conditions, including renal impairment, hypothyroidism, and drug therapy (eg, folate antimetabolites, theophylline, smoking, or oral contraceptives), are also associated with mild hyperhomocysteinemia. Whether this can cause premature arterial thrombosis is a contentious issue. Retrospective case-control studies have associated raised tHcy with both arterial and venous thrombosis. In contrast, results from prospective studies have been inconsistent, both supporting and refuting raised tHcy levels as a risk factor for myocardial infarction (MI).

Consideration of reports of plasma tHcy and stroke (cerebrovascular accident, CVA) identifies similar difficulties. Case-control studies have reported stronger associations than prospective studies, in which some but not others claim that hyperhomocysteinemia is a risk factor for future stroke development. In the case of CVA, 2 further issues are relevant: first, strokes arise from numerous pathophysiological processes, including intracranial hemorrhage, cardiac embolization, atherothrombosis (rupture of either large-vessel atheroma with cerebral embolism or of small-vessel atheroma with occlusion), and vasculitis. Most studies have failed to distinguish between these diverse stroke types, and any individual risk factor might influence only one of these processes. Recent studies in humans have shown that acute hyperhomocysteinemia causes endothelial dysfunction, which might promote atheroma development. Furthermore, raised homocysteine concentrations are associated with asymptomatic carotid artery wall thickening and stenosis.

Received July 14, 2000; final revision received September 11, 2000; accepted September 20, 2000.

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and correlate with the severity of cerebral artery stenosis. It could therefore be postulated that elevated tHcy is a risk factor for atherothrombotic stroke in particular. Second, there is debate about whether tHcy is a causative risk factor in stroke and MI or is merely a secondary marker of risk in survivors. Data regarding tHcy concentration immediately after acute stroke would help to resolve this question, because the observation of a raised tHcy at this time would be more suggestive of a causal association than the occurrence of hyperhomocysteinemia in survivors sampled at a time distant from the event.

We performed a case-control study to address these issues. This was restricted to subjects with atherothrombotic stroke by exclusion of cases of intracranial hemorrhage and probable cardioembolic or vasculitic pathogenesis. We measured fasting tHcy concentrations as a risk factor in both the acute and convalescent periods of stroke and assessed any change in tHcy between these times. Changes in factors known to affect Hcy metabolism, such as B12 and folate concentrations, smoking habit, and drug history, were also assessed to determine whether these were responsible for any observed change in tHcy concentration observed between the acute and convalescent periods.

Subjects and Methods

Consecutive patients admitted to Aberdeen Royal Infirmary between June 1997 and December 1998 within 24 hours of a CVA were considered for participation. This is the sole primary referral center for the Grampian region of Scotland (population ~600 000); patients are therefore representative of the general stroke population. Stroke was defined as a sudden loss of global or focal cerebral function that persisted for >24 hours with a probable vascular cause. Patients were approached on admission, and formal written consent was obtained. In an attempt to study a single pathological cause of CVA, patients with a history of atrial fibrillation, valvular heart disease, or connective-tissue disease were not recruited. A CT brain scan was performed on all patients, and those with evidence of intracranial hemorrhage or of alternative intracranial pathology were excluded. A clinical assessment was then made to exclude a previously undetected cardiac source of thrombus. Patients with evidence of valvular heart disease or thrombus on echocardiography or of atrial fibrillation after recruitment were subsequently excluded. Those considered to have suffered a transient ischemic attack (TIA, symptoms resolving within 24 hours) were included, provided that a cardiac source of embolus was considered unlikely on the basis of the clinical assessment. Duplex ultrasound examinations were performed to identify evidence of carotid atheroma. Healthy, age- and sex-matched control subjects were obtained from the list of a local general practice that cares for a population from a large area of the City of Aberdeen consisting of a racial and social-class mix similar to that of the patient cohort. Those born in the same year as subjects with no history of stroke, TIA, or peripheral vascular or ischemic heart disease and who were not seeing a physician on a regular basis were recruited after written informed consent was obtained. The study was approved by the Grampian Regional Ethical Committee.

Between 7 AM and 9 AM after an overnight fast, 4.5-mL blood samples were taken into vacuum tubes containing EDTA (Becton Dickinson). Plasma was separated by centrifugation at 3000g within 1 hour of venipuncture in all cases and stored at −70°C until analysis. Additional samples were obtained for red-cell folate (RCF) and serum B12 assays, which were performed by competitive magnetic separation on a Technicon Immuno 1 autoanalyzer (Bayer Technicon), and for estimation of serum creatinine and fasting cholesterol concentrations.

Patients were invited to revisit their doctors for repeat sampling in the convalescent period, ≥3 months after the acute event. They attended as outpatients after an overnight fast and provided samples for tHcy analysis. A subgroup of patients provided samples for convalescent-phase RCF and serum B12 and creatinine estimations. The use of medications associated with increased homocysteine was recorded initially and at follow-up.

Samples were analyzed between February and May 1999 by reverse-phase high-performance liquid chromatography (HPLC) with fluorescence detection as previously described. Briefly, tHcy was converted to free thiol by reduction with tri-n-butylphosphine (Sigma) and derivatized with S-BDF (ammonium-7-fluoro-2,1,3-benzoxadiazole sulfonate, Fluka). The samples were passed through a Hichrom RBP solid-phase column (Hichrom) with a Gilson 715 HPLC autoanalyzer. Derivatized thiols were detected fluorometrically, and data were analyzed by 715 HPLC System Controller Software (Gilson Medical Electronics). All samples were analyzed in duplicate. Each assay batch contained a combination of acute, convalescent, and control samples, and the operator was blinded to the identity of individual samples. The interassay and intra-assay coefficients of variation were 11.7% and 4.2%, respectively. Samples with extreme values (<4 μmol/L or >20 μmol/L) were reassayed to confirm reproducibility of results.

Calculations were performed with SPSS for Windows version 8.0 statistical software. Mean differences in normally distributed data between cases and controls were analyzed by Student’s t test, and by the paired t test for differences between acute and convalescent samples. Unpaired skewed continuous variables, including tHcy concentrations, were analyzed by the Mann-Whitney U test, and paired data by the Wilcoxon signed rank test. A 2-tailed value of P<0.05 was considered significant. Results obtained from nonparametric analyses were checked by parametric testing of logarithmically transformed data. Continuous variables influencing tHcy concentration were assessed by stepwise multiple regression analysis that included age, RCF, serum B12, and serum creatinine concentrations in the model. Data were logarithmically transformed to a normal distribution if skewed, and multiple correlation coefficients (R) and partial Pearson correlation coefficients (r) were calculated. The β weight, which expresses the change in the dependent variable in SDs that would result from a 1-SD change in the independent variable, was calculated to predict the likely impact of any observed change in RCF, B12, or creatinine concentrations on tHcy concentrations. The distributions of clinical risk factors for arterial disease in cases and controls were compared by χ2 analyses. Odds ratios and 95% CIs were calculated by standard formulas.

Results

The outcome of patient recruitment is summarized in Figure 1. In all, 135 patients with CVA or TIA consented to participate. Twenty-nine patients were subsequently excluded: 10 with intracranial hemorrhage, 7 with atrial fibrillation, 4 with cardiac thrombi or valvular heart disease, 4 with intracranial tumors, and 4 who were considered to have a diagnosis other than stroke. We obtained measurements of fasting tHcy concentrations in 106 patients (59 men and 47 women) and age- and sex-matched control subjects. The
TABLE 1. Distribution of Clinical Risk Factors and Fasting Lipid Measurements in Patients and Control Subjects

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>106 Subjects, n (%)</th>
<th>106 Controls, n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>53 (50)</td>
<td>26 (24.5)</td>
<td>3.07 (1.71–5.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44 (41.5)</td>
<td>18 (17)</td>
<td>3.47 (1.83–6.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>32 (30.2)</td>
<td>26 (24.5)</td>
<td>1.33 (0.7–2.44)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (6.6)</td>
<td>4 (3.8)</td>
<td>1.8 (0.51–6.35)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>14 (13.2)</td>
<td>25 (23.6)</td>
<td>0.49 (0.24–1.01)</td>
<td>0.054</td>
</tr>
<tr>
<td>No risk factor</td>
<td>15 (14.2)</td>
<td>25 (23.6)</td>
<td>0.53 (0.26–1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean (SD)</td>
<td>5.74 (1.33)</td>
<td>5.96 (1.11)</td>
<td>...</td>
<td>0.20</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L, mean (SD)</td>
<td>3.73 (1.25)</td>
<td>3.82 (1.00)</td>
<td>...</td>
<td>0.57</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L, mean (SD)</td>
<td>1.21 (0.39)</td>
<td>1.49 (0.32)</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride, mmol/L, median (range)</td>
<td>1.53 (0.57–8.20)</td>
<td>1.30 (0.48–4.21)</td>
<td>...</td>
<td>0.042</td>
</tr>
</tbody>
</table>

A diagnosis of hypertension, diabetes mellitus, or hyperlipidemia was defined as receiving current treatment for or having a past history of the condition. A family history was defined as an arterial thrombotic event in a first-degree relative before the age of 55 years. Differences in median triglyceride concentrations were assessed by the Mann-Whitney U test and mean differences in other lipids by Student’s t test.

mean ages (range) were 57.2 (25 to 70) years and 56.7 (24 to 72) years for male patients and control subjects, respectively, and 56.5 (26 to 69) and 56.5 (30 to 71) years, respectively, for female participants. All patients were recruited within 24 hours of admission. Fifty-six (52.8%) were recruited and provided a fasting blood sample within 24 hours, 33 (31.1%) within 48 hours, 13 (12.3%) within 72 hours, and the remaining 4 (3.8%) within 96 hours of the onset of symptoms. Ninety-six patients (90.6%) were considered to have suffered a cerebral infarction and 10 (9.4%) a TIA. A carotid scan was performed in 83 of 106 patients (78.3%), of whom 28 (34%) had evidence of carotid atheroma. All patients were contacted, and 82 agreed to provide a fasting sample in the convalescent period. The mean time to follow-up was 100.3 days (range 68 to 270 days). A search of the local patient registry established that by May 1, 2000, 15 patients had died.

Personal risk factors for ischemic stroke are summarized in Table 1. Current smoking and hypertension were identified as risk factors for atherothrombotic stroke, but the odds ratios for diabetes mellitus and a positive family history did not reach statistical significance. Neither a history of treatment for hyperlipidemia nor fasting total or LDL cholesterol concentrations were associated with increased risk. In contrast, the median plasma triglyceride level was significantly higher in patients (P = 0.001), whereas a protective effect of HDL cholesterol was apparent, the mean concentration being significantly greater in control subjects (P < 0.001).

Data on homocysteine concentrations in the acute and convalescent phases are summarized in Table 2. We found no statistically significant difference in the fasting median plasma homocysteine concentrations in the acute phase compared with control subjects in women (P = 0.58, Mann-Whitney U test). In men, there was a tendency toward a higher median concentration in patients, but this was also not significant (P = 0.09, Mann-Whitney U test). In the 82 patients who underwent repeat testing, we found that the median fasting tHcy concentration increased significantly, from 8.5 (range 4.8 to 19.2) to 10.1 (4.3 to 31.5) μmol/L in the convalescent phase (P < 0.001, Wilcoxon signed rank test). This is illustrated in Figure 2. Of these individuals, 56 had an increase, 25 a decrease, and 1 no change in tHcy between the acute and convalescent phases of their illness. In contrast to the acute phase, we found that the median tHcy concentrations in convalescent patients were significantly greater than in their matched control subjects (n = 82) in both female and male patients (P = 0.048 and 0.035, respectively, Mann-Whitney U test).

We next investigated factors known to influence tHcy concentrations in patients and control subjects by stepwise multiple regression analysis. The major determinants of log_{10} tHcy were creatinine concentration (partial $r^2$ = 0.35, $P < 0.001$, $\beta = 0.42$), RCF (partial $r^2$ = −0.32, $P < 0.001$, $\beta = −0.27$), and B_{12} (partial $r^2$ = −0.28, $P < 0.001$, $\beta = −0.22$). In 25 patients, we assessed the alteration in concentrations of RCF and B_{12} between the acute and convalescent phases. The median RCF concentration in the acute phase (mean [SD] 223.2 [180.4] nmol/L) did not differ significantly from that in the convalescent phase (P > 0.05, Wilcoxon signed rank test). Differences were assessed by the Mann-Whitney U test.

*Patients vs matched control subjects.

TABLE 2. Median Fasting Total Plasma Homocysteine Concentrations in the Acute and Convalescent Phases of Atherothrombotic Stroke

<table>
<thead>
<tr>
<th>Group</th>
<th>Median tHcy, μmol/L (range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (n=47)</td>
<td>8.1 (4.8–32.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>Control (n=47)</td>
<td>7.6 (3.3–14.4)</td>
<td></td>
</tr>
<tr>
<td>Convalescent (n=32)</td>
<td>10.0 (4.9–23)</td>
<td>0.048</td>
</tr>
<tr>
<td>Control (n=32)</td>
<td>7.6 (3.3–14.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute (n=59)</td>
<td>9.2 (4.4–22.8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Control (n=59)</td>
<td>8.7 (4.9–20)</td>
<td></td>
</tr>
<tr>
<td>Convalescent (n=50)</td>
<td>10.2 (4.3–31.5)</td>
<td>0.035</td>
</tr>
<tr>
<td>Control (n=50)</td>
<td>8.2 (4.9–20)</td>
<td></td>
</tr>
</tbody>
</table>

Differences were assessed by the Mann-Whitney U test.
the convalescent period (245.1 [172.3] nmol/L, \( P = 0.061 \), paired \( t \) test). Similarly, there was no evidence of a significant reduction in \( B_12 \) concentrations in the convalescent period to account for the rise in tHcy (acute mean 406 [243] \( \mu \)mol/L versus convalescent mean 376 [128] \( \mu \)mol/L, \( P = 0.4 \), paired \( t \) test). We assessed alterations in renal function between the acute and convalescent periods in a subgroup of 59 patients (37 men and 22 women). There was a significant rise in mean serum creatinine when measured \( \geq 3 \) months after acute stroke (acute mean [SD] 87.7 [19.5] \( \mu \)mol/L, convalescent mean 94.1 [17.7] \( \mu \)mol/L, \( P = 0.006 \), paired-samples \( t \) test). We calculate from the observed \( \beta \) weight of 0.42 that this predicts a rise in mean tHcy concentration of 0.3 mmol/L. In the 59 patients with complete data, the mean change in tHcy after stroke was +1.2 (range \(-14.0 \) to \(+11.9 \) \( \mu \)mol/L), and the mean change in creatinine was +6.5 (range \(-35.0 \) to \(+44.0 \) \( \mu \)mol/L). There was no significant correlation between alteration in plasma Hcy and the corresponding change in creatinine in each patient (\( r^2 = 0.15, P = 0.24 \)).

Other factors known to influence tHcy were examined. No patient began smoking, and there was a nonsignificant increase in the number of patients prescribed medication associated with increased tHcy concentrations between acute CVA and follow-up (20/82 versus 23/82, respectively, \( \chi^2 = 0.28, P = 0.59 \)).

**Discussion**

There are few reports of tHcy concentrations immediately after acute stroke, and these studies have recruited patients with a diversity of causes of stroke. We restricted study to subjects with a similar underlying pathophysiological process by recruiting only those with probable vascular stroke. Those with cardioembolic disease were excluded on the basis of a clinical examination and transthoracic echocardiography, although not all cases may have been detected, because transesophageal echocardiography was not performed. We sought to examine younger patients with stroke, and the mean age of our patients is therefore less than the average for the stroke population. An upper limit of 70 was set to recruit a sufficient number of patients from our center. Our main finding is that fasting homocysteine concentrations were not significantly increased shortly after stroke, but they rose significantly in the ensuing 3 months.

Changes in factors associated with mild hyperhomocysteinemia did not appear to explain our findings. Although RCF and serum \( B_12 \) were significant inverse covariates, the rise in the convalescent-phase tHcy was not associated with a corresponding reduction in their concentrations. Given that RCF and serum \( B_12 \) reflect body stores, a longer follow-up period may be necessary to detect such a change. We found that the number of patients taking medication associated with hyperhomocysteinemia (such as methotrexate, phenytoin, carbamazepine, or oral contraceptives) or the number who smoked did not significantly increase after acute stroke. Our data suggest that alterations in serum creatinine concentrations after stroke, being a significant covariate of tHcy, may explain a small part of the observed increase in tHcy. However, the predicted increase in tHcy concentrations arising from this (0.3 \( \mu \)mol/L) is much smaller than the observed median increase of 1.6 \( \mu \)mol/L, and we calculate that a mean rise of 73 \( \mu \)mol/L would be necessary to explain our data. Furthermore, individual alterations in Hcy did not correlate significantly with corresponding individual changes in creatinine concentration. In summary, changes in the known determinants of Hcy appear to explain only a minor part of the increase that we observed.

Our findings are in accordance with a previous study in *Stroke*, which reported that tHcy was not elevated in the acute phase of cerebral infarction and that the median tHcy concentration was higher in 17 subjects resampled a median of 583 days later, although concentrations were not significantly different from those of control subjects.26 Because we have confirmed these earlier observations and given a report of a similar phenomenon after acute MI,27 it is plausible that the rise in convalescent Hcy is a genuine effect rather than a chance finding associated with study of a modest number of patients. Recruitment of a larger sample size than the earlier report26 also enabled us to determine that convalescent tHcy was statistically significantly greater than in control subjects. We did not assess changes in tHcy over time in healthy subjects, but these have previously been determined to be stable,26 and these observations provide an explanation for data from case-control studies that report an increased prevalence of hyperhomocysteinemia in stroke survivors.3,14

A possible explanation for these findings is that tHcy is elevated in the period predating stroke or MI and that concentrations temporarily fall in the acute phase by an as yet undetermined mechanism. It has been suggested that this may be related to the acute-phase response, with dilution of tHcy.
by increased synthesis of plasma proteins. To adequately test this hypothesis, it would be necessary to measure tHcy both before and after stroke. Given the difficulty in predicting the onset of stroke, however, these data are currently unavailable.

It has been suggested that an increase in methylation reactions after tissue injury results in the conversion of methionine to S-adenosyl homocysteine, which leads to the generation of homocysteine.24 Thus, the suggestion that tHcy may not be a causative risk factor for stroke at all and that plasma levels merely rise secondarily to stroke development is more favorable.24 This hypothesis, unlike the former, provides an adequate explanation for the fact that prospective studies have found a much weaker association than retrospective studies conducted in survivors of stroke.5,14

Further evidence for this view comes from the as yet unexplained observation that although homozgyosity for the T allele of the C677T polymorphism of methylenetetrahydrofolate reductase is associated with mild hyperhomocysteinemia, studies have failed to demonstrate this genotype as a risk factor in MI and stroke.28,30–36 In addition, obligate heterozygotes for cystathionine β synthase deficiency (ie, parents of children with homocystinuria) do not exhibit evidence of carotid or femoral atherosclerosis despite elevated tHcy levels.37 This lack of association between genetic abnormalities resulting in mild hyperhomocysteinemia and arterial disease further weakens the hypothesis that mild elevations in tHcy directly promote atherosclerosis and thrombosis.

Homocysteine has been linked in numerous in vitro studies with a diversity of mechanisms that could potentiate atherothrombosis, including disrupted endothelial function, impaired protein C activation, increased thrombin generation, and platelet aggregation.38 Many of these studies, however, used supraphysiological concentrations of pure free single-amino-acid t-homocysteine, and the data cannot be extrapolated to hyperhomocysteinemia, in which, in addition to much lower concentrations, only 1% of tHcy is present as this reactive species. More recently, transient moderate increases in tHcy after a methionine load have been associated with reversible disturbances in endothelium-dependent arterial vasodilatation,39,40 but data demonstrating that this promotes atherogenesis or thrombosis in humans in the longer term are lacking.

In conclusion, plasma homocysteine concentrations were not statistically significantly elevated immediately after atherothrombotic stroke, but then they increased in the convalescent period. The mechanism for these observations was not attributable to alterations in folate or B12 concentrations, renal function, or drug prescription after stroke and is currently unexplained. It is possible that tHcy increases as a result of the disease process itself.

Acknowledgments

This study was funded by Chest, Heart, and Stroke (Scotland) and by the Aberdeen Royal Infirmary Endowments Fund.

References


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Stroke. 2001;32:57-62
doi: 10.1161/01.STR.32.1.57

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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