Relationship of Stroke to Other Cardiovascular Disease

By Gary D. Friedman, M.D., S.M. in Hyg., Donald B. Loveland, M.S., and S. Paul Ehrlich, Jr., M.D., M.P.H.

SUMMARY

The frequencies of prior cardiovascular abnormalities were compared in 117 stroke patients and 234 control subjects. All were residents of a retirement community who had been examined initially and followed in the local medical clinic before the strokes occurred. Cases and controls were matched for age, sex, length of residence, and blood pressure.

Prior coronary, rheumatic, and hypertensive heart disease were all more frequent in cases than in controls, as were cardiac enlargement, congestive heart failure, and digitalis therapy. There was a stronger association of stroke with atrial fibrillation than with other cardiac abnormalities, suggesting that atrial fibrillation in the elderly is an important precursor of stroke and should not be regarded lightly.

Aortic calcification and intermittent claudication were also more frequent among the stroke cases than the controls. Since the blood pressures of cases and controls were matched, the association of both cardiac disease and noncerebral atherosclerosis with stroke is independent of blood pressure and is not attributable to the fact that hypertension predisposes to all of these conditions.

Additional Indexing Words: Coronary heart disease Hypertension Atherosclerosis
Epidemiology Atrial fibrillation

Although a thorough understanding of the etiology of the various types of stroke has not yet been attained, certain predisposing factors have already been identified with reasonable certainty. Clinically, hypertension has long been found in association with both hemorrhagic and thrombotic strokes.1 Recent epidemiologic studies have confirmed this finding in large population groups.2-4 The presence of cardiac disease and impaired cardiac function also appears to predispose to the development of thrombotic strokes.2 A further association between thrombotic strokes and atherosclerotic diseases elsewhere in the body, such as myocardial infarction and intermittent claudication,5 is consistent with the view that cerebral atherosclerosis is part of a generalized vascular change. However, the contrasting high incidence of stroke and low incidence of coronary heart disease in Japan6 suggest a dissociation between stroke and coronary heart disease, particularly in view of recent evidence that the majority of strokes among the Japanese may be thrombotic rather than hemorrhagic, as was previously thought.7,8 Furthermore, differences in degree of atherosclerosis in cerebral as contrasted to other arteries are often seen at autopsy.9 The preponderant evidence would suggest, though, that clinical manifestations of atherosclerosis elsewhere in the body indicate an increased likelihood of subsequent stroke.
Since hypertension contributes to the development of cardiac disease and of atherosclerosis elsewhere, the observed relationship of stroke to the latter conditions might possibly be explained by hypertension as a factor common to all. Thus it seemed important to determine whether the association of stroke with cardiac disease and with atherosclerosis elsewhere would still be found, when the possible common factor, high blood pressure, is taken into account.

A prospective population study of stroke and other cardiovascular disease is in progress at the Leisure World Retirement Community, Seal Beach, California. The relationship of attributes measured at the initial medical examination to subsequent stroke incidence has already been reported. The present study was carried out in order to examine in detail the relationship of stroke to cardiac disease and to atherosclerosis elsewhere in the body, with the common factor, hypertension, controlled. This study is based on a comparison of the medical records of 117 persons who developed their first strokes while residing in the community with the records of a control group of 234 residents, matched with the stroke cases for age, sex, length of residence, and blood pressure. The attributes and medical experience were obtained from both the initial examination and subsequent medical records prior to the stroke date.

**Method**

The Leisure World Retirement Community, Seal Beach, California, opened early in 1962. Most of the residents have been middle-aged and elderly, the minimum age required for entry into the community being 52 years for at least one member of the household. When construction was completed and all housing occupied in 1964, the community consisted of approximately 10,000 persons. Included in the cost of residing in Leisure World has been a prepaid medical care program utilizing a clinic located on the premises. Approximately 80% of all residents have undergone an initial medical evaluation, including a medical and social history, physical examination, 13-lead electrocardiogram, chest x-ray, and a number of standard blood and urine tests. This information and records of subsequent medical care in the clinic as well as available reports from outside physicians and hospitals constitute the basis for this study.

Persons with stroke were identified by a group of physicians reviewing the records of all residents who had any diagnosis related to cerebrovascular disease on or before December 31, 1965. A stroke was defined as a definite neurologic deficit of abrupt onset based on brain damage and not reasonably attributable to some other pathologic process, such as head injury, brain tumor, or peripheral nerve lesion. The reviewing physicians required a clear description in the record of the neurologic deficit, such as localized weakness, paralysis, sensory loss, or a deficit in speech, in order to classify the stroke as definite. Illnesses were defined as possible strokes when the symptoms and signs were vague and ill-defined, or when noncerebrovascular etiologies were about as likely as stroke. Nonspecific neurologic symptoms, including syncope, confusion, memory impairment, seizures, dizziness, and vertigo without accompanying localizing findings, were not considered to represent a stroke, without other supporting evidence such as a bloody cerebrospinal fluid.

One hundred seventeen persons with first strokes by December 31, 1965, had complete initial examinations and could be included in this investigation. One hundred one had definite strokes and 16 had possible strokes. Fifty-four (46.2%) were men ranging in age at the time of the stroke from 52 to 86, with a mean of 72.7 years. Sixty-three (53.8%) were women ranging in age at the time of the stroke from 52 to 85, with a mean of 72.2 years. Fourteen persons (12.0%) died within 1 month of the stroke onset. Twenty-five (21.4%) were dead by December 31, 1965. The case fatality rate is much lower than that found in hospital series but is consistent with the findings in other population studies. The over-all stroke incidence rate was 1.0% per year in men and 0.7% per year in women.

Despite a paucity of information about some cases, an attempt was made to classify strokes by pathogenetic mechanism using simple clinical criteria. In the absence of a definitive pathologic examination of the brain, the stroke was considered to be due to an embolus if a source of embolus—recent myocardial infarction (within 3 months prior to the stroke), atrial fibrillation, or mitral stenosis—was present. Twenty-three (19.7%) of the strokes were accompanied by atrial fibrillation and were called cerebral emboli. Seven (6.0%) had no source of emboli and were considered to have an intracerebral hemorrhage on the basis of a bloody cerebrospinal fluid or a hospital report giving the diagnosis of intracerebral hemorrhage. In the absence of...
criteria for an embolus or hemorrhage the diagnosis was transient ischemic attack if the signs and symptoms disappeared within 24 hours. Seventeen (14.5%) of the group fell into this category. If of longer or uncertain duration, the stroke was classified as a cerebral thrombosis, essentially a diagnosis of exclusion. Seventy (59.8%) were so classified. No cases with the typical clinical history of subarachnoid hemorrhage were found in the present group. As with the case fatality rate, the frequency of hemorrhagic strokes is low in a population study as compared with a hospital study, where the more severely ill patients gravitate.

A control group was selected to match the cases with respect to age, sex, initial blood pressure, and duration of postexamination experience prior to the stroke date. Two controls were selected for each case, one by going forward and one by going backward in the record number system. (The assignment of record numbers was approximately in chronological order of moving into the community.) The first subject encountered, who was of the same sex, who had not died or moved out by the time the case’s stroke occurred, who did not have a stroke by December 31, 1965, whose date of birth was within the same 5-year interval (previously defined, e.g., 1890-94, 1895-99) whose date of initial medical examination was within the same 3-month interval (e.g., January-March, 1963), and whose systolic blood pressure at entry was in the same 10 mm range (e.g., 140 to 149), was used. For cases for which it was difficult to find matched controls it was sometimes necessary to select both controls from the same side of the case in the number system. If this still did not yield two controls, the limits were relaxed slightly (e.g., control with blood pressure of 136 used for a case with blood pressure of 140).

The medical records of all cases and controls were reviewed in a uniform fashion, and the attributes to be compared were taken both from the initial examination and the subsequent medical follow-up prior to the stroke date for each case, the same cut-off date being used for the two controls. If transient ischemic attacks preceded a thrombosis during the observation period, the stroke date and diagnosis used were those of the thrombosis. Cardiac diagnoses and electrocardiographic and x-ray readings by the Leisure World physicians were accepted as stated in the records.

Significance tests for study factors were derived by extending the test for matched samples described elsewhere11 to the present situation of two controls per case.

Results

Matched Attributes

The adequacy of the matching procedure may be judged by comparing the resulting control group and the stroke cases with respect to the matched characteristics (table 1).

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Stroke cases</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial examination (yr)</td>
<td>Mean 71.3</td>
<td>Mean 71.4</td>
</tr>
<tr>
<td>Interval between initial exam and stroke date (mo)</td>
<td>8.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Initial systolic blood pressure (mm Hg)</td>
<td>24.3</td>
<td>25.9</td>
</tr>
<tr>
<td>Initial diastolic blood pressure (mm Hg)</td>
<td>171.5</td>
<td>170.9</td>
</tr>
<tr>
<td>Last systolic blood pressure before stroke date</td>
<td>92.0*</td>
<td>89.2*</td>
</tr>
<tr>
<td>Last diastolic blood pressure before stroke date</td>
<td>23.8</td>
<td>23.6</td>
</tr>
</tbody>
</table>

*Difference between cases and controls statistically significant: 0.01 < P < 0.05.
The proportions of men and women were exactly the same for the two groups. The mean age at initial examination was 71.3 years for the cases and 71.4 for the controls. Similar intervals between the initial examination and the stroke date were obtained: 14.4 months on the average for the cases, and 14.5 months for the controls.

The matching for blood pressure was carried out using only the initial systolic blood pressure. The mean for the cases was 171.5 mm Hg; that for the controls, 170.9 mm Hg. There was a slight difference in the initial diastolic blood pressures found in the two groups. The cases had a mean of 92.0 mm Hg; the controls had mean of 89.2. This small difference reflects the imperfect correlation between systolic and diastolic blood pressure. While statistically significant, the magnitude of the difference seems insufficient to account for the marked differences in cardiovascular status that will be presented subsequently.

The last blood pressure in the medical record before the stroke date was also noted, to sample more of the subjects' blood pressure experience. In some instances, of course, the last blood pressure before the stroke was the initial blood pressure. Good agreement between the cases and controls was noted for both the mean last systolic and mean last diastolic pressures (table 1). It was of interest to note that the average interval between the last recorded blood pressure and the stroke date was 3.2 months for the cases and 5.0 months for the controls. This agreed with our impression that the stroke cases generally had had more medical problems and had been receiving more intensive medical care prior to the stroke date than had the controls.

**Evidences of Cardiac Disease**

A number of indicators of heart disease or cardiac abnormalities were examined in the stroke cases and in their controls. The

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
</table>

*Previous Evidence of Cardiovascular Disease: All Strokes and Controls*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
<th>Both sexes Stroke cases</th>
<th>Control subjects (174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary or arteriosclerotic heart disease</td>
<td>49 41.9*</td>
<td>57 24.4*</td>
<td>25 46.3*</td>
<td>29 26.9*</td>
<td>24 38.1*</td>
<td>28 22.2*</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>20 17.1*</td>
<td>22 9.4*</td>
<td>12 22.2*</td>
<td>13 12.0</td>
<td>8 12.7</td>
<td>9 7.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18 15.4</td>
<td>19 8.1</td>
<td>11 20.4</td>
<td>13 12.0</td>
<td>7 11.1</td>
<td>6 4.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>8 6.8</td>
<td>5 2.1</td>
<td>1 1.9</td>
<td>1 0.9</td>
<td>7 11.1</td>
<td>4 3.2</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>22 18.5*</td>
<td>26 11.1*</td>
<td>11 20.4*</td>
<td>6 5.6*</td>
<td>11 17.5</td>
<td>20 15.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy: ECG at entry</td>
<td>9 7.7</td>
<td>11 4.7</td>
<td>6 11.1</td>
<td>4 3.7</td>
<td>3 4.8</td>
<td>7 5.6</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac enlargement: chest x-ray at entry</td>
<td>31 26.5</td>
<td>45 19.2</td>
<td>5 9.3</td>
<td>5 4.6</td>
<td>26 41.3</td>
<td>40 31.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23 19.7†</td>
<td>15 6.4†</td>
<td>10 18.5*</td>
<td>6 5.6*</td>
<td>13 20.6*</td>
<td>9 7.1*</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digitalis therapy</td>
<td>32 27.4*</td>
<td>23 9.8*</td>
<td>13 24.1*</td>
<td>10 9.3*</td>
<td>19 30.2†</td>
<td>13 10.3†</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>23 19.7</td>
<td>8 3.4</td>
<td>7 13.0*</td>
<td>2 1.9*</td>
<td>16 25.4†</td>
<td>6 4.8†</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature beats</td>
<td>14 12.0</td>
<td>27 11.5</td>
<td>8 14.8</td>
<td>13 12.0</td>
<td>6 9.5</td>
<td>14 11.1</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic calcification: chest x-ray at entry</td>
<td>49 41.9†</td>
<td>64 27.4†</td>
<td>23 42.6*</td>
<td>24 22.2*</td>
<td>26 41.3</td>
<td>40 31.7</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>9 7.7*</td>
<td>5 2.1*</td>
<td>7 13.0†</td>
<td>2 1.9†</td>
<td>2 3.2</td>
<td>3 2.4</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Difference between cases and controls statistically significant: 0.01 < P < 0.05.
†Difference between cases and controls statistically significant: P < 0.01.
number and percentages of the cases and controls having each abnormality are shown in table 2.

Coronary or arteriosclerotic heart disease was diagnosed prior to the stroke date in 41.9% of the stroke cases and in 24.4% of the control subjects. An almost two-fold difference was also found for the individual manifestations, angina pectoris and myocardial infarction, the former affecting 17.1% of cases and 9.4% of controls and the latter found in 15.4% of cases and 9.4% of controls. Rheumatic heart disease was also associated with stroke, having been diagnosed in 6.8% of strokes and 2.1% of controls. Hypertensive heart disease had been diagnosed in 18.8% of those with strokes and 11.1% of controls, but the difference was almost entirely accounted for by men (20.4% versus 5.6%)

Evidence of cardiac enlargement was also sought. Twenty-six and five-tenths percent of cases of stroke had definite enlargement on initial chest x-ray as compared to 19.2% of controls. For men, the relative differences were more striking, the respective percentages being 9.3% and 4.6%; but this two-fold ratio was reduced when the total group was viewed, because of the predominance of women among those with x-ray cardiac enlargement and the small difference between female cases and controls. On the initial electrocardiogram, left ventricular hypertrophy was present in 7.7% of cases and 4.7% of controls. As with the diagnosis of hypertensive heart disease, the difference among men (11.1% versus 3.7%) essentially accounted for the entire group difference.

Congestive heart failure had been diagnosed much more frequently among stroke cases, 19.7%, than among control subjects, 6.4%. This approximate three-fold difference was also found for the percentages of subjects and controls who had been on digitalis therapy for at least part of their period of observation, 27.4% versus 9.8.

Atrial fibrillation during at least part of the observation period prior to the stroke date was much more frequent among stroke cases, 19.7% versus 3.4%. Not only was the frequency of atrial fibrillation about six times greater among stroke cases than controls, but about one fifth of all strokes observed occurred among persons with atrial fibrillation. The other common arrhythmia in these subjects, premature contractions, was found in about the same frequency among the cases, 12.0%, as among the controls, 11.5%.

The association of cardiac abnormalities with subsequent stroke was generally found to a similar degree in both men and women, even though there were sex differences in the prevalence of certain diseases such as coronary heart disease. For example, while angina pectoris was found in 22.2% of male strokes and in 12.7% of female strokes the controls manifested angina pectoris slightly over half as frequently as the cases in each sex. Some exceptions to this male-female similarity have already been mentioned. The association of stroke with cardiac enlargement and hypertensive heart disease occurred primarily in men. Another sex difference noted was that for rheumatic heart disease, which was three and one-half times as common among female strokes as female controls (11.1% versus 3.2%) and only twice as common among male strokes as controls (1.9% versus 0.9%). Since there were only two men with rheumatic heart disease, one case and one control, small numbers make these percentages unreliable.

Evidences of Noncerebral Atherosclerosis

The association between stroke and manifestations of coronary atherosclerosis has already been described. A greater frequency of aortic calcification on chest x-ray was also noted among strokes (41.9%) than among the controls (27.4%). Intermittent claudication was found in 7.7% of strokes and 2.1% of controls, the difference largely accounted for by the men (13.0% versus 1.9%) (table 2). Thus in our study group, stroke was more likely to occur in persons with evidence of atherosclerosis in the aorta and in the coronary and lower extremity arteries.
Analysis by Type of Stroke

Only the cerebral thrombosis group provided sufficient cases for reliable case-control comparisons when each type of stroke was examined separately. The findings for persons with cerebral thrombosis and their matched controls closely resembled those for the entire stroke group and their controls, respectively. This applied both to prior cardiac abnormalities and to evidences of aortic and peripheral atherosclerosis. The only exception was atrial fibrillation, which was excluded from the thrombosis group by definition.

Preliminary findings for other stroke types seemed consistent with their particular defining or pathogenetic features. Rheumatic heart disease and digitalis therapy were most frequent among persons with cerebral emboli and, of course, atrial fibrillation was universal. Persons with intracerebral hemorrhage had the highest average blood pressure.

Antihypertensive Therapy: A Possible Bias

During the record review it was noted that more of the stroke cases (33.3%) than of the controls (26.1%) were on antihypertensive therapy at entry. This suggested a possible bias in the blood pressure matching. Perhaps the average blood pressure of the stroke cases would have been higher than that of the controls had antihypertensive therapy not been given to more of the case group. To determine whether this difference in antihypertensive therapy affected the case-control comparisons, these were repeated in a subgroup composed of all cases and their controls, where neither the case nor either of his two controls were on antihypertensive therapy at entry. This subgroup of 46 cases and 92 controls contained equal numbers of men and women and, as compared with the total study group, was, on the average, 2 years younger and about 10 mm lower in systolic blood pressure. Most of the differences noted between all cases and controls were found to approximately the same degree when the study group was restricted in this manner to those case-control triads not on antihypertensive therapy at entry (table 3).

If one also divided all cases and controls into two groups, those on and those off

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
</table>

Previous Evidence of Cardiovascular Disease: Stroke-Control Triads with No Members on Antihypertensive Therapy at Entry

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Stroke cases (N=46)</th>
<th>Control subjects (N=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary or arteriosclerotic heart disease</td>
<td>19 (41.3*)</td>
<td>21 (22.8*)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7 (15.2)</td>
<td>7 (7.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (13.0)</td>
<td>7 (7.6)</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>4 (8.7)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>6 (13.0)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>Left ventricular hypertrophy: ECG at entry</td>
<td>0 (0.0)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Cardiac enlargement: chest x-ray at entry</td>
<td>9 (19.6)</td>
<td>15 (16.3)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11 (23.9†)</td>
<td>3 (3.3†)</td>
</tr>
<tr>
<td>Digitalis therapy</td>
<td>14 (30.4†)</td>
<td>6 (6.5†)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (15.2*)</td>
<td>3 (3.3*)</td>
</tr>
<tr>
<td>Premature beats</td>
<td>4 (8.7)</td>
<td>9 (9.8)</td>
</tr>
<tr>
<td>Aortic calcification: chest x-ray at entry</td>
<td>19 (41.3†)</td>
<td>17 (18.5†)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>2 (4.3)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

*Difference between cases and controls statistically significant: 0.01 < P < 0.05.
†Difference between cases and controls statistically significant: P < 0.01.
antihypertensive therapy at entry the case-control differences in prior cardiovascular disease generally persisted within each group. It was also noted that the special group of 46 case-control triads not on antihypertensive therapy showed a much closer match in initial diastolic pressure (87.9 mm Hg mean for the cases and 87.6 mm Hg mean for the controls) than did the entire study group (table 1). The presence of marked differences in cardiovascular status between cases and controls in this subgroup helps confirm that the corresponding differences in the entire study group were not attributable to the 2.8 mm Hg difference in initial mean diastolic pressure.

**Discussion**

While the association of cardiac disease with stroke has been recognized clinically for years and, recently, in some epidemiologic studies as well, to our knowledge it has never been clearly shown that hypertension, which predisposes to both stroke and cardiac impairment, was not ultimately responsible for this apparent relationship. By selecting our controls so that they were matched with the cases for blood pressure, this possible confounding factor was eliminated from the analysis. It was of great interest, therefore, that, by and large, all evidences of cardiac disease examined were more frequent among the stroke cases than among their controls. It would appear likely that some causal relationship is involved since the cardiac abnormalities preceded the stroke and physiologic mechanisms connecting heart disease and stroke can be postulated. It has been suggested frequently that diminished cardiac output decreases the circulation to the brain and might favor the development of ischemic infarction, where the local cerebral circulation was already compromised. The development of a thrombus in a cerebral vessel might similarly be favored.

The finding of an association between stroke and manifestations of atherosclerosis in the coronary arteries, aorta, and lower extremities in this analysis suggests that hypertension is not solely responsible for these relationships, either. It appears that atherosclerosis is a generalized process, even though certain vessels may be affected earlier or more severely than others.

Two possible biases in the blood pressure matching became apparent during subsequent data analysis. A larger proportion of the stroke cases than of the controls were on antihypertensive therapy at the time of the blood pressure measurement, so the basic untreated blood pressure of the case group was probably somewhat higher, on the average, than that of the control group. When the analysis was repeated, excluding the cases on antihypertensive therapy at entry and their controls, the association of stroke with cardiac abnormalities was still apparent. Thus, this bias did not account for the observed relationship. The other possibility of bias lay in the statistically significant discrepancy in the initial diastolic blood pressure of cases and controls. Statistical significance does not imply biologic significance and a difference of 2.8 mm in mean diastolic pressure would seem insufficient to produce two- and three-fold differences in the frequency of cardiovascular abnormalities. Available insurance data on the effects of differences in diastolic pressure with systolic held constant, deal with subsequent mortality rather than cardiovascular disease prevalence. Differences in mortality much smaller than two-fold were usually noted with even larger increments in diastolic blood pressure.

One cannot be sure that some of the blood pressures of the case group were not elevated for a longer period of time than those of the controls or that they were not on the average higher at some crucial early age, if there be such. Thus, an investigation similar to this should be carried out in the context of a long-term follow-up of subjects first examined earlier in life.

The strongest association found between stroke and a prior cardiovascular abnormality was with atrial fibrillation, since the stroke cases had this arrhythmia about six times as frequently as the controls. Because of
the possibility that special attention was
given to the cases at or just before the time
of the stroke, enabling a larger frequency
of atrial fibrillation to be detected at that
time than would be likely with the controls,
this case-control comparison was repeated
just using the electrocardiograms taken at
the initial examination. Twelve (10.3%) cases
and four (1.7%) controls had atrial fibrillation,
again a six-fold difference.

It should be noted that all of the cases
with atrial fibrillation were fibrillating at the
time of the stroke and were therefore con-
sidered to have cerebral emboli, by definition.
Thus it would be meaningless to compare
persons with particular types of strokes with
their respective controls with regard to the
frequency of prior atrial fibrillation, since
the percentage among the cases could be as
high as 100% for cerebral emboli and would
be 0% for all other types. It is not unreason-
able, though, to make this comparison for
all strokes and to note the strong association
of acute neurologic lesions on a vascular
basis with prior atrial fibrillation.

Considering the relationship of atrial fibril-
lization to stroke it is of interest to note that
the other common arrhythmia in these sub-
jects, premature contractions, was found
equally often in cases and controls. Hence,
just the presence of any arrhythmia was not
the important predisposing factor. Nor can
it be concluded that atrial fibrillation merely
reflected the underlying heart disease in pre-
disposing to stroke, since the six-fold differ-
ence in percentage between cases and
controls found with atrial fibrillation was
appreciably larger than the two- or three-
fold difference found with other manifesta-
tions of heart disease. Further subclassification
of persons with atrial fibrillation showed that
atrial fibrillation in the absence of myocardial
infarction, congestive heart failure, or rheu-
matic heart disease was strongly associated
with stroke. This excluded the possibility
that for atrial fibrillation to predispose to
stroke it must be accompanied by severe
cardiac disease, such as congestive heart
failure or previous myocardial infarction or
by the valvular changes of rheumatic heart
disease. The commonly accepted explanation
for the relationship between atrial fibrillation
and stroke is that thrombi form in the fibril-
laying left atrium and that these break off
and eventually occlude cerebral arteries.
While this may be all that is involved there
is much that is not understood about the
pathogenesis of stroke that will only be an-
swered by further physiologic study and
clinicopathologic correlation.

Whether or not the mechanism is fully
understood, the marked association between
atrial fibrillation and subsequent stroke sug-
gests that atrial fibrillation in the elderly is
an ominous abnormality carrying with it a
greatly increased risk of stroke. This excess
risk can be estimated only roughly from this
investigation. With use of the Cornfield for-
mula for estimating relative risk from case-
control data, it would appear that persons
with atrial fibrillation have about seven times
the risk of stroke that is found in persons
without it. The frequency of atrial fibrilla-
tion in the control subjects may be an overestimate
of that which obtains in the entire com-
unity because the control group contains a
larger proportion of hypertensive patients.
The difference between cases and controls
would thus be greater than indicated here,
so that the estimated seven-fold increase
in risk may be an underestimate. Observa-
tions on more stroke cases in this and other
populations will help to supply a more de-
pendable estimate of the increase in risk
indicated by the presence of atrial fibrillation.

Before one can make the therapeutic rec-
ommendation that a vigorous attempt should
be made to convert atrial fibrillation to nor-
mal sinus rhythm in all persons, a further
evaluation is needed of (1) the risks both
of conversion and of therapy needed to main-
tain normal sinus rhythm, (2) the difficulty
of maintaining normal sinus rhythm for a
long period of time following conversion,
and (3) the dangers of allowing atrial fibril-
lation to continue. All these considerations
must be weighed together to reach a deci-
sion, individualized to each patient. The find-

Circulation, Volume XXXVIII, September 1968
ings presented here do tend to support those advocating vigorous attempts at conversion, and argue against complacency when viewing atrial fibrillation in the elderly.

Acknowledgment

We wish to thank the following persons, who made important contributions to the completion of this study: Drs. Reuel Stallones, Darwin Labarthe, John Cutler, Joel Teisch, Elliot Stein, Albert Hesker, and David Kent; Mrs. Dolores Heilig, Mrs. Oneta Ray, Mrs. Florence Keller, Miss Mary Bell, Miss Mary Staller, Mrs. Alton Eustace, Mrs. Tina Wells, Mr. Walter Groch, and Mrs. Iva Christopherson. We are also grateful to Dr. John Messersmith, Medical Director, Mrs. Dorothy Brandes, Nursing Director, and the entire staff of the Leisure World Clinic, without whose assistance this study could not have been carried out.

References


Relationship of Stroke to Other Cardiovascular Disease
GARY D. FRIEDMAN, DONALD B. LOVELAND and S. PAUL EHRLICH, JR.

_Circulation_. 1968;38:533-541
doi: 10.1161/01.CIR.38.3.533
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1968 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/38/3/533

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/