THE MORTALITY RATE for stroke has been on the decline in Japan in recent years, but it is still the highest in the world.1,2 Many studies,3-6 both in Japan and elsewhere, have shown blood pressure to be the most important stroke risk factor. However, in most of these studies, the relationship between blood pressure and stroke has been based on blood pressure as measured at only one point in time. Recently, it has been shown that the change in blood pressure level with time is also an important risk factor.7-12 But most observations on stroke elsewhere, have shown blood pressure to be the most important stroke risk factor. However, in most of these studies, the relationship between blood pressure and stroke incidence has been examined.

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ades, i.e. 1st cycle: July 1958–June 1960, 2nd cycle: July 1960–June 1962, . . . Each individual is examined once during each cycle. Participation in the study has varied from 75 to 85%. Mortality is ascertained through the koseki, a compulsory family registration system in Japan. Autopsies have been obtained on 30–40% of the deceased.

A subject was taken to be “at risk” for a stroke if he or she was free from stroke until the current examination and if his/her blood pressure had been measured at the three preceding biennial examinations as well as the current one. For instance, those individuals who were seen at the 1st–4th examinations and had not had a stroke during the period were assumed to be “at risk” of a stroke in the 4th cycle, and similarly, those seen at the 2nd–5th examination and who had not had a stroke up to that time were taken as “at risk” of stroke in the 5th cycle. Table 1 shows the numbers of persons at risk for each examination cycle.

As mentioned above, individuals examined 4 times in four successive preceding examination cycles were selected, as the subjects of this study, but those persons examined 3 times or less are also shown as a reference in table 1. The small number of subjects in cycle 9 reflects the fact that, the study period extends only six months into this cycle.

2. Index of changes in blood pressure with time

As an index of temporal changes in blood pressure, the linear regression coefficient of the latter regressed on time of measurement (hereafter, slope) which measures increasing or decreasing tendencies, was calculated for each individual. The mean square deviation between the expected and observed values on the regression line (hereafter, deviation) was also calculated as a measure of the fit of the linear model. Since stroke incidence relates to blood pressure, when observing the effect of the temporal change of blood pressure to stroke, the latter level must be controlled. A variety of controls suggest themselves. Since our analysis relates stroke incidence in a particular cycle (T) to blood pressure in four of the immediately preceding cycles (T-3, T-2, T-1, T), we have examined three different ones, namely:

1) the first measurement among those determined at the four points in time BP(T-3)
2) the last measurement BP(T), and
3) the average of the four values \( \frac{1}{4}(BP(T-3) + BP(T-2) + BP(T-1) + BP(T)) \).

Both systolic and diastolic blood pressures were used.

3. Blood pressure measurement

Blood pressure was measured by a physician with a mercury sphygmomanometer. It was obtained on the left arm at the level of the heart with the individual in a sitting position. The systolic and diastolic blood pressures were defined as the blood pressures at the point of onset and cessation of Korotkoff’s sound, that is, at Swan’s first and fifth points.

4. Case ascertainment and criteria

The diagnostic criteria for stroke and its classification by type into cerebral hemorrhage and cerebral infarction have been described elsewhere. Briefly, all medical records were reviewed when there was an indication of stroke from any one or more of the following sources: Adult Health Study clinical diagnosis, death certificate, or autopsy findings, regardless of the principal diagnosis. Since participation rates in the Adult Health Study are fairly high (i.e. 75–85%) and virtually all death certificates can be obtained, there are few if any stroke cases that are missed. The review of medical records used fixed, detailed criteria which were applicable for the entire study period.

Stroke is limited to degenerative disease manifested by clinical or autopsy evidence of cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, or cerebral embolus. Clinical diagnosis of stroke required a history including an abrupt onset of localized neurologic deficit (e.g., hemiparesis or aphasia) with confirming signs on physical examination; in individuals surviving the acute episode, the criteria required that signs and symptoms persist for at least one week and that subsequent gradual progression not occur. The unexpected onset of unconsciousness with blood pressure elevation, but without fever, progressing to death was considered to be stroke, unless there was evidence of another disease such as trauma or cancer. A death certificate of cerebrovascular disease was not accepted unless there was confirming clinical evidence such as hemiplegia. In reviewing autopsy records, simple lacunae were not considered evidence of stroke.

<table>
<thead>
<tr>
<th>No. of blood pressure measurements in 4 cycles prior to the cycle</th>
<th>Total</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>14567</td>
<td>13539</td>
<td>12531</td>
<td>11695</td>
<td>10704</td>
<td>5982</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4223</td>
<td>2493</td>
<td>2152</td>
<td>1989</td>
<td>1683</td>
<td>1885</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1352</td>
<td>918</td>
<td>772</td>
<td>611</td>
<td>505</td>
<td>514</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1202</td>
<td>766</td>
<td>470</td>
<td>366</td>
<td>262</td>
<td>171</td>
<td></td>
</tr>
</tbody>
</table>
LONGITUDINAL CHANGES IN BLOOD PRESSURE AND STROKE INCIDENCE/Shimizu et al

5. Statistical method

Cox's regression analysis was employed. This method combines the features of (1) traditional multivariate analysis which enables one to estimate, when several factors are associated with a disease, the extent of the association for a specific factor upon consideration of all of the other factors and (2) traditional life-table analysis which enables one to calculate survival rates and cumulative survival rates making use of all data, even if the periods of observation of the subjects differ.

The statistical models used in this report may be briefly described as follows: Let \( z(t) \) denote blood pressure measurements and other covariates for a subject in cycle 1. Let \( Z(t) = \{z(1), \ldots, z(t)\} \) denote a subject's covariate history from cycle 1 up to t. Let \( \lambda_s(t;Z(t)) \) denote stroke incidence in cycle t for a subject with covariate history \( Z(t) \) in stratum s. In these analyses strata are defined on the basis of sex and age in 10 year classes. The relative risk (Cox) regression models applied presume that

\[
\lambda_t(t;Z(t)) = \lambda_{0s}(t) \exp \{ (X(t) - X_0(t)) \beta \}
\]

where the modelled covariate \( X(t) \) may consist of functions of \( Z(t) \) and product terms between such functions and t (i.e. blood pressure level, "slope" or "deviation" derived from a subject's covariate history up to t cycle). \( X_0(t) \) is the modelled covariate corresponding to some 'standard' covariate history \( Z_0(t) \), \( \lambda_{0s}(t) \) is the baseline incidence rate in stratum s and cycle t for subjects with this standard covariate history and \( \beta \) is a vector of relative risk parameters to be estimated. Estimation of \( \beta \) and its standard error were obtained by the partial likelihood method. Covariates were standardized by dividing by their sample standard deviations to facilitate comparisons among regression parameter estimates (standardized coefficient). To determine the importance of adding a set of q covariates to a model twice the difference between maximum log likelihoods corresponding to the model with q covariates and the model without the q covariates may be compared to a chi-squared distribution with q df. Note that \( \exp \{ (X(t) - X_0(t)) \beta \} \) is a relative risk of the stroke incidence for a subject with general covariate history \( Z(t) \) compared to that for a subject with the standard covariate history \( Z_0(t) \). As a refinement the regression parameter \( \beta \) may be allowed to vary among strata.

In interpreting significance levels in subsequent tables the reader should keep in mind the usual qualification that applies if numerous statistical tests are being carried out. In view of the concentration on a rather small number of associations pertaining to blood pressure levels and changes, such multiple testing considerations are not too serious in the context of the present study.

Results

Since this study is based on those members of the Adult Health Study who were examined in four con-

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>Cycle of examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4   5   6   7   8   9</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>6   4   4   1   4   —</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>17  16  11  17  13   —</td>
</tr>
<tr>
<td>Other</td>
<td>2   5   2   —  1    —</td>
</tr>
</tbody>
</table>

TABLE 2 Number of Stroke Cases by Type and Examination Cycle

TABLE 3 Multiple Cox Regression Analyses of Stroke Incidence in Relation to Slope, Deviation and Level (as Measured Most Distant from Onset) of 4 Previous Cycles' Blood Pressures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized coefficient†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>(T-3)</td>
<td>0.51†</td>
</tr>
<tr>
<td>slope</td>
<td>0.27†</td>
</tr>
<tr>
<td>deviation</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>(T-3)</td>
<td>— 0.57†</td>
</tr>
<tr>
<td>slope</td>
<td>— 0.42†</td>
</tr>
<tr>
<td>deviation</td>
<td>— 0.18</td>
</tr>
</tbody>
</table>

Maximum log likelihood — 553.3 — 554.3 — 550.4

* 0.01 ≤ p < 0.05
† p < 0.001
‡ each column represents a distinct analysis
T: examination cycle

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Table 4
Multiple Cox Regression Analyses of Stroke Incidence in Relation to Slope, Deviation and Level (as Measured Closest to Onset) of 4 Previous Cycles’ Blood Pressures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized coefficient†</th>
<th>Maximum log likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (T)</td>
<td>0.53‡</td>
<td>-553.3</td>
</tr>
<tr>
<td>slope</td>
<td>-0.12</td>
<td>-0.14</td>
</tr>
<tr>
<td>deviation</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td>Diastolic blood pressure (T)</td>
<td>0.62*</td>
<td>-552.2</td>
</tr>
<tr>
<td>slope</td>
<td>-0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>deviation</td>
<td>-0.21</td>
<td>-0.35</td>
</tr>
</tbody>
</table>

Sug.: 0.05 ≤ p < 0.10
†: p < 0.05
‡: p < 0.001
†: each column represents a distinct analysis
T: examination cycle

In other words, given the value of the most recent blood pressure, stroke incidence is more elevated the higher the value of the more distant measurement. This leads to negative coefficient estimates for “slope” in Table 4. This is true for either systolic and diastolic blood pressure.

A possible explanation for these two phenomena would be that stroke incidence is higher the greater the cumulative blood pressure in a specific period. Therefore, the effect of a temporal change in blood pressure on stroke should be examined by controlling for the cumulative blood pressure level.

We, then, examined the effect of a temporal change in blood pressure on stroke incidence taking into account cumulative blood pressure. For instance, as shown in Figure 1, stroke incidence is compared in the following three cases: a) increase in blood pressure, b) no change in blood pressure, and c) decrease in blood pressure with time, even though the cumulative blood pressure is the same for all three. As an index of the cumulative blood pressure, the average blood pressure over four cycles was used. Stroke was further subclassified into cerebral hemorrhage and cerebral infarction. Table 5 shows the results.

For cerebral hemorrhage, the coefficient of “slope” is significantly positive. Thus, the risk is higher, the greater the blood pressure increase with time. For cerebral infarction this trend is not observed. These tendencies are observed when either systolic blood pressure or diastolic blood pressure is used. The results of an analysis in which only systolic or diastolic blood pressure were considered, show that diastolic blood pressure gives a maximum log likelihood of -89.6, whereas systolic blood pressure gives -98.2. Moreover, the addition of systolic blood pressure to diastolic blood pressure does not significantly improve the fit (p = 0.20). These analyses indicate that cerebral hemorrhage risk can be explained by diastolic blood pressure only, and systolic blood pressure does not add significantly to the risk factors in the presence of diastolic blood pressure. On the other hand, for cerebral infarction, systolic blood pressure is slightly more important as a predictor, though, both systolic and diastolic blood pressures contribute almost equally.

Whether or not the kind and extent of association between stroke incidence and temporal change of blood pressure differ by blood pressure level was examined. The present data failed to demonstrate any interaction between the change in blood pressure with time and the average blood pressure.

Patients receiving treatment for hypertension had to be excluded in the analysis so as to study the association between stroke and the natural change in blood pressure with time. Information on treatment for hypertension was not complete for all subjects in the present study. As a simple trial to examine the effects of treatment for hypertension on this kind of analysis, the following was done. Since it is quite likely that treatment was offered to all individuals whose systolic blood pressure exceeded 180 mmHg or diastolic blood pressure exceeded 110 mmHg, the simple information on treatment (yes or no — based on the subjects declarations on their past histories) was checked against their medical records for those persons whose blood pressure exceeded the above levels even once in the period from the 1st to the 9th examination cycles. Among 16,031 individuals who were examined at least once during the 1st–9th cycle, those whose blood pressure exceeded the above levels in any cycle numbered 3,153 of whom 1,955 were taking treatment. Thus, subjects receiving treatment accounted for 62% of the aforementioned hypertensive group. All other individuals, that is, those with no information on treatment within the hypertension group and those in the nonhypertensive group

![Figure 1](http://stroke.ahajournals.org/ Downloaded from)
pertension group, were considered to be untreated. The association of average blood pressure, "slope" and "deviation" with cerebral hemorrhage, cerebral infarction, was investigated in untreated subjects (table 6).

The coefficients of "slope" were positive in cerebral hemorrhage; the coefficient in diastolic blood pressure was statistically significant. However, there is no clear association of cerebral infarction with "slope". These results are the same as those shown in table 5 where all of the cases were examined. Because the linear regression line was applied to the temporal change in blood pressure of individuals, the goodness of fit of the regression line should be considered. So far, in order to control "deviation", it was put in the model. An analysis was also made excluding those individuals where a linear regression fitted the observation badly, arbitrarily taken to be a mean square deviation of more than 100. The results are similar to those shown in table 5 where all of the cases were examined.

Since we limited subjects to those individuals who were examined four times in four successive preceding cycles, the numbers of cerebral hemorrhage and cerebral infarction cases are small. To increase the number of cases studied, the relationship of stroke to average blood pressure, "slope" and "deviation" were observed among those individuals who were examined 3 or more times including the prior examination cycle. The number of cases of cerebral hemorrhage and cerebral infarction are now 27 and 93, respectively, and the results tend to be similar to those shown in table 5.

**Discussion**

Many studies have reported blood pressure to be the most important risk factor for stroke. Most of these studies merely observed the relationship between...
blood pressure at one point in time and subsequent incidence of stroke. Recently, however, in the relationship between stroke and blood pressure at two points in time, it has been reported that the risk of stroke among individuals, whose blood pressures at one point in time were the same but at another point in time were not, was different.\textsuperscript{7-12} Kikumura et al\textsuperscript{12} compared stroke incidence in Hisayama’s study by a combination of WHO criteria for hypertension in two points in time (i.e. hypertension at both points, decreased from hypertension to non-hypertension, elevated from non-hypertension to hypertension, remained non-hypertension at both points). It was reported that the incidence in the group “hypertension at both points” is higher than in other groups. Tsukamoto et al,\textsuperscript{7} from the standpoint of life insurance, state that not only blood pressure at the time of taking out an insurance policy but also values prior to that time should be taken into consideration when risk factors are considered. Thus, blood pressure measured at one time is not sufficient for predicting stroke and the relationship between blood pressure measured consecutively and stroke incidence should be observed.

Not only predicting stroke incidence by several blood pressures as measured consecutively, but also to know what pattern of temporal change of blood pressure is most related to stroke incidence, is interesting. In the present study, we have examined the effects of the cumulative blood pressure (integral of blood pressure over time) and temporal change in blood pressure on stroke using blood pressure at four points in time. As an index of cumulative blood pressure, the average over 8 years has been used. The present study took the regression coefficient as an index of temporal change in blood pressure over 8 years. The estimated regression coefficient is influenced by such factors as variability in the number of measurements, the length of exposure time, and the time of exposure between individuals (See Hsu et al\textsuperscript{a}). To take into account these problems, the present study divided a period into two intervals from which changes in blood pressure were calculated, and for which stroke incidence was observed. Subjects were limited to those persons who were examined 4 times in the interval from which change was calculated.

For cerebral hemorrhage, it is observed that the risk is greater the greater the increase in blood pressure, even though the cumulative blood pressure is the same, whereas this is not true for cerebral infarction. Apparently cerebral hemorrhage, a disease caused by the rupture of an aneurysm of a cerebral arteriole, results from the development of hypertension, onset is considered to be “triggered” by a sharp elevation of blood pressure, in cerebral infarction, a disease which develops by aggravation of arteriosclerosis by high blood pressure, the extended persistence of high blood pressure (cumulative blood pressure) is believed to have a more important meaning than a sharp increase in blood pressure immediately before onset. It has been reported that in stroke-prone spontaneous hypertensive rats (SHR-SP) cerebral hemorrhage is frequent among cases with high blood pressure of greater seriousness and shorter duration, whereas cerebral infarction is frequent among cases with high blood pressure of relatively low degree of seriousness and slightly long duration.\textsuperscript{22, 23} Our results are consistent with this report.

Rabkin et al\textsuperscript{4} observed the effect of the difference in blood pressure at two points in time (last blood pressure — initial blood pressure) using the initial blood pressure. They reported that the greater the difference the higher the risk. However, since the greater the difference, the higher the blood pressure close to onset and the higher the cumulative blood pressure, the greater difference in blood pressure itself can not also be a risk factor.

Diastolic blood pressure is thought to be a more important risk factor than systolic blood pressure in cerebral hemorrhage. The latter disorder is caused by the rupture of an aneurysm of a cerebral arteriole resulting from the development of hypertension, and the hypertension in this case is essential hypertension, where there is a remarkable elevation in diastolic blood pressure.\textsuperscript{5, 21} Systolic blood pressure is more closely associated with cerebral infarction for this disorder is essentially related to arteriosclerosis and, though the association here with blood pressure is less than in the case of cerebral hemorrhage, systolic blood pressure appear to be relatively more closely associated to arteriosclerosis than diastolic blood pressure.\textsuperscript{20, 21}

In general in follow-up studies, the relationship of a factor at the beginning of observation (baseline) and subsequently developing disease is observed. However, there are two kinds of factors: 1) those such as sex and genetic make-up which do not change during the follow-up period and 2) those like laboratory test values which do. When observing associations with a variable like blood pressure level which change with time, the meaning of a particular measurement as a risk factor may lessen as time passes from the beginning of observation.

Prentice et al\textsuperscript{19} examined the incremental predictive level of earlier blood pressures, given recent ones. They determined that recent blood pressures are more strongly predictive for stroke than are blood pressure levels determined some years earlier, while earlier blood pressures make an additional important contribution to risk prediction. Truett and Sorlie\textsuperscript{5} proposed a method to test the hypothesis of the equality of the difference between the blood pressure of members of two groups (case, non-case) measured at different times prior to the onset of stroke. Using the method of Truett and Sorlie,\textsuperscript{5} Rabkin et al\textsuperscript{4} found an increasing linear trend in the difference in systolic blood pressure between the stroke and non-stroke groups with repeated measurements closest to the onset. Thus the blood pressure closest to the onset best distinguishes the two groups.

We also examined this issue prospectively and classified stroke into subtypes cerebral hemorrhage and cerebral infarction. The associations with cerebral hemorrhage and cerebral infarction were studied by employing either blood pressure values for 0–2 years,
LONGITUDINAL CHANGES IN BLOOD PRESSURE AND STROKE INCIDENCE/SHIMIZU ET AL

TABLE 7 Coefficients of Previous Cycles’ Blood Pressures by Type of Stroke, Simple Cox Regression Analyses§

<table>
<thead>
<tr>
<th>Type of stroke</th>
<th>0–2 years</th>
<th>2–4 years</th>
<th>4–6 years</th>
<th>6–8 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral hemorrhage</td>
<td>systolic blood pressure</td>
<td>0.037‡</td>
<td>0.020‡</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>diastolic blood pressure</td>
<td>0.080†</td>
<td>0.053‡</td>
<td>0.034*</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>systolic blood pressure</td>
<td>0.015‡</td>
<td>0.015‡</td>
<td>0.017%</td>
</tr>
<tr>
<td></td>
<td>diastolic blood pressure</td>
<td>0.027†</td>
<td>0.019*</td>
<td>0.030‡</td>
</tr>
</tbody>
</table>

*: 0.01 ≤ p < 0.05.
†: 0.001 ≤ p < 0.01.
‡: p < 0.001
§: analysis with SBP or DBP were done separately

2–4 years, 4–6 years or 6–8 years before the onset of stroke in the analysis (table 7). For cerebral hemorrhage, the association is greater the closer to onset the coefficient of blood pressure is determined. That is to say, whereas the relative risk of a person with a systolic blood pressure of 180 mmHg as against 140 mmHg 0–2 years before onset was 4.4, the risk was 2.1 for the same blood pressure 6–8 years before, suggesting that, though the blood pressure may be at the same level, the risk is higher in a person with high blood pressure closer to onset. In cerebral infarction, the coefficients of blood pressure as determined close to onset and several years before onset showed almost the same value. Therefore, it is suggested that although blood pressure measurements from several years before onset may be used to predict the risk of cerebral infarction, blood pressure as close as possible to onset should be used in predicting the risk of cerebral hemorrhage.

In the present study, the relations between stroke incidence in a specific cycle, and changes in blood pressure for the immediately preceding cycle were analyzed. With Cox’s regression analysis, it is possible not only to observe the association between the time dependent variable, that is, the one changing with time and the onset of disease as in the present study. But, as usual, one may observe the association of a variable at baseline and the subsequent onset of disease. For the purpose of comparing these two methods, the results pertaining to association between blood pressure values of the 1st–4th cycles and stroke incidence rate thereafter up to the 9th cycle (using variables at baseline), and the results pertaining to association with blood pressure at four points in time immediately before onset (using time dependent variables) are shown (table 8). For cerebral hemorrhage, the coefficients of “slope” in the time dependent analyses are larger than those in the baseline analyses for both diastolic and systolic blood pressure, especially, the coefficients in the time dependent case are statistically significant. On the contrary, for cerebral infarction, the coefficients of “slope” in two methods of analysis do not differ. The present analysis is considered an example of a way of making the relationship of stroke to risk factors more clear by using risk factor values closer to the onset of stroke in a time-dependent method instead of traditional analyses which employ risk factors at baseline.

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Cerebral Aneurysms and Variations in the Circle of Willis

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SUMMARY In order to obtain information about the relationship between variations in the circle of Willis and aneurysms, 44 complete circles of Willis with aneurysm were studied macroscopically.

The incidence of variations was significantly higher in the aneurysm series than in the control circles without aneurysm. There was a definite correlation between asymmetric proximal segments of the anterior cerebral artery and aneurysms of the anterior communicating artery, and a tendency to correlation was found in the case of asymmetric posterior communicating arteries and aneurysms on the internal carotid artery-posterior communicating artery junction.

In the light of these findings it seems likely that through hemodynamic changes variation in the circle of Willis plays some role in the development of cerebral aneurysms.

THE CIRCLE OF WILLIS has been shown to exhibit many kinds of anatomical variations.1-3 A possible relationship between these variations and aneurysms has been the subject of some reports in the literature, particularly in regard to congenital association and hemodynamic factors. However, most of such studies were unsatisfactory because of their methodology, that is poor handling of statistical data, lack of control series.4-8

The purpose of the present macroscopical study of 44 cases of complete circles of Willis with aneurysms was to obtain wider, more precise and more detailed information about the relationship between variations of the circle of Willis and aneurysms. We focussed on a) the incidence of variations in the aneurysm series and b) the relation between variations and aneurysm sites. We compared the results on incidence with our previous data from 148 circles of Willis without aneurysm.9

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Relationship between longitudinal changes in blood pressure and stroke incidence.

Y Shimizu, H Kato, C H Lin, K Kodama, A V Peterson and R L Prentice

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