a low level of NOR release from nerves to the CBV this would account for the low or absent neurogenic tone reported by many workers, and would provide an explanation for our data, since release might be so slow that inhibition of synthesis would fail to deplete NOR sufficiently to be reflected as a diminution of nerve counts. Alternatively, AMT levels might remain lower in nerves to CBV than in nerves to ECV, and, therefore, AMT would have a lesser effect on the former. The latter hypothesis is amenable to an experimental test. But even if correct, it would not rule out a reduction in drug effects on NOR concentration in cerebrovascular nerves as noted earlier, but are also seen with AMT, as reported here.

**References**

2. Rosenblum WI: Further notes on the binding of norepinephrine by nerves to cerebral blood vessels. Stroke 4: 813, 1973

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**Sudden Death from Stroke**

**LAWRENCE H. PHILLIPS II, M.D., JACK P. WHISNANT, M.D., AND THOMAS J. REAGAN, M.D.**

**SUMMARY** Sudden death is defined as any death that occurs less than 24 hours after the onset of first symptoms. Strokes account for 10 to 20% of all sudden deaths. The records of all residents of Rochester, Minn., who had their first stroke during the period 1955 through 1969 were analyzed. Among 255 deaths caused by the first stroke, 52 were sudden. Twenty-six of the deaths were due to primary intracerebral hemorrhage, and 26 to primary subarachnoid hemorrhage. Only two of the sudden deaths were caused by infarction: one by pontine and cerebellar infarct and the second by a cortical infarct, which resulted in death from status epilepticus. Among the nine patients who died within 2 hours of the onset of symptoms, six had primary subarachnoid hemorrhage. Hypertension was noted in 23 of the 26 patients (88%) who died of primary intracerebral hemorrhage; 8 patients with primary intracerebral hemorrhage were on long-term oral anticoagulant therapy, and all 8 were hypertensive.

**SUDDEN DEATH** is commonly defined as any death that occurs less than 24 hours after the onset of clinical symptoms and is not attributable to trauma or known preexisting illness. The most frequent cause is cardiovascular disease, specifically coronary artery disease. It has been reported to have been responsible for between 50 and 90% of all sudden deaths.

Neurologic disease, although not a common cause, has been responsible for many sudden deaths. The most common disease of the central nervous system responsible for sudden death is stroke. In a review that pooled the results of 10 studies of sudden death, 14% of all deaths were found to have a neurologic basis, and the major, if not the only, diagnosis was some type of cerebrovascular disease. In general, most studies have found that stroke accounts for 10 to 20% of sudden deaths.

Patients who have fatal intracranial hemorrhage usually die more quickly than do those who die after ischemic infarction. In a study done between 1929 and 1938 at Charity Hospital in New Orleans, Newbill found 63 cases of stroke among 296 autopsied cases in which death occurred within 24 hours of onset of symptoms. Only 18 cases of stroke were attributed to thrombosis or embolism. The remaining cases were diagnosed as being due to hemorrhage, types not otherwise specified.

The literature contains some confusing and at times contradictory conclusions concerning the timing of sudden death from stroke. Secher-Hansen found that 100 of 130 patients who died suddenly from subarachnoid hemorrhage in a forensic series died instantaneously. In a series of 250 medicolegal cases of subarachnoid hemorrhage from intracranial aneurysm, Freytag found that 60% of patients had "no survival" and another 29% died within 24 hours.

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**TABLE 1** 

**Fluorescent Nerve Counts on Rat Cerebral and Femoral Arterioles**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Cold</th>
<th>AMT + Room temp</th>
<th>Cold + AMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>0.46 ± 0.18</td>
<td>0.44 ± 0.17</td>
<td>0.45 ± 0.20</td>
<td>0.37 ± 0.10</td>
</tr>
<tr>
<td>Femoral</td>
<td>1.15 ± 0.25</td>
<td>1.43 ± 0.12</td>
<td>0.34 ± 0.14**</td>
<td>0.58 ± 0.36**</td>
</tr>
</tbody>
</table>

*Nerve crossings per 14 μm length of grid line.

**Alpha methyl tyrosine significantly diminished number of fluorescing nerves only in femoral artery bed (p < .01).
Newbill, however, found only two patients who died within 1 hour of the onset of intracranial hemorrhage.

Some confusion exists in the literature concerning the exact cause, time course, and relative frequency of stroke in sudden death. However, the epidemiologic study of this subject has been accomplished primarily through the use of data obtained from metropolitan medical examiners' offices. This approach has some limitations in that the types of cases found include many deaths that are medically unattended. Of course, the diagnostic data are accurate, but the disadvantage of this method is that a significant number of cases would be missed because they would not come to the attention of a medical examiner. Also, patients who survive long enough to die in a hospital or who die under nonmysterious circumstances are not as likely to require a medicolegal diagnosis of the cause of death and, hence, would not be included in the medical examiner's practice.

Two prospective studies in retrospect have been done in the population of the city of Rochester, Minn. These studies concerning the epidemiology of stroke over a 25-year period have been accepted as accurate collections of all cases of stroke in a defined population. The purpose of the present study is to determine the number and type of strokes that resulted in sudden death in this defined population during the years 1955 through 1969.

Method

The procedure used in identifying all cases of stroke that occurred among residents of Rochester, Minn., from 1955 through 1969 has been described previously. Briefly, all patients who had their first stroke while a resident of Rochester during the time period from Jan. 1, 1955, through Dec. 31, 1969, were identified and reviewed. This was accomplished primarily through the use of the Mayo Clinic record system and the record-linkage system for all medical facilities in Rochester.

In the original study, "stroke" was broadly defined to include all types of cerebrovascular disease: cerebral thrombosis, cerebral embolus, intracerebral hemorrhage, primary subarachnoid hemorrhage, and type unknown (a likely stroke from clinical presentation but without adequate documentation to allow more definite etiologic diagnosis). For the present study, four classifications of stroke were used: intracerebral hemorrhage (ICH), primary subarachnoid hemorrhage (SAH), cerebral infarction due to cerebral embolism or thrombosis (CI), and type unknown (U). The last group included patients whose clinical course was that of a stroke but on whom an autopsy was not performed and evidence (either from angiography or cerebrospinal fluid examination) was insufficient to differentiate between types of hemorrhagic strokes (ICH or SAH) and cerebral infarction (CI).

Sudden death was defined as any death that occurred 24 hours or less from the onset of the first symptoms of a stroke. Hospital records, autopsy protocols, and death certificates were abstracted to obtain diagnostic evidence of the cause of death and an accurate time course of the terminal event. A diagnosis of stroke based solely on evidence on the death certificate was insufficient for a case to be included because of the previously noted inaccuracy of such diagnoses. Any case with another preexisting or coexisting illness, which may have caused the patient's death, was excluded. Also excluded were cases in which trauma or surgical intervention may have contributed to the patient's death.

The cases were assigned to one of the four diagnostic categories on the basis of the best available evidence. In cases in which an autopsy was not performed, the clinical history, angiographically proved lesion, or the presence of bloody cerebrospinal fluid allowed all but four cases to be assigned to one of three diagnostic categories: ICH, SAH, or CI. The four remaining cases were classified as strokes of unknown causes (U).

Review of the cases included identification of each patient's blood pressure as it was recorded at the last observation before the terminal hospitalization. This was usually an outpatient visit or the first recorded blood pressure of the last hospitalization before the terminal one. A patient was classified as definitely hypertensive if the systolic pressure was greater than 160 mm Hg or the diastolic pressure was greater than 90 mm Hg. It was also possible to determine whether the hypertension was diagnosed by the physician who treated the patient and, in all but one case, to determine which patients were receiving treatment for hypertension.

The number of cases in the sudden death group that were examined by the county coroner also was determined. A coroner's case is one in which death occurred outside of a hospital under unusual or unexpected circumstances and an autopsy was ordered by the county coroner. The autopsies were performed at the Mayo Clinic in all but one case.

Results

Among 993 new cases of stroke of all types during the 15-year period from 1955 through 1969, there were 255 deaths due to the first stroke. Fifty-two deaths satisfied the criteria for classification as sudden death caused by stroke. In each case, this was the first clinically apparent stroke. The 52 sudden deaths represent 20% of the patients who died as a consequence of their first stroke.

There were 30 women and 22 men. The ages ranged from 28 to 87 years, with a median age of 65 years. Autopsies were performed in 40 cases.

The clinical presentation and course of four cases classified as unknowns (U) indicated that death most likely occurred from hemorrhagic events. These four were not specifically classified because neither an autopsy nor an angiographically proved lesion nor evidence of bloody cerebrospinal fluid were obtained which would allow us to determine the diagnosis with certainty.

Sudden deaths of patients with no previous history of stroke were caused by intracranial hemorrhage in all but two

Table 1 Causes of Sudden Death from Stroke

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients with stroke</th>
<th>Deaths from 1st stroke</th>
<th>Sudden death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracerebral hemorrhage</td>
<td>100</td>
<td>75</td>
<td>26</td>
</tr>
<tr>
<td>Primary subarachnoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemorrhage</td>
<td>63</td>
<td>33</td>
<td>20</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>777</td>
<td>126</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>53</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>993</td>
<td>255</td>
<td>52</td>
</tr>
</tbody>
</table>
cases (table 1). The two deaths caused by infarction were both unusual events. One involved a 73-year-old man who died in status epilepticus precipitated by a small left parietal cortical infarction. The other involved a 72-year-old man who suffered a basilar-artery thrombosis with infarction of the pons and cerebellum 1 month after oral anticoagulation therapy had been discontinued. He had been treated with anticoagulants because of transient cerebral ischemic attacks in the vertebral-basilar arterial system.

A reasonably accurate estimate of the time course from the onset of the stroke to the time of death was obtained in all cases. The median time from onset to death was 10 hours. Three deaths were virtually instantaneous; all three were due to subarachnoid hemorrhage. Another six patients died in 2 hours or less from the onset of their stroke. Several of these may have been instantaneous but were unWitnessed. The time of death was set at the time they were first found, and the onset was set at the time they were last seen alive. Three of these six deaths were also from subarachnoid hemorrhage, and three were from intracerebral hemorrhage. Thus, six of these nine patients died of subarachnoid hemorrhage. Two of the six, however, died of subarachnoid hemorrhage with intracerebral extension of the hemorrhage.

Overall, the type of event did not seem to influence the length of survival. The median length of survival ranged from 9 hours in the SAH group to 10.5 hours in the U group.

The location of the stroke did seem to influence the duration of survival. Patients who had a stroke in a supratentorial location tended to survive longer than did those with lesions in the posterior fossa and those with pure subarachnoid hemorrhage (table 2). For each location, there were patients who died instantly.

No relationship existed between the duration of survival and the age of the patient. The type of event, however, was more closely related to age. The median age of patients in the ICH, CI, and U groups was 71 years for each group. The SAH group, in contrast, had a median age of 54 years.

Hypertension is an important predisposing factor in cerebrovascular disease. Of the 52 patients, 1 who suffered an intracerebral hemorrhage had no record of previous medical attention in the community. Among the remaining 51 patients, about half of the patients who died from SAH and CI had histories of hypertension, but 88% (23 of 26) of patients who died from ICH were hypertensive (table 3). Overall, only one-third of the hypertensive patients were treated for hypertension. Two factors that must be considered are (1) the less effective drugs for control of hypertension in the early years of this study and (2) the histories of most of the hypertensive patients made it difficult to determine patient compliance with the treatment regimens prescribed.

An important subgroup was identified in the ICH group. This was a group of eight patients who were receiving long-term oral anticoagulation with warfarin for various complications of atherosclerosis (table 3). Four of the eight had had acute myocardial infarctions, two had had transient cerebral ischemic attacks, and two had had recurrent arterial emboli or claudication. At the time of their deaths, these patients had been receiving oral anticoagulant therapy for a median time of 1.5 years (range 4 months to 5 years); four patients had been on anticoagulant therapy for less than 1 year. For five of the eight patients, prothrombin times had been obtained within a week of death and these were either low or within the therapeutic range (1½ to 2½ times control). None of the eight had a history of head trauma preceding death, and all of the hemorrhages were supratentorial.Significantly, all eight patients were hypertensive, but only three were receiving antihypertensive therapy at the time of their deaths.

An additional patient who had been taking warfarin for 5 years after a pontine infarct was not included in this study because she did not die from her first clinically apparent stroke. This patient was an 80-year-old woman who died of massive intracerebral extension of hemorrhage from a ruptured aneurysm of the left middle cerebral artery. She died 3 hours after the onset of her symptoms. We may have missed other patients who died suddenly (as we have defined sudden death) after a second or subsequent stroke.

Hemorrhage in the SAH group occurred from aneurysms or other bleeding sources (table 4). Two of the aneurysms were considered to be atherosclerotic. Seven patients had had significant intracerebral extension of hemorrhage, including two with ruptured arteriovenous malformation.

We found, as have others,1' 17 that most of these sudden deaths occurred after the patient had reached the hospital. Of the 52 deaths in our study, 42 occurred in the hospital. The remaining 10 occurred at home or in a public place before medical assistance could be given. Only nine cases were coroner’s cases.

| TABLE 3  Hypertension in Patients with Sudden Death from Stroke |
|------------------|------------------|------------------|
| Diagnosis      | No. of pts. | With hypertension history | Treated for hypertension |
|------------------|------------------|------------------|
| Intracerebral hemorrhage | 18          | 15                  | 5                   |
| Intracerebral hemorrhage on oral anticoagulants | 8          | 8                  | 3                   |
| Primary subarachnoid hemorrhage | 20          | 9                  | 3                   |
| Cerebral infarction | 2          | 1                  | 1                   |
| Unknown | 4          | 2                  | 0                   |
| Total | 32          | 35                 | 12                  |

<p>| TABLE 4  Sources of Subarachnoid Hemorrhage in 20 Cases of Sudden Death from Stroke |
|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Source</th>
<th>No. of pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cerebral-anterior communicating arteries</td>
<td>5</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>4</td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>2</td>
</tr>
<tr>
<td>Vertebrobasilar system</td>
<td>3</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>2</td>
</tr>
<tr>
<td>No aneurysm found</td>
<td>3</td>
</tr>
<tr>
<td>Not known (no autopsy)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
</tr>
</tbody>
</table>
**Discussion**

We believe that all sudden deaths caused by first stroke in our community during the period 1955 through 1969 have been identified. Some differences between this type of study and the medical examiner format are apparent. Studies of autopsies from the coronor's office result in a significant number of cases being missed. In our study, only 9 of 52 cases (17%) were coroner's cases. All but 10 of the patients survived to reach a hospital, and in all but a few of the cases, the nature of the illness was known before death occurred.

In 12 of our 52 cases (23%), autopsy was not done. We believe that, in all but four of these cases, the nature of the clinical evidence was clear enough that we can be confident of the diagnosis. Based on the available clinical information, deaths in the four unknown cases probably were from intracerebral hemorrhages, and these four will be considered with that group in the remainder of the discussion.

Many more sudden deaths probably occur from stroke in a given population than would have been picked up by methods used in past studies. Of the patients in the community who died of their first intracerebral hemorrhage, 35% (26 of 75) died within 24 hours. Sixty-one percent (20 of 33) of the patients who died from their first SAH died within 24 hours; while less than 2% (2 of 126) of patients who died from their first cerebral infarct died within 24 hours.

All of the instantaneous deaths and most of the deaths that occurred within 2 hours of the onset of symptoms were from subarachnoid hemorrhage. Contrary to the findings of Secher-Hansen and Freytag, we found that most patients with subarachnoid hemorrhage survived to reach medical attention.

Most of the patients in our study had intracerebral hemorrhage as the terminal event. They were significantly older than those in the SAH group, and 88% were hypertensive. In the previous study from which our cases are drawn, the patient who had an intracerebral hemorrhage had the lowest probability of survival for 30 days (16%). Prevention of death from this type of stroke must involve preventing the stroke.

It is acknowledged that even closely controlled patients will have prothrombin times above the therapeutic range, as often as 30% of the time. There is believed to be an increased risk of intracerebral hemorrhage in older patients who are receiving oral anticoagulants, especially in those with hypertension. Among the eight patients with intracerebral hemorrhage who were on long-term oral anticoagulation therapy, all were hypertensive. It is necessary to have strict control of hypertension in any patient in whom long-term anticoagulation is used.

**Acknowledgment**

The authors wish to thank James R. Wentz of the Department of Medical Statistics and Epidemiology for his assistance in gathering the data.

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