Rebound Phenomena after Anticoagulant Therapy in Cerebrovascular Disease

By John Marshall, M.D.

The occurrence of myocardial infarction and embolic incidents in patients with ischemic heart disease after cessation of anticoagulant therapy is well recognized. Likewise, the recurrence of intermittent ischemic attacks in the carotid and vertebro-basilar territory when anticoagulant treatment has been stopped has been described. These experiences have led to the suggestion that following the cessation of anticoagulant therapy there is a "rebound phenomenon" during which further clinical incidents are more likely to occur.

Ascertaining whether such a phenomenon exists meets with two difficulties. The first is that if anticoagulant therapy is effectively suppressing a continuing tendency to thromboembolism, stopping therapy allows the tendency to reassert itself; hence there is likely to be a recurrence of clinical incidents. It has indeed been suggested that the "rebound phenomenon" is simply "a return to the status quo ante" and not a rebound in the usual sense. But others have envisaged "a rebound hypercoagulable state," at least when therapy is stopped because of hemorrhage. Evidence for a state of hypercoagulability following cessation of heparin therapy in dogs has been found, but attempts to find hematologic evidence of a similar state in man have not yet been successful.

The second difficulty is that atherosclerosis is a progressive condition, hence the disease must of necessity be more advanced after a period of therapy that is suppressive and not curative, than it was before. An apparent increase in thrombo-embolic incidents after cessation of anticoagulant therapy might well be due to the more advanced stage of the disease.

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An opportunity to overcome the first of these difficulties was provided by the termination of a controlled clinical trial of long-term anticoagulant therapy in cerebrovascular disease. Usually clinical trials of anticoagulant therapy have shown the therapy to be effective in suppressing thrombo-embolic incidents. In this trial, however, there was no difference in the incidence of nonfatal cerebrovascular episodes between the treated and control groups, suggesting that the anticoagulant therapy was ineffective. There was therefore a unique opportunity to observe what happened when the ineffective therapy was withdrawn. The second difficulty was overcome in this study by a prolonged follow-up of all patients after cessation of therapy. This enabled the course of the disease to be compared during two periods before and two periods after therapy was stopped.

Material

Ninety patients received anticoagulant therapy during the 4 years of a controlled clinical trial. These were patients under 70 years of age who had experienced one or more disturbances of neurologic function each lasting more than 24 hours and attributed to nonhemorrhagic disease of the carotid, vertebral, or intracerebral arteries (completed strokes). During the first phase of the trial there were five cerebrovascular incidents among the 71 treated patients as against four among the 71 controls. During the second phase there were 17 incidents among 66 treated patients against 18 among 65 controls. There was thus no evidence that the anticoagulants were effective.

Of the patients who received anticoagulants 22 died while on treatment (16 during the period of trial and six subsequently), four had treatment permanently stopped because of hemorrhage, and three are still receiving anticoagulants. This leaves 61 patients from whom anticoagulant therapy was withdrawn as a deliberate measure by the gradual reduction of dosage over a minimum period of 4 weeks. During the period of therapy the patients were seen at intervals of not longer than 4 weeks, and subsequently the same procedure was continued for the vast majority. The follow-up of a
few of the patients, in the later months after therapy was stopped, was by personal letter. No patient was lost sight of after therapy had been discontinued.

Results

The results are set out in table 1. During the period on therapy, which comprised 2,399 patient-months, there were 25 nonfatal cerebrovascular incidents, giving a rate of 1.0 per 100 patient-months. At this rate the expected number of incidents during the first 3 months after the drug was finally stopped was 1.9. The observed incidence during this period was 6 (3.2 per 100 patient-months) (table 1). The probability that a difference as large as that between the expected and observed incidence would occur by chance may be obtained from the Poisson distribution and is about one in 50. The observed incidence during the fourth to twelfth month after stopping therapy was 2.0 per 100 patient-months. There is therefore good evidence that during the 3 months after treatment was stopped there was an increased incidence of nonfatal cerebrovascular episodes and that the increase was beyond what might be expected as a result of chance variation in the incidence rate.

The problem as to whether this increased number of incidents following cessation of therapy might be attributable to the natural progress of the disease was next examined by comparing the incidence rate over various periods (table 2). This shows that there was no increased incidence in four periods each of 6 months’ duration prior to the stopping of treatment. Similarly, although the incidence over the whole year after treatment was stopped was higher than at any time during therapy, it was less in the second 6 months than it was in the first. Moreover, the average rate of occurrence of nonfatal accidents was much less in the second 6 months after cessation of therapy than it was in the 3 months immediately after stopping therapy. There is therefore nothing to suggest that the increased incidence in the first 3 months after therapy was stopped was due to the natural progress of the disease.

During the time these patients were under treatment there were seven temporary interruptions of therapy of less than 28 days because of hemorrhage; none of these patients experienced a cerebrovascular accident within the succeeding 3 months. There were four instances in which treatment was permanently discontinued because of hemorrhage and, again, there were no cerebrovascular accidents within the next 3 months. There were 24 interruptions of therapy for reasons other than hemorrhage (two of 4 weeks, one of 3 weeks, five of 2 weeks, seven of 1 week, and nine of

| Table 1 |
| Incidence of Cerebrovascular Accidents before and after Anticoagulant Therapy |

<table>
<thead>
<tr>
<th></th>
<th>Patient-months</th>
<th>Nonfatal cerebrovascular accidents</th>
<th>Accidents per 100 patient-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>During therapy</td>
<td>2,399</td>
<td>25</td>
<td>1.0</td>
</tr>
<tr>
<td>1st month after stopping</td>
<td>65</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>2nd month after stopping</td>
<td>62</td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td>3rd month after stopping</td>
<td>62</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>1-3 months after stopping</td>
<td>189</td>
<td>6</td>
<td>3.2</td>
</tr>
<tr>
<td>4-12 months after stopping</td>
<td>348</td>
<td>7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

| Table 2 |
| Incidence of Nonfatal Cerebrovascular Accidents during 6-Month Periods before and after Cessation of Therapy |

<table>
<thead>
<tr>
<th>Months before treatment stopped</th>
<th>Patient-months</th>
<th>Nonfatal cerebrovascular accidents</th>
<th>Accidents per 100 patient-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-19</td>
<td>308</td>
<td>5</td>
<td>1.6</td>
</tr>
<tr>
<td>18-13</td>
<td>368</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>12-7</td>
<td>349</td>
<td>6</td>
<td>1.7</td>
</tr>
<tr>
<td>6-1</td>
<td>378</td>
<td>4</td>
<td>1.1</td>
</tr>
<tr>
<td>Months after treatment stopped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-6</td>
<td>340</td>
<td>9</td>
<td>2.6</td>
</tr>
<tr>
<td>7-12</td>
<td>197</td>
<td>4</td>
<td>2.3</td>
</tr>
</tbody>
</table>
1 to 5 days); one of these was followed by a cerebrovascular incident, which occurred 32 days after resumption of treatment. One patient died of a myocardial infarction 19 days after an interruption of therapy of 9 days' duration for dental extractions. Three patients died while therapy was being reduced, one of left ventricular failure, one of cerebral hemorrhage proved at autopsy, and one of a myocardial infarct.

Discussion

The value of anticoagulant therapy in abolishing intermittent cerebrovascular ischemic attacks is well established.7, 18, 14 The hope was that therapy would be of equal value in patients who had recovered from a major cerebrovascular accident by preventing recurrences. This proved not to be the case.11, 12, 15, 16 The present series did, however, fortuitously provide a group of patients in whom therapy had been ineffective and from whom it was to be withdrawn. The possibility that any increase after therapy was due to the restoration to normal levels of a suppressed thromboembolic tendency was eliminated, for there was no evidence that this tendency had been suppressed by the therapy; the incidence of nonfatal cerebrovascular episodes in these patients during therapy did not differ from that in a control group chosen by random selection and shown to be constituted similarly in all material respects. Thus the difficulty innate in the study of the "rebound phenomenon" in any group of patients in whom anticoagulant therapy had been effective was avoided.

The value of a study of this kind depends largely upon the accuracy with which further cerebrovascular accidents are diagnosed and recorded. It was for this reason that the assessment was based on the incidence of nonfatal cerebrovascular accidents and fatal accidents were not included. The accuracy with which the cause of a fatal stroke can be determined clinically is not high,17 and this is especially so if the patient cannot be seen personally. The possibility that fatal cerebrovascular accidents due to intracerebral hemorrhage might be attributed to the "rebound phenomenon" was therefore considerable; this source of inaccuracy was avoided by confining attention to the nonfatal accidents in which the possibility of a small hemorrhage mimicking a thrombo-embolic incident is less. Complete records were obtained by ensuring that the patients were seen regularly at intervals of 4 weeks or less.

When therapy was withdrawn from these patients, even by gradual reduction of dosage over a minimum of 4 weeks, there was an increased incidence of nonfatal cerebrovascular accidents in the first 3 months after cessation of therapy, an increase that is likely to have occurred by chance only 1 in 50 times. Subsequently, the incidence rate fell, though not to pretreatment levels. The influence of a possible seasonal factor in the incidence of cerebrovascular accidents cannot be entertained as the patients were withdrawn from therapy throughout the year. Nor can the natural progress of the disease be held responsible, as comparison of the incidence rate over 6-monthly periods showed no progressive increase. The observation therefore provides strong evidence for the existence of a true "rebound phenomenon." Despite the fact that anticoagulants did not influence the incidence of cerebrovascular accidents, withdrawal of therapy did produce an increased incidence, which might well be attributed to a hypercoagulable state.

The suggestion that the "rebound phenomenon" is more likely to appear when treatment is stopped because of hemorrhage than as part of a planned withdrawal9 finds no support in the present study, though the number of temporary and permanent stoppages for hemorrhages (11 instances) was too small to permit firm conclusions to be drawn. But confirmation is provided for the view that temporary interruptions of treatment for reasons other than hemorrhage do not carry much risk,9 as there was only one incident in 24 such interruptions and this occurred 32 days after treatment had been resumed.

Although anticoagulant therapy is not indicated for the major cerebrovascular accidents (completed strokes) from which the
patients in the present series suffered, its undisputed value in patients with transient ischemic attacks makes it relevant to consider in the light of the present study how long therapy should be continued in the latter type of case and how it should be withdrawn. The gradual reduction of therapy over 4 weeks does not appear to have prevented the "rebound phenomenon" in this series; nevertheless it would seem wise not to stop therapy suddenly except when this is unavoidable. Intermittent ischemic attacks often begin to recur when the prothrombin time is allowed to fall just below therapeutic levels. It would seem best therefore to reduce therapy to this level while continuing to observe the patient closely. If attacks recur, effective levels of anticoagulation should be promptly restored. If, on the other hand, the patient remains free from attacks he should be maintained at this level for 3 months before treatment is finally withdrawn.

Summary
Anticoagulant therapy did not reduce the incidence of further nonfatal cerebrovascular accidents in 90 patients who had already experienced one or more such accidents as compared with a control group. Following gradual withdrawal of therapy, however, there was a significantly increased incidence of nonfatal cerebrovascular accidents during the first three months after therapy. This suggests that following cessation of anticoagulant therapy there is a period of true "rebound" during which thrombo-embolic incidents are more likely to recur.

Acknowledgment
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References
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