A Prospective Study of Cerebrovascular Disease in Japanese Rural Communities, Akabane and Asahi

Part 1: Evaluation of Risk Factors in the Occurrence of Cerebral Hemorrhage and Thrombosis

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SUMMARY An epidemiological study of cerebrovascular disease in Akabane and Asahi, Japan, was made. (These cities are located near Nagoya, Japan.) The study population included 4,737 men and women aged 40 to 79 at the time of entry into the study. There were 4,186 persons who were examined and, of these, 264 cases of cerebrovascular attacks were observed between 1964 and 1970. The incidence rate of stroke in those persons not responding to the survey was 15.9 times higher than in those persons examined according to person-year observation in Akabane. The risk factors for cerebral hemorrhage and thrombosis were evaluated by age-adjusted and sex-adjusted relative risks. The predisposing factors to cerebral hemorrhage appeared to be high blood pressure, high left R wave, ST depression, T abnormality, capillary fragility counts, previous medical history of stroke, and albuminuria. For cerebral thrombosis, the predisposing factors appeared to be high blood pressure, ST depression and funduscopic sclerotic findings, and those factors assumed to be significant were glycosuria and smoking habits. Ocular funduscopic abnormality was the most prominent risk factor for cerebral thrombosis, while high blood pressure and ECG abnormalities were highly related to cerebral hemorrhage. It was suggested that those subjects with a relatively higher blood pressure may have a higher relative risk of cerebral hemorrhage than those with a lower (normal range) blood pressure. A previous or family history of stroke also appeared significantly related to cerebral hemorrhage.

ESPECIALLY in Japan, cerebrovascular disease may have some etiological features different from those of coronary heart disease. Risk factors for coronary heart disease have been evaluated and those for cerebrovascular disease have been investigated only recently. The incidence ratio of cerebral hemorrhage to thrombosis is still controversial in Japan, while it is consistently less than 1.0 in Western countries and the United States. The incidence of cerebrovascular disease has been highest in the northern part of the Japanese mainland. Low temperatures associated with housing inadequacy and excessive salt intake have been suspected as major factors in the high morbidity and mortality rates. Recently, it was stated that unbalanced nutrition might be a risk factor for cerebral hemorrhage. The incidence of cerebral hemorrhage has been decreasing steadily, possibly due to the continuous medical care (supported by a nationwide health insurance program) of hypertension in Japan.

The study started in 1963 in order to investigate the incidence and prevalence of cerebrovascular diseases and to evaluate risk factors. An epidemiological follow-up study has been conducted in two rural Japanese communities, Akabane and Asahi (near Nagoya), located in the central part of the Japanese mainland. This is a preliminary report describing the two communities, the survey method and the incidence of cerebrovascular diseases in the two populations during a seven-year period. The risk factors (medical history, physical signs and laboratory values) for cerebral hemorrhage and thrombosis are assessed.

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Methods

Akabane is located along the southern coast of the Atsugi peninsula south of Nagoya. The major industry is agriculture. Asahi is located in the low mountain area about 70 km northeast of Nagoya. The principal industries are agriculture and forestry. The majority of the residents are only part-time farmers, and they work at other occupations. Their economic level of life is steadily improving, but is still poorer than the urban area.

The total 1965 census of Akabane and Asahi was 6,696 and 6,482 persons, respectively, gradually decreasing by 1970 to 6,400 and 5,753, respectively. Akabane has three general practitioners and a regional health center, Atsumi Hospital. There are two general practitioners in Asahi and the Asuke Hospital is the regional health center. The medical personnel of both communities were very cooperative in this follow-up study by immediately reporting any new or suspected cases of cerebrovascular disease or, when periodically asked, by thoroughly listing their cases of cerebrovascular disease. Death certificates also were studied.

The general practitioners made differential diagnoses of cerebrovascular diseases based on specified diagnostic criteria, which were a modification of the classification reported by Millikan et al. When the diagnosis was uncertain, we tried to contact the general practitioner to discuss the case and determine the diagnosis. Autopsied cases of cerebrovascular disease were rare, even in the regional key hospitals, due to traditional or religious custom.

The age of the subjects was 40 or more at entry to the study in 1964. They were examined periodically by the study physicians along with paramedical personnel and nutritionists. Their symptoms and medical histories of stroke, hypertension, cardiac and renal diseases, and diabetes were checked and recorded by trained laymen.
against a self-administered questionnaire, which had been mailed to the subjects prior to examination. The questionnaire covered such topics as daily activities (casual or restrained work) and smoking and drinking (occasional or regular) habits. “Casual work” meant sometimes and “restrained work” referred to the usual work-week with limited working hours and/or physical activity. The occasional drinker did not have alcoholic beverages every day whereas the regular drinker did.

The physical and laboratory examinations included anthropometric measurements of height, weight and skinfolds on R-triceps and subscapular sites, neck circumference, casual BP, resting and exercise (Master’s two-step test) ECGs, ocular funduscopy, urinalysis by test tape of protein and sugar, serum cholesterol determinations, and capillary fragility test.

Funduscopic color pictures were taken with a Mamiya fundus camera. These were identified by simultaneous recording of the date and name and identification number of the subject appearing side by side. The pupil of the right eye was dilated by applying eye drops of tropicamide and phenylephrine hydrochloride. After extensive visual observation, at least three different parts of the retina were photographed. The funduscopic picture was enlarged and diagnosed by the study physicians by using a viewer called “Medical Vision,” which was based on a modification of the classification cited by Aoki.*

All of the data were coded and punched on IBM cards and processed for analysis by an IBM sorting machine and a FACOM 230-60 electronic computer in the Nagoya University Computation Center. The significance of each finding was tested by $X^2$ and t-test. Age-adjusted and sex-adjusted relative risks for each category were calculated and statistically tested against the overall incidence rate of cerebral hemorrhage and thrombosis and then a ratio of relative risk for a specified category was calculated in order to eliminate the error due to small numbers of observations in a specific category.

### Results

The cumulative response rate and the age and sex distributions of the subjects are shown in table 1. The overall response rate was 90.3% in Akabane and 86.7% in Asahi. Generally, the response rates in younger age groups were lower than in older age groups, and those in men were consistently lower than in women.

As shown in table 2, cerebral hemorrhage occurred in 143 of 264 patients diagnosed as having cerebrovascular disease in Akabane and Asahi between 1964 and 1970, while cerebral thrombosis occurred in 109 subjects during the same time period. The incidence ratio of cerebral hemorrhage to thrombosis was 1.31. Subarachnoid hemorrhage (eight), cerebral embolism (one) and unclassified event (three) also were diagnosed in these two populations.

After the first examination, cerebral hemorrhage and thrombosis occurred in 71 and 58 patients (age: 40 to 79 years), respectively, and these patients had further analyses to evaluate the significance of risk factors (table 3). In the first survey of persons 40 years of age or more with cerebrovascular events, the incidence rate in the non-respondents was much higher than in those who were examined; the ratio of incidence rates was 15.9 (table 4). Thus, the non-respondents were assumed to be the high-risk group for cerebrovascular disease.

### Table 1 Cumulative Response Rates by Age and Sex in Population Survey of Akabane and Asahi (1964 to 1968)

<table>
<thead>
<tr>
<th></th>
<th>Men (age)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Women (age)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40-49</td>
<td>50-59</td>
<td>60-69</td>
<td>70-79</td>
<td>Total</td>
<td>40-49</td>
<td>50-59</td>
<td>60-69</td>
<td>70-79</td>
<td>Total</td>
</tr>
<tr>
<td>Akabane</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered</td>
<td>332</td>
<td>271</td>
<td>229</td>
<td>115</td>
<td>1,035</td>
<td>331</td>
<td>371</td>
<td>268</td>
<td>144</td>
<td>1,197</td>
</tr>
<tr>
<td>Examined</td>
<td>293</td>
<td>229</td>
<td>115</td>
<td>90</td>
<td>908</td>
<td>331</td>
<td>268</td>
<td>144</td>
<td>1</td>
<td>1,107</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>85.6</td>
<td>86.9</td>
<td>93.4</td>
<td>94.3</td>
<td>97.7</td>
<td>87.9</td>
<td>83.0</td>
<td>90.0</td>
<td>92.5</td>
<td>89.0</td>
</tr>
<tr>
<td>Asahi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registered</td>
<td>357</td>
<td>329</td>
<td>305</td>
<td>170</td>
<td>1,161</td>
<td>457</td>
<td>379</td>
<td>326</td>
<td>182</td>
<td>1,344</td>
</tr>
<tr>
<td>Examined</td>
<td>260</td>
<td>276</td>
<td>285</td>
<td>154</td>
<td>975</td>
<td>396</td>
<td>351</td>
<td>317</td>
<td>312</td>
<td>1,196</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>72.8</td>
<td>83.9</td>
<td>93.4</td>
<td>90.6</td>
<td>84.0</td>
<td>86.7</td>
<td>92.6</td>
<td>97.2</td>
<td>72.5</td>
<td>89.0</td>
</tr>
</tbody>
</table>

Overall response rate: Akabane 90.3% and Asahi 86.7%.
BP and ST-T abnormality had a relative risk for cerebral hemorrhage of 3.7, and a low risk (1.9) of cerebral thrombosis. In those with high BP, abnormal ST-T and funduscopic findings was not higher (2.7) than in those with only high BP and ST-T abnormality (risk: 3.7); while in those subjects with high BP, abnormal ST-T and funduscopic findings was higher (2.7) in those having only abnormal ST-T and funduscopic findings (3.0).

Anthropometric Measurements

Relative weight of those examined from Akabane and Asahi was less than the average figure in Japan as seen from the distribution cited in table 5. The first category of relative weight had the lowest risk of cerebral hemorrhage and the second category of relative weight had the lowest risk of cerebral thrombosis, but the difference from the other categories was not statistically significant.

We found that the lowest incidence rate of cerebral hemorrhage was in the first category (< 34 cm) of neck circumference while the larger the neck circumference, the higher the relative risks of both cerebral hemorrhage and thrombosis.

The third category of triceps skinfold (3.0 to 4.9 mm) had the lowest relative risks for both cerebral hemorrhage and thrombosis. The second category (34 to 35 cm) of neck circumference had the lowest relative risk for cerebral hemorrhage, while the first category (< 34 cm) of neck circumference had the lowest relative risk for cerebral thrombosis. The larger the neck circumference, the higher were the relative risks of cerebral hemorrhage and thrombosis, although the relationship did not reach a statistically significant level.

Urinalysis

Albuminuria was detected in 169 of 4,231 subjects, and the positive cases showed a relative risk of 2.7 for cerebral hemorrhage with statistical significance (table 9). In those patients with a trace level of albuminuria the relative risks for cerebral hemorrhage and thrombosis were 1.4 and 1.9, respectively.

Those persons with glycosuria had a 1.7 relative risk of cerebral hemorrhage.

Serum Cholesterol Level and Capillary Fragility Test

Age-adjusted and sex-adjusted relative risk of cerebral hemorrhage by serum cholesterol levels was highest (1.8) in the first category (< 130 mg/dl) with statistical significance. The second category (130 to 159 mg/dl) which had the lowest relative risk for cerebral thrombosis. The larger the serum cholesterol levels, the higher the relative risk of cerebral hemorrhage and thrombosis.

| TABLE 6 | Age-Adjusted and Sex-Adjusted Relative Risk of ECG and Funduscopic Findings |
|-----------------|-------------------------------|-----------------|-----------------|-----------------|-----------------|
|                | No. pts. | Cerebral hemorrhage | Cerebral thrombosis |
|                |          | No. cases | RRa (ratio) | No. cases | RRa (ratio) |
| ECG            |          |            |              |            |              |
| Normal         | 2,194    | 13        | 0.42 (1.0) | 19        | 0.78 (1.0)  |
| Q-QS           | 51       | 3         | 2.54 (3.3x)| 3         | 2.75 (3.2x) |
| High left R-wave | 869      | 32        | 1.90 (3.2x)*| 17        | 1.14 (1.4x) |
| ST depression  | 412      | 21        | 2.56 (4.5x)*| 12        | 1.90 (2.5x) |
| T abnormality  | 229      | 13        | 2.83 (5.1x)*| 4         | 1.14 (1.4x) |

| Funduscopic    |          |            |              |            |              |
| Hypertension   |          |            |              |            |              |
| Grade: 0       | 1,700    | 16        | 0.77 (1.0) | 11        | 0.69 (1.0)  |
| 1              | 1,275    | 21        | 0.97 (1.3x)| 13        | 0.74 (1.1x) |
| 2              | 618      | 16        | 1.26 (1.6x)| 17        | 1.60 (2.3x) |
| 3-4            | 115      | 2         | 0.87 (1.1x)| 4         | 2.00 (2.9x) |
| Not examined    | 405      | 12        | 1.37 (1.8x)| 13        | 1.74 (2.5x) |

| Sclerosis      |          |            |              |            |              |
| Grade: 0       | 1,324    | 11        | 0.65 (1.0) | 3         | 0.23 (1.0)  |
| 1              | 1,973    | 32        | 1.04 (1.6x)| 25        | 0.99 (4.2x) |
| 2              | 367      | 7         | 0.98 (1.5x)| 15        | 2.53 (10.8x)*|
| 3-4            | 136      | 5         | 1.84 (2.8x)| 2         | 0.91 (3.9x) |
| Not examined    | 405      | 12        | 1.37 (2.1x)| 13        | 1.74 (7.5x) |

* p <0.001, tp <0.05, tp <0.01.
The relative risks of cerebral hemorrhage and thrombosis were higher in subjects who had a previous history of hypertension than in those who did not. Those persons with a previous history of hypertension had relative risks for cerebral hemorrhage at 2.7 and for cerebral thrombosis at 1.6, comparable to those of patients taking antihypertensive agents. On the other hand, patients with a family history of stroke or hypertension showed a significantly higher relative risk of cerebral hemorrhage rather than thrombosis. The incidence rate in patients with previous or family history of heart disease was less but not significantly different.

**Daily Activity and Smoking and Drinking Habits**

Subjects with no or casual daily activity had a relative risk of 2.5 for cerebral hemorrhage with statistical significance (table 11). It was quite impressive that the relative risks of cerebral hemorrhage and thrombosis in non-smokers was lower than in smokers or ex-smokers, but the difference was not statistically significant. Habitual drinkers had the highest relative risk for cerebral thrombosis, and occasional drinkers the lowest incidence rate of both cerebral hemorrhage and thrombosis.

A reverse relationship was found between the relative risks of cerebral hemorrhage and thrombosis and food intake, i.e., those persons ingesting 20 bowls of rice or more per day had the lowest relative risk of cerebral hemorrhage but the highest relative risk of cerebral thrombosis (table 11).

**Medical History**

Subjects previously having a stroke had a very high relative risk of cerebral hemorrhage (5.4) and thrombosis (2.7) (table 12). Those persons with a previous history of hypertension had relative risks for cerebral hemorrhage at 2.2 and for cerebral thrombosis at 1.6, results comparable to those of patients taking antihypertensive agents. On the other hand, patients with a family history of stroke or hypertension showed a significantly high relative risk of cerebral hemorrhage (statistically significant) than thrombosis; however, there was no difference between the relative risks of cerebral thrombosis in patients who either previously received or regularly used antihypertensive agents.

**Table 8**  
**Age-Adjusted and Sex-Adjusted Relative Risk by Anthropometric Measurements**

<table>
<thead>
<tr>
<th>Relative weight (%)</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pts.</td>
<td>RRa (ratio)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>−15</td>
<td>1,449</td>
<td>25</td>
</tr>
<tr>
<td>−14 ~ −5</td>
<td>1,398</td>
<td>13</td>
</tr>
<tr>
<td>−4 ~ +4</td>
<td>756</td>
<td>10</td>
</tr>
<tr>
<td>+5 ~</td>
<td>569</td>
<td></td>
</tr>
</tbody>
</table>

| Skinfold (mm)       |                    |                     |                     |                     |
| Tripes              |                     | 4                  | 0.91 (1.2x)         | 6                  | 1.34 (1.7x)          |
|                      | 2.0-2.9             | 8                  | 1.03 (1.4x)         | 7                  | 0.88 (1.1x)          |
|                      | 3.0-4.9             | 4                  | 0.73 (1.0)          | 3                  | 0.79 (1.0)           |
|                      | 5.0                 | 5                  | 1.50 (2.1x)         | 2                  | 1.25 (1.6x)          |
| Subscapular         | 1-1.9               | 8                  | 0.98 (1.0)          | 9                  | 1.23 (1.6x)          |
|                      | 2.0-2.9             | 8                  | 1.03 (1.1x)         | 8                  | 1.14 (1.5x)          |
|                      | 3.0-3.9             | 6                  | 1.10 (1.1x)         | 3                  | 0.77 (1.0)           |
| Umbilical           | −4.9                | 6                  | 1.18 (1.3x)         | 4                  | 0.78 (1.0)           |
|                      | 5.0-5.9             | 10                 | 1.07 (1.2x)         | 9                  | 0.96 (1.2x)          |
|                      | 10.0−               | 6                  | 0.91 (1.0)          | 7                  | 1.26 (1.7x)          |

<table>
<thead>
<tr>
<th>Neck circumference (cm)</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>−33</td>
<td>904</td>
<td>9</td>
</tr>
<tr>
<td>34-35</td>
<td>475</td>
<td>5</td>
</tr>
<tr>
<td>36-37</td>
<td>262</td>
<td>6</td>
</tr>
<tr>
<td>38−</td>
<td>156</td>
<td>4</td>
</tr>
</tbody>
</table>

**Table 9**  
**Age-Adjusted and Sex-Adjusted Relative Risk of Albuminuria and Glycosuria**

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>3,743</td>
<td>52</td>
</tr>
<tr>
<td>±</td>
<td>320</td>
<td>9</td>
</tr>
<tr>
<td>+ ~ + + +</td>
<td>169</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glycosuria</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>−</td>
<td>4,907</td>
<td>66</td>
</tr>
<tr>
<td>+</td>
<td>133</td>
<td>5</td>
</tr>
</tbody>
</table>

* − = negative, ± = trace, + ~ + + + = positive.

*p < 0.01.
Capillary fragility counts

Subjective Symptoms

The subjects with any one of 26 subjective symptoms (table 13) had nonsignificant age-adjusted and sex-adjusted relative risks for cerebral hemorrhage and thrombosis. More than four cases of cerebral hemorrhage with subjective symptoms (speech disturbance, fainting, insomnia, stiff gait) had a relative risk more than 2.0, while none of these occurred in cerebral thrombosis.

Discussion

Some investigators in the United States and Europe doubt the diagnostic accuracy of cerebrovascular diseases in Japan. The Classification of Cerebrovascular Diseases has been familiar to Japanese general practitioners, but this has not been familiar to Japanese general practitioners as well as investigators of cerebrovascular diseases, but this has not altered the general practitioner’s habits of differential diagnosis. Hirota and Lau reported that clinical diagnosis of cerebral hemorrhage was correct in 70% of the autopsied cases and that the accuracy rate was unchanged during the last ten years. They pointed out that in Japan the accuracy rate for diagnosing cerebral infarction and subarachnoid hemorrhage was less than that of cerebral hemorrhage but did improve during the last ten years.

The incidence ratio of cerebral hemorrhage to thrombosis in these communities (Akabane and Asahi) was slightly higher than that reported in other epidemiological studies of Japanese populations but was lower than that in national death statistics. Some investigators reported that cerebral hemorrhage was overdiagnosed as compared to thrombosis, while others considered the high ratio characteristic of strokes in Japan.

High blood pressure is the most predominant risk factor of stroke, especially hemorrhage, but there have been many various opinions regarding borderline hypertension. Relative risk of borderline systolic hypertension (i.e., 140 through 159 mm Hg) was three times as high as the lowest figure for cerebral hemorrhage and double the figure for thrombosis. Although the difference in incidence rates was statistically tested to the overall rate (because a few cases were found in the lowest category of systolic BP), it was concluded that borderline systolic hypertension could give an additional risk of cerebral hemorrhage or thrombosis. This fact does not directly justify the lifelong pharmacological therapy for borderline hypertensives, but at least suggests that their BP should be periodically checked and that they should control every aspect of their daily life.

Furthermore, the subjects with systolic pressures of 120 through 139 mm Hg showed a higher relative risk of cerebral thrombosis than those with a BP of 119 mm Hg or less; the risks are similar for diastolic pressures and cerebral hemorrhage (even when pressures are within normal ranges).

It was noteworthy that in subjects with systolic pressures of 160 through 179 mm Hg the relative risk of cerebral hemorrhage was much higher than for thrombosis. For pressures of 180 mm Hg or more the relative risk for

### Table 10: Age-Adjusted and Sex-Adjusted Relative Risk by Serum Cholesterol Levels and Capillary Fragility Counts

<table>
<thead>
<tr>
<th>Serum cholesterol (mg/dl)</th>
<th>No. pts.</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>RRa (ratio)</td>
<td>No. cases</td>
</tr>
<tr>
<td>-129</td>
<td>370</td>
<td>10</td>
<td>1.75 (3.1x)</td>
</tr>
<tr>
<td>130-159</td>
<td>878</td>
<td>8</td>
<td>0.56 (1.0)</td>
</tr>
<tr>
<td>160-189</td>
<td>1,159</td>
<td>14</td>
<td>0.76 (1.4x)</td>
</tr>
<tr>
<td>190-219</td>
<td>936</td>
<td>15</td>
<td>0.97 (1.7x)</td>
</tr>
<tr>
<td>Capillary fragility counts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-3</td>
<td>661</td>
<td>4</td>
<td>0.47 (1.0)*</td>
</tr>
<tr>
<td>4-11</td>
<td>410</td>
<td>6</td>
<td>1.18 (2.5x)</td>
</tr>
<tr>
<td>12-19</td>
<td>273</td>
<td>4</td>
<td>1.11 (2.4x)</td>
</tr>
<tr>
<td>20-</td>
<td>566</td>
<td>12</td>
<td>1.63 (3.5x)</td>
</tr>
</tbody>
</table>

* p <0.05.

### Table 11: Age-Adjusted and Sex-Adjusted Relative Risk by Daily Activity and Habits and Medications

<table>
<thead>
<tr>
<th>Work activity</th>
<th>No. pts.</th>
<th>Cerebral hemorrhage</th>
<th>Cerebral thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>RRa (ratio)</td>
<td>No. cases</td>
</tr>
<tr>
<td>None</td>
<td>203</td>
<td>9</td>
<td>1.74 (2.3x)</td>
</tr>
<tr>
<td>Casual</td>
<td>168</td>
<td>10</td>
<td>2.48 (3.2x)*</td>
</tr>
<tr>
<td>Restrained</td>
<td>441</td>
<td>9</td>
<td>0.98 (1.3x)</td>
</tr>
<tr>
<td>Regular</td>
<td>2,837</td>
<td>31</td>
<td>0.77 (1.0)</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2,420</td>
<td>33</td>
<td>0.90 (1.0)</td>
</tr>
<tr>
<td>1-9</td>
<td>323</td>
<td>13</td>
<td>1.75 (1.9x)</td>
</tr>
<tr>
<td>10-19</td>
<td>621</td>
<td>16</td>
<td>1.32 (1.5x)</td>
</tr>
<tr>
<td>20-</td>
<td>414</td>
<td>7</td>
<td>1.07 (1.2x)</td>
</tr>
<tr>
<td>Drinking</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2,427</td>
<td>43</td>
<td>1.03 (1.1x)</td>
</tr>
<tr>
<td>Occasional</td>
<td>1,070</td>
<td>19</td>
<td>0.93 (1.0)</td>
</tr>
<tr>
<td>Regular</td>
<td>295</td>
<td>8</td>
<td>1.28 (1.4x)</td>
</tr>
<tr>
<td>Rice intake (bowls/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-5</td>
<td>740</td>
<td>13</td>
<td>1.00 (1.4x)</td>
</tr>
<tr>
<td>6-11</td>
<td>1,916</td>
<td>36</td>
<td>1.11 (1.6x)</td>
</tr>
<tr>
<td>12-19</td>
<td>869</td>
<td>11</td>
<td>0.91 (1.3x)</td>
</tr>
<tr>
<td>20-</td>
<td>206</td>
<td>2</td>
<td>0.70 (1.0)</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>3,104</td>
<td>23</td>
<td>0.51 (1.0)</td>
</tr>
<tr>
<td>Regular</td>
<td>351</td>
<td>18</td>
<td>2.21 (4.4x)f</td>
</tr>
<tr>
<td>Previous</td>
<td>376</td>
<td>19</td>
<td>2.29 (4.5x)f</td>
</tr>
</tbody>
</table>

*p <0.01, tp <0.05, f p <0.001.
cerebral hemorrhage rose remarkably (from 9.8 to 20.9) while decreasing for cerebral thrombosis (from 7.3 to 5.4). Some epidemiological studies of cerebrovascular and cardiovascular diseases suggest that the relative risk of cerebral hemorrhage and thrombosis would be high in subjects with the highest diastolic BP. This controversial statement, in our opinion, needs further investigation for clarification.

The incidence rates of cerebral hemorrhage and thrombosis were lowest in those with diastolic pressures of 69 mm Hg or less. The relative risks increased sharply with the increase in diastolic pressure. It is noteworthy that diastolic blood pressures of 70 through 89 mm Hg gave additional risk of stroke compared with much lower diastolic pressures, although both categories have been assumed to be in the normal range.

Most stroke epidemiological studies indicate that ECG abnormalities were very important risk factors not only for ischemic heart disease but also for stroke.3 While the relative risk of cerebral hemorrhage was higher than cerebral thrombosis in subjects with ECG abnormalities, the risk of cerebral thrombosis was remarkably higher than for cerebral hemorrhage in patients with abnormal funduscopic findings.

The low incidence rate of cerebral thrombosis in those subjects without sclerotic findings (by Scheie's classification) was quite impressive, and this accounted for the higher risk ratio of the other categories, including the risk ratio to the contraindicated group for funduscopic examination.

Aoki reported the significance of further precise funduscopic findings in cerebral hemorrhage and thrombosis, based on similar material. Although several Japanese investigators have stressed the significance of funduscopic findings in predicting the occurrence of cerebrovascular diseases,5-22 there still is some hesitation in applying the ocular funduscopic examination for screening purposes, even in Japan. Glaucoma patients (high-risk group) should be excluded from the ocular funduscopic examination. The fundus camera is still expensive and inconvenient and requires a specialist, thus limiting the practical use of this equipment.

It was quite impressive that most of our subjects had a lower weight than the average value (obtained by the National Nutrition Survey conducted in Japan) in persons of the same age, sex and height.

Several reports have suggested that excess body weight alone was not related to the severity of cerebral atherosclerosis,5-7,14,22 and we confirmed that in this study relative weight did not show any significant relationship with the relative risk of either cerebral hemorrhage or thrombosis. Although the leanest people had the lowest relative risk, the lowest relative risk according to triceps skinfold was found in the third category (3.0 to 4.9 mm). In other words, those with thin triceps skinfold showed higher relative risk of cerebral hemorrhage and thrombosis, and this was true of subscapular skinfold and cerebral thrombosis. Thin skinfold could be considered a sign of poor unbalanced nutrition, which is an important contributing factor to the occurrence of stroke, especially hemorrhage.5,6

Neck circumference has been considered a representative measure of constitutional predisposition to stroke (a popular idea in Japan), and it was suggested in this study that the larger the neck circumference, the more frequently cerebral hemorrhage and thrombosis occurred.

Albuminuria was found in 169 cases during the first examination, and showed a significantly higher relative risk of cerebral hemorrhage. Several investigators have reported that albuminuria showed a modestly high risk of stroke.5-9,24 Albuminuria (common in these communities) might be due to hypertension or arteriosclerotic renal dysfunction rather

### Table 12: Age-Adjusted and Sex-Adjusted Relative Risk by Medical History

<table>
<thead>
<tr>
<th>Medical History</th>
<th>No. pts.</th>
<th>Cerebral hemorrhage No. cases</th>
<th>RRa (ratio)</th>
<th>Cerebral thrombosis No. cases</th>
<th>RRa (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>2,120</td>
<td>17</td>
<td>0.61 (1.0)</td>
<td>19</td>
<td>0.85 (1.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>45</td>
<td>6</td>
<td>5.35 (8.8x)*</td>
<td>3</td>
<td>2.71 (3.2x)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>635</td>
<td>29</td>
<td>2.24 (3.7x)*</td>
<td>17</td>
<td>1.60 (1.9x)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>477</td>
<td>6</td>
<td>0.73 (1.2x)</td>
<td>6</td>
<td>0.97 (1.2x)</td>
</tr>
</tbody>
</table>

* p <0.001, tp <0.05.

### Table 13: Age-Adjusted and Sex-Adjusted Relative Risk of Subjects With Subjective Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. pts.</th>
<th>Cerebral hemorrhage No. cases</th>
<th>RRa (ratio)</th>
<th>Cerebral thrombosis No. cases</th>
<th>RRa (ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>761</td>
<td>12</td>
<td>1.01</td>
<td>12</td>
<td>1.34</td>
</tr>
<tr>
<td>Dull headache</td>
<td>818</td>
<td>17</td>
<td>1.25</td>
<td>11</td>
<td>1.05</td>
</tr>
<tr>
<td>Vertigo</td>
<td>573</td>
<td>11</td>
<td>1.15</td>
<td>4</td>
<td>0.56</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>629</td>
<td>12</td>
<td>1.07</td>
<td>9</td>
<td>0.99</td>
</tr>
<tr>
<td>Weak memory</td>
<td>1,258</td>
<td>29</td>
<td>1.28</td>
<td>23</td>
<td>1.25</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>113</td>
<td>4</td>
<td>2.02</td>
<td>3</td>
<td>1.58</td>
</tr>
<tr>
<td>Fainting</td>
<td>137</td>
<td>4</td>
<td>2.14</td>
<td>1</td>
<td>0.71</td>
</tr>
<tr>
<td>Fastidious</td>
<td>343</td>
<td>6</td>
<td>1.12</td>
<td>5</td>
<td>1.19</td>
</tr>
<tr>
<td>More sentimental</td>
<td>502</td>
<td>9</td>
<td>1.02</td>
<td>6</td>
<td>0.97</td>
</tr>
<tr>
<td>Insomnia</td>
<td>252</td>
<td>8</td>
<td>2.07</td>
<td>6</td>
<td>1.73</td>
</tr>
<tr>
<td>Numbness</td>
<td>530</td>
<td>9</td>
<td>1.13</td>
<td>6</td>
<td>0.99</td>
</tr>
<tr>
<td>Stiff shoulder</td>
<td>1,469</td>
<td>27</td>
<td>1.13</td>
<td>13</td>
<td>0.70</td>
</tr>
<tr>
<td>Tremor</td>
<td>184</td>
<td>3</td>
<td>0.92</td>
<td>4</td>
<td>1.46</td>
</tr>
<tr>
<td>Sluggish</td>
<td>568</td>
<td>13</td>
<td>1.15</td>
<td>9</td>
<td>0.94</td>
</tr>
<tr>
<td>Flush</td>
<td>225</td>
<td>3</td>
<td>0.86</td>
<td>1</td>
<td>0.41</td>
</tr>
<tr>
<td>Feverish</td>
<td>92</td>
<td>2</td>
<td>1.62</td>
<td>2</td>
<td>2.41</td>
</tr>
<tr>
<td>Stiff gait</td>
<td>235</td>
<td>11</td>
<td>2.07</td>
<td>4</td>
<td>0.85</td>
</tr>
<tr>
<td>Palpitation</td>
<td>845</td>
<td>18</td>
<td>1.32</td>
<td>10</td>
<td>0.99</td>
</tr>
<tr>
<td>Chest oppression</td>
<td>372</td>
<td>10</td>
<td>1.65</td>
<td>7</td>
<td>1.51</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>555</td>
<td>13</td>
<td>1.28</td>
<td>8</td>
<td>1.02</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td>495</td>
<td>5</td>
<td>0.66</td>
<td>6</td>
<td>1.02</td>
</tr>
<tr>
<td>Edema</td>
<td>549</td>
<td>11</td>
<td>1.16</td>
<td>7</td>
<td>0.95</td>
</tr>
<tr>
<td>Nosebleed</td>
<td>35</td>
<td>2</td>
<td>2.37</td>
<td>1</td>
<td>1.31</td>
</tr>
<tr>
<td>Joint pain</td>
<td>332</td>
<td>4</td>
<td>0.84</td>
<td>3</td>
<td>0.83</td>
</tr>
<tr>
<td>Joint swelling</td>
<td>60</td>
<td>2</td>
<td>2.00</td>
<td>2</td>
<td>3.11</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>3</td>
<td>8.00</td>
<td>1</td>
<td>2.74</td>
</tr>
</tbody>
</table>
Blood Pressure

Relative risk in those with systolic pressures of 180 mm Hg or higher was 3.44 for cerebral hemorrhage compared with the overall incidence rate in the same age ranges, and the ratio was 20.9 compared with those having systolic pressures between 120 and 139 mm Hg (table 5). The latter figure was significant. It should be noted that the lowest incidence rate of cerebral hemorrhage was not necessarily observed in the lowest systolic pressure level, although the difference from the second lowest was not statistically significant.

The highest relative risk for cerebral thrombosis was observed in those persons with the second highest systolic blood pressure (160 to 179 mm Hg), and the lowest risk was in the lowest systolic BP (< 120 mm Hg).

The highest relative risk for cerebral hemorrhage was observed in those persons with the highest diastolic BP (>110 mm Hg). The lowest relative risk for both cerebral hemorrhage and thrombosis occurred at the lowest diastolic BP (<70 mm Hg).

ECG Findings

The Q-QS pattern on ECG at entry had the highest relative risk for three patients with cerebral hemorrhage (2.5) and for three patients with cerebral thrombosis (2.7) (table 6). These figures are impressive since most of the patients had no myocardial infarction. For subjects with high left R waves the relative risk was greater for cerebral hemorrhage than for cerebral thrombosis. In those patients with ST depression and T abnormality, the high relative risks might be related to hypertensive heart disease. The risk of cerebral hemorrhage was greater in patients with T abnormality than in those with ST depression; however, the reverse was true for thrombosis, i.e., the risk of cerebral thrombosis was greater in patients with ST depression than in those with T abnormality.

Ocular Funduscopic Findings

The relationship of funduscopic findings to the occurrence of stroke was more remarkable for cerebral thrombosis than cerebral hemorrhage (table 6). Those patients whose funduscopic examination could not be performed due to various eye diseases showed a fairly high relative risk for cerebral hemorrhage, especially thrombosis.

Grade 1 hypertensive retinal changes in patients with cerebral hemorrhage and thrombosis and Grade 1 sclerotic findings in patients with cerebral hemorrhage, according to Scheie's classification (cited by Aoki), were usually assumed to be within normal range. In those patients having cerebral thrombosis with Grade 1 sclerotic findings, the relative risk was 4.2. Although, as usual, the grade classification was sometimes inconsistent (even by the same physician), it would be advisable to discriminate the subjects with Grade 1 sclerotic findings from the others as a high-risk group for cerebral thrombosis.

Combination of BP, ECG and Funduscopic Findings

Those subjects with BP of 160/95 mm Hg or higher and an ECG ST-T abnormality had greater age-adjusted and sex-adjusted relative risk of cerebral hemorrhage than thrombosis, respectively (table 7). Abnormal funduscopic findings were significant risk factors for cerebral thrombosis and hemorrhage. When combined, those persons with a high

<table>
<thead>
<tr>
<th>Table 2: Cerebrovascular Attacks Observed in Akabane and Asahi (1964 to 1970)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
</tr>
<tr>
<td>Cerebral thrombosis</td>
</tr>
<tr>
<td>SAH</td>
</tr>
<tr>
<td>Cerebral embolism</td>
</tr>
<tr>
<td>Unclassified</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

SAH = subarachnoid hemorrhage.

<table>
<thead>
<tr>
<th>Table 3: Index Cases of Cerebral Hemorrhage and Thrombosis for the Evaluation of Risk Factors (Akabane and Asahi, 1964 to 1970)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Subtotal</td>
</tr>
<tr>
<td>Cerebral Thrombosis</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Subtotal</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4: Incidence Rates of Cerebrovascular Diseases in the Examined Persons and in Non-Respondents (Akabane, 1964 to 1970)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Number of strokes</td>
</tr>
<tr>
<td>Incidence rate/100,000/year</td>
</tr>
<tr>
<td>Relative rate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5: Age-Adjusted and Sex-Adjusted Relative Risk by BP Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>- 119</td>
</tr>
<tr>
<td>120 - 139</td>
</tr>
<tr>
<td>140 - 159</td>
</tr>
<tr>
<td>160 - 179</td>
</tr>
<tr>
<td>180 -</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
</tr>
<tr>
<td>- 69</td>
</tr>
<tr>
<td>70 - 89</td>
</tr>
<tr>
<td>90 - 99</td>
</tr>
<tr>
<td>100 -</td>
</tr>
<tr>
<td>110 -</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.001, ***P < 0.01.
RRs: adjusted relative risk (ratio); relative risk ratio to the lowest.
than to chronic nephritis or nephrosis (which are uncommon in these communities).

While elevated blood sugar as the primary determinant of stroke risk is mentioned, our subjects with glycosuria showed only a slightly higher relative risk of cerebral hemorrhage and thrombosis. Although the diabetes did not always have glycosuria, those with consistent fasting glycosuria frequently had diabetes by further laboratory tests. It is well known that diabetes frequently accompanies arteriosclerosis rather than hypertension, and this fact could account for the high relative risk of stroke in patients with glycosuria. Some Japanese investigators, however, reported that glycosuria or diabetes mellitus was not significantly related to stroke.* In our study, albuminuria and glycosuria were correlated with the occurrence of cerebral hemorrhage and thrombosis. To investigate the relationship of renal diseases or diabetes to cerebral hemorrhage and thrombosis, further investigation should be carried out. Low serum cholesterol levels could be a risk factor for cerebral hemorrhage;* in this study, the relative risk of cerebral hemorrhage in those with serum cholesterol of 129 mg/dl or less also was significantly higher (3.1) than that in thrombosis. The lowest incidence rate of cerebral hemorrhage was found in the group with cholesterol levels of 130 to 159 mg/dl.

In the Framingham study the risk of atherothrombotic brain infarction was proportional to the serum cholesterol values in persons under age 50; however, this observation did not apply to intracerebral hemorrhage. Serum cholesterol levels are much higher in persons in the United States than in Japan, and this fact suggests that hypercholesterolemia was not a risk factor for cerebral hemorrhage or thrombosis in this study.

Serum triglyceride levels might be a more significant predisposing factor for stroke than the serum cholesterol levels,* but we were unable to present follow-up data of triglyceride levels at this time. Although fragile capillaries would not directly cause bleeding in the brain, capillary fragility counts might be related to the incidence rate of stroke. High capillary fragility counts proved to be associated with high relative risk of cerebral hemorrhage. This may be related to the fact that cerebral hemorrhage was more prevalent than thrombosis in women (table 3).

In daily life, work activity could be an important index of the physical condition of our subjects, reflecting old age, retirement from work, or illness. The reason for a higher relative risk of cerebral hemorrhage or thrombosis in the casual work activity group was not very clear, but this group consisted of those who positively answered the question: "Are you working sometimes?" Details of the occupation were unclear, and further analysis of the group is necessary.

It was unexpectedly remarkable that smoking habits were related to the occurrence of stroke, especially thrombosis, but the dose-response relationship was not demonstrated, and would be modified by other related factors such as moderate smoking by sick persons. As it is widely accepted that smoking is harmful to persons with cardiovascular diseases, one reason for the high relative risk in mild smokers might be their hesitation to admit excessive smoking. The precise pathophysiological mechanism of smoking in relation to the high incidence of stroke is not known, but one could be that smoking affects peripheral vascular constriction leading to higher systemic BP and also raises the coagulability of blood contributing to the occurrence of cerebral thrombosis. We obtained no history of smoking for analysis and therefore are unable to report on the chronic effects of continuous smoking. Although it was suggested that drinking habits did not show any significant relationship with the incidence rate of stroke, daily drinking of alcoholic beverages accompanied the tendency toward a higher rate of stroke and especially thrombosis. The effect of drinking would be the direct effect of alcohol in the circulatory system and the indirect effect of high-calorie foods, usually salty in Japan, taken with an alcoholic beverage. There is some doubt about the chronic effect of alcohol on the occurrence of stroke.

No statistically significant relationship between rice intake by bowls per day and cerebral hemorrhage was found, although relative risk was lower in our subjects ingesting 12 to 19 bowls of rice per day. Excessive rice intake, usually accompanied by large amounts of salt, and a monotonous diet could reflect a healthy condition in our subjects.

Oral administration of antihypertensive drugs is associated with a high relative risk of stroke, especially hemorrhage; this simply is another facet of the strong relationship between hypertension and stroke. It might be suspected that hypertensive patients without therapy would show a much higher relative risk of stroke than these figures indicate.

Subjects with a previous history of stroke showed a very high relative risk of having another attack, especially cerebral hemorrhage. Relative risk in our subjects with a previous history of hypertension was well matched to that of persons with previous oral administration of antihypertensive drugs.

Alter and Kluznik reported that in the absence of certain predisposing illnesses, close relatives of CVA patients appeared to have no greater risk of CVA than genetically unrelated individuals. However, in our subjects with a family history of stroke there was a statistically significant high risk of cerebral hemorrhage. The possibility of genetic or social inheritance of stroke exists. A study of twins or further investigation of hereditary aggregation may disclose some inheritance.

It is not simple to evaluate subjective symptoms for the occurrence of stroke because of unreliable reporting by our subjects. Although some investigators reported that the incidence of stroke was high in subjects complaining of chest pain, nocturia, vertigo, dyspnea, and numbness, and so forth, all 26 subjective symptoms in our study showed no significantly higher relative risks of cerebral hemorrhage and thrombosis. Age-adjusted and sex-adjusted relative risk of cerebral hemorrhage (2.0) was observed in more than four patients with the following subjective symptoms: speech disturbance, fainting, insomnia, and stiff gait. These symptoms may be related to cerebrovascular dysfunction or peripheral circulatory disturbance.

Conclusions

In Akabane and Asahi (Japan), 4,186 of 4,737 registered residents (40 to 79 years of age) were examined, and 264
cases of cerebrovascular attacks were observed between 1964 and 1970. Age-adjusted and sex-adjusted relative risks of cerebral hemorrhage and thrombosis were evaluated on the following bases: physical signs and laboratory values such as anthropometric measurements, BP levels, ECG findings, ocular funduscopic findings, serum cholesterol levels, and medical history. It was stressed that elevated BP (even when within normal limits) could be a recognizable risk factor to the occurrence of stroke and especially thrombosis. Relative risk of cerebral hemorrhage in our subjects with the highest category of BP was formidable, while risk of cerebral thrombosis was less than in those with the second highest category of BP. Abnormal ECG findings were more predictive of cerebral hemorrhage than thrombosis, and the ocular funduscopic findings showed a much higher relationship to cerebral thrombosis than hemorrhage. Among the concomitant presence of high BP, ST-T abnormality, and/or abnormal fundus, BP and ECG were most predictive of cerebral hemorrhage and ECG and funduscopic findings were predictive of cerebral thrombosis. Among the less significant anthropometric measurements, neck circumference was most impressively related to the occurrence of cerebral hemorrhage and thrombosis, and those with the least skinfold did not necessarily show the lowest relative risk of stroke. While relative risk of cerebral hemorrhage in subjects with albuminuria was significantly high, risk of cerebral thrombosis was highest in those with glycosuria. The patients in the lowest category of cholesterol level (< 130 mg/dl) had the highest relative risk of cerebral hemorrhage. Capillary fragility had a high relative risk of stroke, especially hemorrhage.

No or restricted daily work activity suggested high risk of cerebral hemorrhage and thrombosis. Smoking habit was significantly related to cerebral thrombosis rather than cerebral hemorrhage, although this report lacks the dose-response relationship between the number of cigarettes smoked and the relative risks. Previous history of stroke or hemorrhage, especially hemorrhage. Capillary fragility had a high relative risk of stroke, especially hemorrhage.

These risk factors were related together and not independently compared to the occurrence of stroke. Multivariate analysis (to be reported in another paper) might give additional information about the relationship between these risk factors and cerebrovascular disease.

Acknowledgment

The authors would like to express their appreciation to Drs. Yasushi Mizuno, Haruo Takahashi, Tohru Iwatsuka, Masao Ito, and Naohiko Ozawa for their cooperation and for the assistance of their colleagues in the First Department of Internal Medicine and in the Department of Health, Aichi Prefecture.

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