Associations of Serum Total Cholesterol, Different Types of Stroke, and Stenosis Distribution of Cerebral Arteries

The Akita Pathology Study

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Background and Purpose: The relation between serum total cholesterol levels and stroke is controversial. The Akita Pathology Study provides data on the association of serum total cholesterol, different types of stroke, and distribution of stenosis in cerebral arteries.

Methods: The data are based on 750 autopsied men aged 30 years and older who were admitted to a local hospital in northeast Japan between 1966 and 1984. The overall autopsy rate was 88%. The grade of stenosis in the cerebral arteries was determined blindly by one pathologist using Baker’s method for basal cerebral arteries (atherosclerosis scores) and using microscopic examination of a single basal ganglion slide for the intracerebral penetrating arteries (arteriosclerosis scores).

Results: The age-adjusted mean value of serum total cholesterol concentration was 164 mg/dL for cerebral hemorrhage, 177 mg/dL for infarction in penetrating artery regions, and 200 mg/dL for infarction in cortical artery regions. Mean serum cholesterol was lower in deaths caused by cerebral hemorrhage than in those caused by myocardial infarction and other cardiovascular disease. Mean atherosclerosis score of basal cerebral arteries was low for cerebral hemorrhage, intermediate for penetrating artery infarction, and high for cortical artery infarction. Stenosis of both basal and penetrating arteries was minimum or absent in cases of cerebral hemorrhage. Only the basal arteries were stenotic in cases of cortical artery infarction, whereas both basal and penetrating arteries were stenosed in cases of penetrating artery infarction. There were positive associations of serum cholesterol with stenosis of basal and penetrating arteries. Among cases of cerebral hemorrhage, serum total cholesterol levels were even lower in men with no significant stenosis in either basal or penetrating arteries than in men with stenosis in either type of artery.

Conclusions: The association of serum cholesterol with pathogenesis varies among stroke types. Elevated serum cholesterol levels were associated with the presence of cortical artery infarction, while low serum cholesterol levels were associated with cerebral hemorrhage. (Stroke 1993;24:954-964)

Key Words • autopsy • cerebral arteries • cholesterol • stenosis

Although the relation between serum total cholesterol concentration and coronary heart disease has been well established, the association between serum cholesterol and stroke is unresolved. Evidence has been presented that the association differs by type of stroke. Epidemiological studies for Japanese3-5 and Japanese Americans6,7 have shown that serum total cholesterol concentration was inversely associated with the incidence of cerebral hemorrhage. On the other hand, reports from the United States8 and Europe9 indicate a weak but positive association of serum cholesterol concentration with cerebral infarction or stroke of all types. Recently, a 6-year follow-up study of more than 350,000 American men screened for the Multiple Risk Factor Intervention Trial showed that serum total cholesterol was inversely associated with death from cerebral hemorrhage and was positively associated with death from cerebral infarction.10,11 In these epidemiological studies, however, the diagnosis of stroke and its type was based on clinical data or death certificates. To our knowledge, no pathological study has examined the association of serum cholesterol with stroke type diagnosed by autopsy.

The present study was performed to examine whether serum total cholesterol distributions differ among the different pathological manifestations of stroke. A main point of the study was to explore two observations. The

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first was that cerebral hemorrhage appears to be characterized by arteriolosclerosis in the intracerebral penetrating arteries (100 to 300 μm in diameter), inversely related to serum cholesterol. The second was that other forms of stroke such as infarction in the cortical artery regions appear to be characterized by atherosclerosis in larger cerebral arteries (0.2 to 6 mm in diameter), positively related to serum cholesterol.

**Subjects and Methods**

**Surveyed Population**

The Akita Pathology Study is a hospital-based autopsy study conducted at the Yuri General Hospital between 1966 and 1984.12 The hospital is located in the city of Honjo, Japan, surrounded by the Yuri area in the Akita prefecture, 250 miles north of Tokyo. There is no other hospital with more than 20 beds in the area. Patients admitted to the hospital are predominantly from Honjo and the Yuri area. The census population of Honjo plus the Yuri area (500 square miles) has been stable during the period of this study: 125,968 in 1970 and 127,175 in 1980.

Subjects were all men who died in the hospital and were autopsied. Between 1966 and 1984, 845 men aged 30 years and older were autopsied. Autopsied men who did not live in the city of Honjo or the Yuri area (n = 26) were excluded from this number. Eighty-eight percent of all in-hospital deaths were autopsied. Of the 845 men, 750 (89%) had serum total cholesterol levels measured on the first day of admission. Table 1 depicts the number of autopsied men with serum total cholesterol concentration by disease and age group. The proportion of autopsied cases with serum total cholesterol measured was 95% for stroke and 80% for nonstroke.

**Diagnosis of Stroke and Stroke Type**

Stroke was regarded as a clinical syndrome with neurological findings sudden or rapid in onset that persisted for more than 24 hours, the origins of which were rupture or occlusion of brain arteries. Asymptomatic stroke or symptomatic stroke without significant pathological findings was not regarded as stroke. Classification of stroke type was done by autopsy findings; one exception was discrimination of cortical artery infarction from embolic infarction, in which case the presence or absence of atrial fibrillation in resting electrocardiograms at admission was also considered. The other causes of death were determined mostly by autopsy findings.

Stroke constituted 63% of deaths among the 750 men who undertook examination of serum total cholesterol. There were 172 strokes attributed to cerebral hemorrhage (intracerebral parenchymal hemorrhage) and 35 to subarachnoid hemorrhage. Penetrating artery infarction (n = 77) was defined as small infarction in the basal ganglion regions where the penetrating arteries are located. This type of stroke was mostly lacunar infarction. Cortical artery infarction (n = 57) was a larger infarction in the cortical artery regions with no hemorrhagic infarction, no cardiac embolus, and no evidence of atrial fibrillation in the resting electrocardiogram. This type of stroke was mostly thrombotic infarction. Cortical artery infarction with evidence of possible embolic origin such as cardiac embolus, atrial fibrillation, and hemorrhagic infarction was classified as embolic infarction (n = 95). Other types of infarction.

### Table 1. Number of Autopsied Men With Serum Total Cholesterol Measured at Admission by Disease and Age Group

<table>
<thead>
<tr>
<th></th>
<th>30-54</th>
<th>55-64</th>
<th>65-74</th>
<th>&gt;74</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>72</td>
<td>122</td>
<td>171</td>
<td>107</td>
<td>472</td>
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<tr>
<td>Cerebral hemorrhage</td>
<td>48</td>
<td>50</td>
<td>45</td>
<td>29</td>
<td>172</td>
</tr>
<tr>
<td>Penetrating artery infarction</td>
<td>1</td>
<td>19</td>
<td>33</td>
<td>24</td>
<td>77</td>
</tr>
<tr>
<td>Cortical artery infarction</td>
<td>6</td>
<td>15</td>
<td>29</td>
<td>7</td>
<td>57</td>
</tr>
<tr>
<td>Embolic infarction</td>
<td>6</td>
<td>25</td>
<td>40</td>
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<td>95</td>
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<td>Unclassified infarction</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>10</td>
<td>10</td>
<td>12</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Nonstroke</td>
<td>73</td>
<td>64</td>
<td>84</td>
<td>57</td>
<td>278</td>
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<tr>
<td>Myocardial infarction</td>
<td>8</td>
<td>13</td>
<td>18</td>
<td>9</td>
<td>48</td>
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<tr>
<td>Other cardiovascular disease</td>
<td>7</td>
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<td>8</td>
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<td>25</td>
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<tr>
<td>Cancer</td>
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<td>14</td>
<td>17</td>
<td>15</td>
<td>68</td>
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<tr>
<td>Respiratory disease</td>
<td>8</td>
<td>6</td>
<td>13</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>Liver/digestive disease</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>Trauma</td>
<td>6</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Others</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>12</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>145</td>
<td>186</td>
<td>255</td>
<td>164</td>
<td>750</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate number of all autopsied men.
mostly infarction in both penetrating and cortical artery regions, were regarded as unclassified infarction (n=36).

Determination of Atherosclerosis Scores of Basal Cerebral Arteries

Brains were fixed in 10% buffered formalin, and grades of atherosclerosis in the basal cerebral arteries of the circle of Willis were scored according to Baker's method.13 This method assigns a grade of 0 (for no stenosis) to 4 (for 50% or more stenosis) in each of 22 sites of the basal cerebral arteries. The total score ranges from 0 to 88. A Baker's score of 22 or greater was regarded as significant stenosis in the basal cerebral arteries. A score of 22 was obtained, for example, if all 22 arterial sites exceeded 25% of the stenosis (grade 1 and higher). Associations of the atherosclerosis scores were examined stratified by the size of arteries as well as in total. Large arteries were approximately 1.5 to 6 mm in diameter, which included the internal carotid, the middle and posterior cerebral, the basilar, and the vertebral arteries (12 sites). Small arteries were 0.2 to 1.4 mm in diameter (10 sites).

All grading was performed within a year of death by one of the authors (M.K.), a certified pathologist, blinded to subjects' age, blood pressure, and serum cholesterol values. Reliability of Baker's score was tested by rereading 28 samples from 1984 3 years later blinded to the initial score. The mean±SD values in 1984 and 1987 were both 29±2.1. The correlation coefficient between the two values was 0.98 (P<.001). Baker's score was available for 624 (85%) of the 750 autopsied men: 460 (97%) for stroke and 164 (59%) for nonstroke.

Determination of Arteriolosclerosis Scores of Intracerebral Penetrating Arteries

For men with cerebral hemorrhage, penetrating artery infarction, or cortical artery infarction, grade of stenosis (mostly caused by intimal thickening) in intracerebral penetrating arteries in a basal ganglion region was also examined using a single microscopic slide of the coronal section of the cerebrum including most of the putamen and globus pallidus. The percentage of narrowing for each artery of 100 to 300 μm in diameter was initially graded as − (no narrowing), ± (1% to 24%), + (25% to 49%), and ++ (50% and more), as shown in Fig. 1. Usually 10 to 15 sections of arteries were examined in each slide. If half or more of the sections had narrowing graded ++ (50% or more), we coded significant stenosis as being present; we otherwise entered a code in the data base for no significant stenosis.

In theory, the process of scoring stenosis in intracerebral penetrating arteries may emphasize severe isolated stenosis but emphasizes widespread stenosis of the arteries. However, severe isolated stenosis of intracerebral penetrating arteries was rare, and there was widespread moderate stenosis in most cases with any stenosis.

Reliability of significant stenosis was tested by re-reading 87 samples at least 6 years later blinded to the initial score. There were 42 samples with significant stenosis in both readings, 33 with no significant stenosis in both readings, 9 with positive in the first and negative in the second reading, and 3 with negative in the first and positive in the second reading. The κ coefficient was 0.72 (95% confidence interval, 0.51 to 0.93), indicating good reliability. Examination of intracerebral penetrating arteries was completed for 246 (85%) of the three selected types of stroke with Baker's score available.

Determination of Blood Pressures and Serum Total Cholesterol

Blood pressures were measured on the first day of admission by physicians or nurses using standard mercury sphygmomanometers for all subjects. The first measurement at admission was used for the analyses. A resting electrocardiogram was obtained for 99% of the subjects. Serum total cholesterol was also measured at the first day of admission by the Liebermann-Burchard direct method.12 Quality control of the laboratory has been maintained by internal methods since 1966. An individual history of cigarette smoking was rarely available. However, independent surveys in this geographic area suggest that 65% to 85% of men were cigarette smokers during this period.

Statistical Analyses

Age-adjusted mean values of blood pressure, serum cholesterol, and atherosclerosis scores of basal cerebral arteries among diseases were calculated using analysis of covariance. Age-adjusted mean values of blood pressures and serum total cholesterol by stenosis of basal and intracerebral penetrating arteries were estimated by analysis of covariance. Difference in proportions of combination of stenosis of basal and intracerebral penetrating arteries among stroke types was tested by a χ² test. A multiple linear regression model was applied to model the associations of age, blood pressure, serum total cholesterol, and dichotomous variables representing stroke types with atherosclerosis scores of basal cerebral arteries. Independent variables, which were significantly associated with atherosclerosis scores after adjusting for age, were blood pressure, serum total cholesterol, and stroke types of penetrating artery, cortical artery, embolic, and unclassified infarctions. These variables were included in the multivariate regression. All probability values presented were two-tailed.

Results

Mean age at admission was 61 to 62 for hemorrhagic strokes, 67 to 74 for infarction strokes, 64 to 65 for myocardial infarction and other cardiovascular disease deaths, 57 for trauma, and 62 to 66 for other causes of death (Table 2). Mean systolic and diastolic blood pressures were highest for cerebral hemorrhage, followed by other types of stroke, myocardial infarction and other cardiovascular diseases, and other causes of death. Mean serum cholesterol concentration was high for cortical artery and unclassified infarction and myocardial infarction, and low for cerebral hemorrhage, cancer, respiratory disease, and trauma. Full distributions of serum total cholesterol according to the type of stroke are shown in Fig 2.

In both men aged 30 to 64 years and men aged 65 years or older, age-adjusted mean atherosclerosis score was highest in infarctions of cortical artery, penetrating artery, and unclassified type, followed by cerebral hemorrhage, myocardial infarction, embolic infarction, subarachnoid
FIG 1. Photomicrographs illustrate arteriolosclerosis scores of intracerebral penetrating arteries, showing grades of narrowing: – (no narrowing) (top left), ± (1% to 24%) (top right), + (25% to 49%) (bottom left), and ++ (50% or more) (bottom right) (hematoxylin-eosin stain).
hemorrhage, and other causes of death (Table 3). There was a clear increase in mean atherosclerosis score with age for all causes of death except for penetrating artery, cortical artery, and unclassified infarction. As a result, the differences between causes of death in mean atherosclerosis score were more evident in men aged 30 to 64 years than in men aged 65 years and older.

According to linear regression analysis, serum total cholesterol concentration was significantly associated with atherosclerosis scores of basal cerebral arteries in total after controlling for age and systolic blood pressure and for stroke types (Table 4). As expected, age and blood pressure were also independently associated with the stenosis scores. Significantly higher atherosclerosis scores were observed in infarctions of penetrating artery, cortical artery, and unclassified type. Atherosclerosis scores for the larger arteries were associated with age, systolic blood pressure, and serum total cholesterol. For the smaller arteries, atherosclerosis scores were associated with age and systolic blood pressure but not with serum cholesterol. These results were not altered when systolic blood pressure was replaced by diastolic blood pressure in the models.

Table 5 shows mean age and age-adjusted mean values of blood pressures and serum total cholesterol concentration according to significant stenosis of intracerebral penetrating arteries in three types of stroke combined, ie, cerebral hemorrhage, penetrating artery infarction, and cortical artery infarction, and in each type of stroke separately. For the three types of stroke combined, mean values of age, blood pressure, and serum total cholesterol were higher in men with significant stenosis than in those without it. For cerebral hemorrhage, mean values of blood pressure and serum total cholesterol were higher in men with significant stenosis than in those without it. However, differences of these variables were less evident for infarctions of penetrating and cortical arteries.

Table 6 indicates the proportion with significant stenosis in either basal or intracerebral penetrating arteries, or both, in the three selected types of stroke. For men aged 30 years and older, 96% of men with

| TABLE 2. Mean Values of Age and Age-Adjusted Mean Values of Blood Pressure and Serum Total Cholesterol by Disease |
|--------------------------------------------------|-----------------|-----------------|-----------------|
| Stroke                                           | Age (y)         | Systolic BP (mm Hg) | Diastolic BP (mm Hg) | Serum cholesterol (mg/dL) |
| Cerebral hemorrhage                              | 62±1            | 186±2            | 104±1            | 164±2                   |
| Penetrating artery infarction                    | 70±1            | 175±3            | 98±2             | 177±3                   |
| Cortical artery infarction                       | 67±1            | 174±4            | 100±2            | 200±4                   |
| Embolic infarction                               | 69±1            | 165±3            | 97±2             | 176±3                   |
| Unclassified infarction                          | 74±1            | 166±5            | 95±3             | 191±5                   |
| Subarachnoid hemorrhage                          | 61±2            | 162±5            | 95±3             | 177±5                   |
| Nonstroke                                        |                 |                  |                  |                         |
| Myocardial infarction                            | 65±1            | 160±4            | 91±2             | 197±4                   |
| Other CVD                                        | 64±3            | 156±6            | 89±3             | 181±6                   |
| Cancer                                           | 62±2            | 136±4            | 79±2             | 167±4                   |
| Respiratory disease                              | 66±2            | 137±5            | 80±3             | 162±5                   |
| Liver/digestive disease                         | 62±3            | 144±6            | 82±3             | 172±6                   |
| Trauma                                           | 57±4            | 135±8            | 83±4             | 161±8                   |
| Others                                           | 62±2            | 143±4            | 84±2             | 170±4                   |

Values are mean±SE. BP, blood pressure; CVD, cardiovascular disease.

![Figure 2](http://stroke.ahajournals.org/)  
**FIG 2.** Line graph shows distribution of serum total cholesterol according to stroke type for men aged 30 years and older.
penetrating artery infarction had significant stenosis, 81% in both sets of arteries. Ninety-eight percent of those with cortical artery infarction had significant stenosis as well, but in this case the finding of significant stenosis limited to basal cerebral arteries only was common, whereas the finding of significant stenosis limited to intracerebral arteries only was rare. The result was similar when stratified by age group. Cerebral hemorrhage evidenced a different pattern. For this end point, no significant stenosis was found in 34% of men (50% of men aged 30 to 64 years and 12% of men aged 65 years and older); significant stenosis in intracerebral

**TABLE 4. Regression Coefficients for Estimating Atherosclerosis Scores of Basal Cerebral Arteries in Total and Stratified by Artery Size (n=624)**

<table>
<thead>
<tr>
<th>Risk variables</th>
<th>Regression coefficient β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larger and smaller arteries combined</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.32±0.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>0.13±0.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>0.04±0.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Penetrating artery infarction</td>
<td>7.63±1.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cortical artery infarction</td>
<td>12.10±1.38</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Embolic infarction</td>
<td>−0.06±0.18</td>
<td>.96</td>
</tr>
<tr>
<td>Unclassified infarction</td>
<td>8.44±1.67</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Larger arteries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.08±0.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>0.07±0.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>0.003±0.008</td>
<td>.75</td>
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<tr>
<td>Penetrating artery infarction</td>
<td>4.70±0.80</td>
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<td>Cortical artery infarction</td>
<td>5.21±0.89</td>
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<tr>
<td>Embolic infarction</td>
<td>−0.74±0.70</td>
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<tr>
<td>Unclassified infarction</td>
<td>3.62±1.08</td>
<td>&lt;.001</td>
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</table>

Values are mean±SE. BP, blood pressure.
TABLE 5. Mean Values of Age and Age-Adjusted Mean Values of Blood Pressure and Serum Total Cholesterol According to Stenosis in Intracerebral Penetrating Arteries in the Three Selected Types of Stroke

<table>
<thead>
<tr>
<th>Penetrating artery stenosis</th>
<th>Positive</th>
<th>Negative</th>
<th>P</th>
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</thead>
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<tr>
<td>Three types of stroke combined</td>
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<td>106</td>
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<tr>
<td>Age (y)</td>
<td>70±1</td>
<td>59±1</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>187±3</td>
<td>175±3</td>
<td>&lt;.01</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>104±1</td>
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<td>.04</td>
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<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>180±3</td>
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<td>.03</td>
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<tr>
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<tr>
<td>Number</td>
<td>61</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>66±1</td>
<td>57±1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
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<tr>
<td>Serum cholesterol (mg/dL)</td>
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<tr>
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<td>59±1</td>
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<td>Serum cholesterol (mg/dL)</td>
<td>178±4</td>
<td>156±11</td>
<td>.05</td>
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<td>Cortical artery infarction</td>
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<tr>
<td>Number</td>
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<tr>
<td>Age (y)</td>
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<td>.12</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>99±3</td>
<td>101±3</td>
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<tr>
<td>Serum cholesterol (mg/dL)</td>
<td>195±6</td>
<td>207±7</td>
<td>.23</td>
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</table>

Values are mean±SE. BP, blood pressure.

arteries only was also more common in cerebral hemorrhage than in the other two conditions.

Risk variables in cerebral hemorrhage according to the combination of stenosis of basal and intracerebral arteries are shown in Table 7. For men aged 30 years and older, mean age was higher in men with stenosis in both arteries and men with stenosis in only intracerebral arteries than in the other two groups. Age-adjusted

TABLE 6. Combination (Percent Frequency) of Stenosis of Basal Cerebral Arteries and Intracerebral Penetrating Arteries by Selected Stroke Type and Age Group

<table>
<thead>
<tr>
<th></th>
<th>Stenosis in both arteries</th>
<th>Stenosis only in BCA</th>
<th>Stenosis only in IPA</th>
<th>No stenosis in BCA or IPA</th>
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<tr>
<td>All ages</td>
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<td></td>
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<tr>
<td>Cerebral hemorrhage (n=138)</td>
<td>32</td>
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<td>12</td>
<td>34</td>
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<tr>
<td>Penetrating artery infarction (n=52)</td>
<td>81</td>
<td>7</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Cortical artery infarction (n=55)</td>
<td>55</td>
<td>38</td>
<td>5</td>
<td>2</td>
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<tr>
<td>P*</td>
<td>&lt;.001</td>
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<tr>
<td>Ages 30-64</td>
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<td>7</td>
<td>50</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Cortical artery infarction (n=20)</td>
<td>40</td>
<td>50</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>P*</td>
<td>&lt;.001</td>
<td></td>
<td></td>
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<tr>
<td>Ages ≥65</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cerebral hemorrhage (n=58)</td>
<td>52</td>
<td>17</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Penetrating artery infarction (n=42)</td>
<td>79</td>
<td>9</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Cortical artery infarction (n=35)</td>
<td>63</td>
<td>31</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>P*</td>
<td>&lt;.01</td>
<td></td>
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BCA, basal cerebral arteries; IPA, intracerebral penetrating arteries.

*Difference in proportion of four categories of artery stenosis among three stroke types.
mean values of blood pressures and serum cholesterol were highest in men with stenosis in both arterial locations and intracerebral penetrating arteries only, intermediate in men with stenosis in only basal cerebral arteries, and lowest in men with no stenosis at either arterial location. When stratified by age group, these differences in risk variables were more evident in men aged 50 to 64 years than in men aged 65 years and older.

**Discussion**

The present study showed a distinct difference in both pathology and serum total cholesterol levels among stroke types. Intracranial cerebral hemorrhage was characterized by arteriosclerosis, whereas cortical artery infarction was characterized by atherosclerosis. The serum cholesterol difference was particularly evident between cerebral hemorrhage and cortical artery infarction. Age-adjusted mean value of serum cholesterol was nearly 200 mg/dL in cortical artery infarction versus 164 mg/dL in cerebral hemorrhage. Mean serum cholesterol for penetrating artery infarction was intermediate. A population-based study in a neighboring community to the surveyed area showed that mean serum total cholesterol was 175 to 179 mg/dL in the 1970s and 1980s. Therefore, mean serum total cholesterol seems to be lower for cerebral hemorrhage and higher for cortical artery infarction than is characteristic of the free-living population from which the subjects were drawn. This observation is consistent with the results of other epidemiological studies. An incidental finding is that serum cholesterol is reduced in men who died of cancer, respiratory disease, or trauma. This finding agrees with findings in recent articles. Not supporting the findings of this research is a recent clinical study that reported no difference in serum total cholesterol levels among stroke types, either for 3-month survivors or all fatal and nonfatal cases.

In the present study, serum total cholesterol levels were measured after the onset of disease. Serum cholesterol concentrations are reduced in various diseases, including the later stages of cancer and liver and digestive disorders. Although this issue has not, to our knowledge, been studied specifically, the possibility that low cholesterol is a consequence of stroke seems unlikely. Wot et al. and Mendez et al. suggest that the cholesterol level does decline during the recovery period. In our study, measurement of serum cholesterol was done on the first day of admission, so that lower cholesterol levels expected after stroke secondary to poor nutrition or liver or renal dysfunction had not yet developed for most cases. Sixteen of the men (13 with stroke) in this study had serum cholesterol measured by us as a part of a separate population survey, and the mean ± SD of cholesterol was 161 ± 22 mg/dL compared with 167 ± 28 mg/dL for those same men measured during their terminal hospitalization. The correlation coefficient between the two values was 0.60 (P < 0.01). Therefore, cholesterol values at admission appear to be representative of usual cholesterol levels before the onset of disease.

This study's findings for blood pressure should be regarded with caution because the blood pressure level on the first day of admission may be influenced by a stroke in progress.

A significant positive association was found between serum total cholesterol concentration and atherosclerosis scores of basal cerebral arteries. This result is consistent with other pathology studies of American Japanese and whites. Furthermore, this positive association was found predominantly for the larger arter-
ies, which is consistent with the pathology study of American Japanese.\textsuperscript{29} It was demonstrated that lipid depositions and atheroma were observed in atherosclerotic lesions of larger basal cerebral arteries such as coronary arteries.\textsuperscript{31,32} although the development of atherosclerosis in basal cerebral arteries was delayed by approximately 20 years, and the grade of atherosclerosis was weaker than atherosclerosis in coronary arteries.\textsuperscript{32} Animal experiments demonstrated that a long-term high-fat, high-cholesterol diet in 3 or 4 years induced atheroma in basal cerebral arteries as well as in coronary arteries,\textsuperscript{33,34} whereas experiments of a shorter duration failed to detect gross atherosclerosis in basal cerebral arteries.\textsuperscript{35,36} More recent studies using hypercholesterolemic diets during several months induced fat depositions with accumulation of foam cells in the intima of the larger basal cerebral arteries.\textsuperscript{37,38} These findings together indicate that high serum cholesterol levels contribute to development of atherosclerosis in the larger basal cerebral arteries, as in coronary arteries.

Mean serum total cholesterol was higher in men with stenosis in intracerebral penetrating arteries than in men without it for the three selected types of stroke combined and cerebral hemorrhage. However, it is noteworthy that mean serum cholesterol was less than 200 mg/dL even in men with significant stenosis. A lack of lipid depositions in penetrating arteries of stroke cases\textsuperscript{31} implies that the stenosis in penetrating arteries may have a different pathogenesis from the stenosis in basal cerebral arteries. It has been suggested that stenosis in the penetrating arteries reflects arteriosclerosis, mostly as a result of hypertension.\textsuperscript{31}

Distribution of stenosis in basal cerebral and intracerebral penetrating arteries also varied among stroke types, especially for the younger age group. Less evident differences in stenosis distributions for the older group were probably due to multiple pathogenetic processes occurring with increasing exposure at older ages. Stenosis of basal cerebral arteries was prominent for cortical artery infarction, whereas stenosis of both basal and intracerebral arteries was seen in penetrating artery infarction. On the other hand, a finding of no stenosis was more characteristic of cerebral hemorrhage. In each of these diagnoses, the arteries involved in the clinical event are those showing the most stenosis. However, cerebral hemorrhage, particularly in those aged 65 years and older, may represent multiple pathological processes, in that a substantial incidence of basal cerebral artery stenosis was also seen in these cases.

For cerebral hemorrhage, 34\% of the cases showed no significant stenosis in either basal or intracerebral arteries, whereas the respective proportion of cortical artery infarction and penetrating artery infarction was less than 5\%. Furthermore, within cerebral hemorrhage, serum cholesterol levels were even lower in men without stenosis in either basal or intracerebral arteries than in men with stenosis in either type of artery. These results imply that the disease process of cerebral hemorrhage is different from that for thrombotic infarction. Previous pathological studies showed that the pathogenesis of cerebral hemorrhage is the rupture of microaneurysm resulting from angionecrosis (arteriolonecrosis, fibrinoid necrosis, or lipohyalinosis) in intracerebral penetrating arteries.\textsuperscript{31,39} Fig 3 shows an example of angionecrosis in a case of cerebral hemorrhage from the present study. Pathological findings of angionecrosis are the loss of medial smooth-muscle cells, the infiltration of blood plasma into the intima, the histolysis of internal elastic lamina and intimal collagen fibers, intimal fibrin deposition (fibrinoid degeneration), and luminal dilatation. Unlike atherosclerosis, there are neither clear proliferative changes nor lipid deposition in the intima. Disappearance of medial smooth-muscle cells contributes to fragility of the vascular wall, which leads to microaneurysm in the presence of high blood pressure. It was reported that angionecrosis was found in almost 100\% of cerebral hemorrhage cases when examined in a series of consecutive microscopic slides.\textsuperscript{40}

The pathological relation between low serum cholesterol levels and cerebral hemorrhage is uncertain. We hypothesize that a very low serum cholesterol contributes to the development of a fragile cerebrovascular endothelium, eventually leading to the development of angionecrosis and cerebral hemorrhage in the presence of hypertension. There are several lines of evidence that support

\textbf{Fig 3.} Microscopic findings of angionecrosis with microaneurysm in an intracerebral small artery (diameter, 200 \(\mu\)m). Arrows indicate a microaneurysm (elastica-van Gieson stain).
this hypothesis. Our previous study indicated that men
with cerebral hemorrhage had a significantly higher
degree of erythrocyte fragility and lower serum and
erthrocyte cholesterol levels than age-matched control
subjects. In vitro studies demonstrated increased os-
motic fragility of erythrocyte membranes when the mem-
brane cholesterol was reduced. Stroke-prone hyper-
tensive rats showed a significantly lower cholesterol
in both serum and erythrocyte membranes and showed
increased osmotic fragility of erythrocyte membranes
when compared with Wistar-Kyoto rats. On the other
hand, a high-cholesterol or high-fat diet increases total cho-
lesterol in erythrocyte membrane and leukocytes as well as in
plasma. A high-fat diet was also reported to reduce the
occurrence of stroke in stroke-prone hypertensive rats.
Furthermore, an animal study using Wistar rats
with a renal artery clamp showed that a diet-induced
increase in the serum total cholesterol level from very
low (118 mg/dL) to moderate (242 mg/dL) was
associated with a significant reduction in the degree of
angioneurosis, in which the degree of angioneurosis was
measured with percent area occupied by smooth-muscle
cells in the media of middle cerebral arteries.

Although a causal relation between low serum cho-
lesterol levels and cerebral hemorrhage has not been
established, our observations confirm a positive associ-
ation of serum total cholesterol with cortical artery
infarction and an inverse association with cerebral
hemorrhage. Further studies are needed to determine
the precise nature of this association.

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