The Risk of Interrupting Long-Term Anticoagulant Treatment
A Rebound Hypercoagulable State Following Hemorrhage

By HERBERT S. SISE, M.D., CHRISTOS B. MOSCHOS, M.D., JACQUES GAUTHIER, M.D., AND ROBERT BECKER, B.S.

LONG-TERM anticoagulation is an accepted mode of treatment for prevention of emboli from fibrillating hearts, thrombotic occlusions in arteriosclerotic disorders, and pulmonary emboli in phlebitis. The degree of success in coronary artery disease is somewhat disappointing because it does not completely eradicate death from this cause although the incidence of thrombotic complications is clearly reduced.1-3 These results, of course, suggest that intravascular coagulation plays a secondary although important role rather than a primary role as postulated by Duguid.4 The experience acquired during the past 15 years based on laboratory research and clinical observations has led to the establishment of a more or less safe technic of anticoagulant administration. In experienced hands the benefits derived from the use of anticoagulant drugs in carefully selected cases outweighs the risk from bleeding complications due to these drugs. Besides bleeding, as a major complication it has also been noted that discontinuance of treatment for one reason or another carried with it a risk of recurrence of a thrombotic condition. This has been called the rebound phenomenon. In this paper the term “rebound” refers to such post-anticoagulant thrombosis.

Thus, Gosgraf5 in reporting on anticoagulant treatment in recurrent embolism of cardiac origin observed that of 17 patients who stopped treatment, 12 developed 14 embolic episodes. Eight of them happened within 4 weeks after stopping treatment, the other six between the third and twenty-third month. Further, Keyes, Drake, and Smith6 noted new infarcts in 14 of 28 patients who stopped anticoagulation during a period of 3 days to 20 months. There were six fatalities. Interruption of treatment in half of the instances was because of hemorrhage. Carter, McDevitt, Gatje, and Wright7 found a higher tendency to recurrent thromboembolism following discontinuation of anticoagulants within the first 6 weeks, particularly in those with a more pronounced tendency to recurrent thromboembolism or those with congestive heart failure. It is of interest that this incidence of recurrent thromboembolism was higher in the group that stopped anticoagulation than in the group that after a thromboembolic episode remained off anticoagulants. Results of a follow-up study of 293 patients who stopped anticoagulation “for various reasons including hemorrhage” are reported by Nichol et al.8 A total of 90 patients died of “heart attack”; 20 within the first month and 70 within the subsequent 4 years. In their “discontinued group” of 203 patients, Thomas, Scallen, and Savage9 noticed a high recurrence rate during the first year after stopping treatment. The longer the treatment the higher was the observed rate of recurrence after stopping. In 13 instances the treatment was discontinued because of bleeding. Of the total, six had a recurrence within the first year after stopping treatment, in four of whom it was fatal. Bjerklund10 did not notice

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Table 1

Composition of Material*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>Mean age</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Coronary heart disease</th>
<th>Cerebral vascular disease</th>
<th>Peripheral embolus</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>45 (20)</td>
<td>25 (15)</td>
<td>20 (5)</td>
<td>59 ± 11 (59)</td>
<td>6 (3)</td>
<td>12 (7)</td>
<td>16 (11)</td>
<td>14 (5)</td>
<td>6 (0)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Group B</td>
<td>53 (15)</td>
<td>27 (7)</td>
<td>26 (8)</td>
<td>55 ± 13 (55)</td>
<td>7 (2)</td>
<td>14 (4)</td>
<td>27 (11)</td>
<td>17 (2)</td>
<td>8 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Group C</td>
<td>38 (3)</td>
<td>21 (2)</td>
<td>17 (1)</td>
<td>55 ± 12 (54)</td>
<td>4 (0)</td>
<td>7 (2)</td>
<td>12 (1)</td>
<td>6 (1)</td>
<td>17 (1)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>136 (38)</td>
<td>73 (24)</td>
<td>63 (14)</td>
<td>55 (23)</td>
<td>37 (8)</td>
<td>55 (13)</td>
<td>17 (5)</td>
<td>33 (13)</td>
<td>13 (4)</td>
<td></td>
</tr>
</tbody>
</table>

*Figures in parentheses apply to patients who had complications, fatal and nonfatal. From a consecutive series of 310 patients on long-term anticoagulant therapy, either phenprocoumon or warfarin, all patients were collected into either Group A or Group B. Group A consisted of those who had interrupted treatment for a reason other than bleeding, either the beginning or interruption of their own choice, or treatment was interrupted because of a second unrelated disease. Group B consisted of all those who gave up treatment after their first period of anticoagulation because of a second unrelated disease, an operation, or other reason. In Group B, the patient recovered after treatment was reinitiated. In Group C, the patient recovered after treatment was stopped for 3 days or more.

Material and Methods

From a consecutive series of 310 patients on long-term anticoagulant therapy, either phenprocoumon or warfarin, all patients were collected into either Group A or Group B. Group A consisted of those who had interrupted treatment for a reason other than bleeding, either the beginning or interruption of their own choice, or treatment was interrupted because of a second unrelated disease. Group B consisted of all those who gave up treatment after their first period of anticoagulation because of a second unrelated disease, an operation, or other reason. In Group B, the patient recovered after treatment was reinitiated. In Group C, the patient recovered after treatment was stopped for 3 days or more.

These observations suggest that there may be a hypercoagulable state after interrupting anticoagulation. Since it is inevitable that some patients will have to stop anticoagulation, there should be some other bleeding procedures, other illnesses, or some other reason, and thereby expose themselves to a potential risk. This problem was investigated.

SISE, MOSCHOS, GAUTIER, BECKER and VANDER VELT, reported on 20 cases with an increase in the mortality rate as compared to the control group when patients stopped treatment after 3 to 5 years. Finally, Dixon and others have shown that some patients experience a recurrence of acute myocardial infarction within 4 weeks after stopping abruptly or relatively rapidly oral anticoagulation.
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Figure 1

Time intervals between interruption of anticoagulant treatment and appearance of a complication.

**Results**

In group A there were 10 fatal and 10 non-fatal complications. Fourteen of the 20 complications happened within 4 weeks of stopping treatment. This was a distinct difference from groups B and C and suggested a rebound effect.

In group B there were seven fatal and eight nonfatal complications. Only one complication happened in the first 4 weeks, and this was nonfatal.

In group C there were only three complications, all of which were nonfatal. They consisted of an embolus to the leg in one patient with rheumatic heart disease 5 days after interruption of treatment for an appendectomy, coronary insufficiency in a patient 5 days after interruption for a tooth extraction, and transient cerebral vascular insufficiency in a patient 7 days after interruption of treatment because it was thought that the anticoagulant preparation might be producing a syndrome of dry mouth. From the observations in groups B and C it appeared that interruption of treatment for short periods of time could be accomplished without a great risk. Because of its different composition group C was dropped from further considera-

tify this conclusion. Death was considered to have been due to a vascular disorder unless the circumstances clearly indicated that it was not. This free interpretation of a complication was necessary because in some instances in which the patient died suddenly at home there was only the history of the event on which to base the diagnosis. Twenty-four of the total of 38 complications were under circumstances in which the diagnosis could be definite (i.e., autopsy, electrocardiogram, paralytic stroke) and in the remaining 14 the diagnosis was empirical.

Details in regard to the composition of the three groups are shown in table 1. They were similar in age distribution, incidence of diabetes, and hypertension. There were a few more women in group B than in the other two groups. More patients were treated for peripheral emboli from the heart in group C and fewer patients were treated for coronary artery disease in group A. Thus, group C is a distinctly different group, but groups A and B are comparable. At least the differences are not sufficient to explain the results noted below.
tion and comparisons between groups A and B only were made.

The high incidence of complications occurring shortly after interruption because of bleeding suggested a real difference in this group (fig. 1). This was even more evident when the period of exposure was taken into account. Since the patients in group B were withdrawn permanently they were continuously exposed to a risk. On the other hand, in group A many of the patients were started on treatment again as soon as the bleeding problem was controlled. From the formula for calculating rates of survival and for survival without a complication for each month of exposure, it was observed that the difference in the mortality in the first month between group A and group B was sufficiently great to give a critical ratio of difference to standard error of 2.26 (p less than 0.05). If the same was calculated for both fatal and nonfatal complications, the critical ratio was 2.65 (p less than 0.01). After the first month there was no significant difference between the two groups (table 2).

The possibility was considered that a difference in the composition of the two groups might account for the results. It might be expected that the slight predominance of men in group A could bias this group toward an increased number of complications. It does not explain, however, why these should come any sooner. Moreover, group B was biased by having more patients with coronary artery disease in whom the chance of complication was greater and the prognosis consequently worse.

It is suggested that discontinuance of treatment early in the course of long-term anticoagulation might be accompanied by a higher complication rate than late discontinuance. The possibility that patients in group A interrupted treatment earlier than those in group B was examined. The results indicated to the contrary that patients in group A had been on treatment slightly longer than those in group B before interruption. Those who had complications showed the same duration of treatment as those who did not. This applied in both groups (table 3).

Since differences in the composition of the groups did not seem to explain adequately the early appearance of complications in group A, other explanations were sought. Administration of vitamin K₁ might induce a return to a hypercoagulable state. Transfusions with banked blood might introduce thromboplastic substances analogous to the clot-promoting property of serum described by Wessler. Tissue ischemia secondary to blood loss might

### Table 2

**Differences in Mortality and Total Complication Rates of Groups A and B**

<table>
<thead>
<tr>
<th>Month</th>
<th>Mortality rate</th>
<th>Diference</th>
<th>SE of difference</th>
<th>Critical ratio</th>
<th>Total complication rate</th>
<th>SE of difference</th>
<th>SE of difference</th>
<th>Critical ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>.219</td>
<td>0</td>
<td>.219</td>
<td>.0972</td>
<td>2.26</td>
<td>.406</td>
<td>.022</td>
<td>.384</td>
</tr>
<tr>
<td>2</td>
<td>.154</td>
<td>.027</td>
<td>.127</td>
<td>.133</td>
<td>.8</td>
<td>.231</td>
<td>.027</td>
<td>.204</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>.029</td>
<td>.029</td>
<td>.156</td>
<td>.2</td>
<td>0</td>
<td>.029</td>
<td>.299</td>
</tr>
</tbody>
</table>

*Mortality rate was calculated as the ratio \( \frac{d_r}{O_r - \frac{1}{2} W_x} \) in which \( d_r \) = the number of deaths, \( O_r \) the number of cases exposed to the risk, and \( W_x \) = the number of cases withdrawn from observation because of loss to follow up. Those who resumed treatment during the month were subtracted from \( O_r \) of the subsequent month. The total complication rate was calculated in the same way except \( d_r = \) sum of the number of fatal plus the number of nonfatal complications. The standard error was calculated by the formula SE = \( \sqrt{\frac{\left( \frac{d_r}{O_r - \frac{1}{2} W_x} \right)^2}{O_r (O_r - \frac{1}{2} W_x)}} \) in which \( O_r = O_r - \frac{1}{2} W_x \) and SE of difference = \( \sqrt{\frac{\text{SE}^2}{\text{difference}}} \) Critical ratio = \( \left( \frac{\text{difference}}{\text{SE}} \right) \).
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Table 3

<table>
<thead>
<tr>
<th>Duration of Treatment before Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Uncomplicated</td>
</tr>
<tr>
<td>Complicated*</td>
</tr>
<tr>
<td>Complicated within 4 weeks*</td>
</tr>
<tr>
<td>Group B</td>
</tr>
<tr>
<td>Uncomplicated</td>
</tr>
<tr>
<td>Complicated*</td>
</tr>
</tbody>
</table>

*Refers to all thromboembolic complications, fatal and nonfatal.

initiate a series of events culminating in a thrombus formation. The role of these three factors was observed by comparison of complicated and uncomplicated patients in group A. There is some tendency toward complications in those who had ischemic symptoms such as chest pain or transient cerebral symptoms, as may be seen in table 4, but the numbers are too small to be of significance. There is no clear indication that vitamin K\textsubscript{1} or transfusions should be withheld for fear of precipitating a thrombotic complication. There is overlap in the figures given because a single patient often fell into more than one category.

The complications showed no definite relation to the source of the bleeding (table 5). Even after relatively minor bleeding such as hematuria and a small hematoma, fatal complications were observed. The presence of associated conditions such as ulcer or diabetes was not associated with an observable difference in rate of complications, but the figures are too small to be of significance.

Discussion

Two possible conclusions seem to be justifiable from the observations. First, a hypercoagulable state is induced as a direct result of the bleeding by a mechanism that is not clear. Second, a common factor might induce both the bleeding and the complication. It is possible, for instance, that a patient who is deteriorating might become sensitive to the anticoagulant and start bleeding. Since there were no differences in the composition of the groups, the latter hypothesis does not seem likely, and we are inclined to favor the first.

Whatever the mechanism, the results strongly point out that bleeding is a more undesirable complication than has generally been appreciated. To the risk of inducing a fatality as a direct result of bleeding there is added the more subtle risk of inducing a rebound complication that may be fatal. There are sufficient reports to indicate that the general incidence of a fatal bleeding episode during long-term anticoagulation is somewhere in the neighborhood of 1 per cent. The incidence of bleeding is around 10 per cent. If one assumes a bleeding rate of 10 per cent in patients on long-term treatment and a rebound (1 month) fatality rate of 16 per cent (seven out of 45 instances), then there could be expected to be 1.6 per cent greater mortality rate, making a total mortality rate of about 2.6 per cent. This is a figure comparable to that of many surgical operations and should instill further caution in the use of anticoagulants. Furthermore, reports that compare the future of patients who continue treatment with those who stop treatment because of bleeding are introducing a bias.

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Summary

From a series of 310 patients on long-term anticoagulant treatment for various conditions 136 instances were collected in which treatment was interrupted. This was because of bleeding in 45 instances, for permanent reasons in 53 instances, and for temporary reasons in 38 instances.

Rebound thromboembolic complications were observed significantly more frequently in those who stopped treatment for bleeding. The cause of the rebound effect could not be ascribed to vitamin K₁ administration, transfusions, or overt ischemic effects from blood loss although the latter might have been contributory to a small extent. The observations suggested a hypercoagulable state induced directly in some obscure way as a result of the bleeding.

Interruption of treatment for reasons other than bleeding was not associated with early complications. The risk of interruption of treatment for short periods was relatively small (three nonfatal complications in 38 instances). In those who stopped permanently, complications were most often seen after 2 months.

Acknowledgment

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References

3. SISE, MOSCHOS, GAUTHIER, BECKER
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