The Relationship with activity seconds
20 has been instances between
of the relationship between prothrombin time and bleeding met in the clinical use of dicumarol.

The low incidence of bleeding (about 5 per cent of postoperative cases) which accompanies careful use of dicumarol has been associated with vigilant regulation of the dose of dicumarol dependent on daily determinations of prothrombin time. The method of determination of prothrombin times used at the Mayo Clinic is Magath's modification of Quick's procedure. With this test, the respective values for 100, 30, 20 and 10 per cent of normal prothrombin activity are 17 to 19 seconds, 27 seconds, 35 seconds and 60 seconds. The therapeutic goal has been to reduce the prothrombin time to between 10 and 30 per cent of normal.

In our study, bleeding was considered to result from dicumarol in all cases. In some instances it would have occurred, obviously, had dicumarol not been used, as postoperative bleeding occurs occasionally when dicumarol has not been administered. It appears improbable to us, however, that the results of this study have been significantly influenced because we have considered all bleeding to result from dicumarol. We considered hemorrhage to have been minor (epistaxis, hematuria, ecchy-
mosis and oozing from a surgical wound) if transfusion was not required and to have been major if transfusion was required.

In a group of 2456 cases, predominantly postoperative, in which the patients received dicumarol, there were 147 instances of bleeding. Records were maintained and every twentieth patient who did not bleed was used as a control. In the course of treatment, the mean prothrombin time rose rapidly at first and slowly declined to a fairly stable level (fig. 1). Because of this variation, we compared separately for each day of treatment and on the same day, the mean prothrombin time of patients who bled with the mean prothrombin time of controls. We considered the prothrombin time on the day of bleeding as the only significant figure for the bleeders, as the prothrombin time may have been low prior to bleeding, risen abruptly at the time of bleeding and declined subsequently owing to institution of countermeasures. Henceforth, when we speak of prothrombin time of the bleeders, we speak of the prothrombin time obtained only on the day of bleeding.

The mean prothrombin time of bleeders is higher in most instances than that of controls for the same day of treatment (fig. 1). In spite of the striking difference in mean prothrombin times, the relationship between bleeding and prothrombin is not a close one. Bleeding occurred in some instances when prothrombin time was not increased much above normal and failed to occur in other instances when prothrombin time was greatly increased (table

From the Division of Medicine, Mayo Clinic, Rochester, Minn.
TABLE 1.—Comparison of Range, Mean and Median of Prothrombin Time for a Control Group and a Group of Patients Having Major and Minor Hemorrhages

<table>
<thead>
<tr>
<th>Day of treatment</th>
<th>Number of Cases</th>
<th>Prothrombin time in seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control* Hemorrhage</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>Minor</td>
<td>Major</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
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</tr>
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<td>5</td>
<td>87</td>
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<td>6</td>
<td>88</td>
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<td>7</td>
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<td>12</td>
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<td>9</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>6</td>
</tr>
</tbody>
</table>

* Represents 5 per cent of the total cases without bleeding.
† Represents values, above and below which there were an equal number of cases.

1. The overlapping of prothrombin times of the two groups, controls and bleeders, is so great (fig. 2) that prothrombin time should not be used to predict the onset of bleeding or immunity from bleeding in the individual patient. Of all patients who had hemorrhages only 57 per cent had a prothrombin time greater than thirty-five seconds which was the desired value and one not generally considered to predispose to bleeding.

The mean prothrombin time of those who had major bleeding was higher than the mean prothrombin time of those who exhibited minor bleeding, but the same marked variations existed between bleeders, as a group, and controls (table 1).

Age was apparently not a factor in the incidence of bleeding. The mean ages of the different groups were: controls forty-nine years, minor bleeders forty-four years and major bleeders forty-seven years. The differences in incidence were not significant.

The daily incidence of bleeding is interesting. Hemorrhage induced by experimental administration of dicumarol to animals and that which affects patients receiving excessive doses of dicumarol may occur about two weeks after institution of treatment. In our series, the incidence of bleeding was greatest on the eighth day of treatment with a relatively high incidence from the sixth to tenth day. The frequency of cases during the first few days might have been explained plausibly on the basis of delayed onset of prothrombin deficiency, but the mean prothrombin time reached a maximum by the fourth day (fig. 1) and slowly declined thereafter while the incidence of bleeding increased. We could not attach special significance to the lower incidence of bleeding after the eighth day of treatment without allowing for the reduction in number of patients maintained on treatment. We expressed the relative incidence of bleeding on each day of treatment as a proportion of the number of patients still receiving dicumarol on that day. When this necessary allowance was made, the
relative incidence of bleeding still declined rapidly after the eighth day (fig. 3).

Thus the increased incidence of bleeding about the eighth day cannot be explained simply as the result of delayed appearance of a prolonged prothrombin time and a later decline in numbers of patients receiving dicumarol. The unique incidence remains unexplained. There is an implied dissociation between daily mean prothrombin time (single-stage method) and incidence of bleeding.

The day of most frequent bleeding was not only the eighth day of treatment but also was the tenth day after operation. This was to be expected because administration of dicumarol was started on the third day after operation in 107 of the 147 cases in which bleeding occurred. Bruzelius, who began treatment on the first day after operation, observed a maximal incidence of bleeding on the eighth postoperative day. This suggests that the incidence of bleeding is related more to the duration of treatment with dicumarol than to the lapse of time after operation.

**Comment**

The foregoing factual study leads to an important question that can be answered only in part: as longer prothrombin times may not be accompanied by an increase of bleeding sufficient to prohibit use of dicumarol, are we justified in demanding repeated prothrombin determinations as an obligatory prerequisite to dicumarol therapy? A more universal clinical use of dicumarol, sought to combat the ubiquitous threat of intravascular thrombosis, will remain unrealized when use depends on availability of repeated reliable prothrombin determinations. In spite of this pressing consideration, two aspects of therapy suggest continued dependence on prothrombin determinations.

![Figure 2](http://circ.ahajournals.org/)

**Fig. 2.** The percentage incidences of various prothrombin times, given separately for the two groups. For the controls, percentage incidence of all prothrombin times for the period under consideration is shown; for the bleeders, percentage incidence of stated prothrombin times of the day of bleeding. (Note: Only values obtained on fourth to twelfth days of treatment were included in calculating the incidence in each group.)

![Figure 3](http://circ.ahajournals.org/)

**Fig. 3.** Daily incidence of bleeding as a proportion of patients still receiving dicumarol therapy.

The prothrombin time in response to a given dose of dicumarol is unpredictable. Use of dicumarol without prothrombin determinations exposes a patient to the hazard of bleeding without guaranteeing the present high protection against intravascular thrombosis. There is also an unverified possibility that large doses of dicumarol may, by virtue of the magnitude of the dose itself, increase the risk of bleeding, a risk not necessarily reflected by a proportionate increase of prothrombin time. Therefore, until statistical technics have apportioned the risks, we must continue to advocate that dicumarol be used only when its administration is guided by repeated determinations of prothrombin time, in order that we can insure a deficiency of prothrombin sufficient to prevent intravascular thrombosis and in order that the therapeutic goal is achieved with the smallest possible dose of dicumarol. However, the physician must not disregard the fact that bleeding may occur when prothrombin times are not greatly prolonged. He must be espe-
cially alert for the appearance of postoperative bleeding of patients after the sixth day of treatment.

**Summary**

In general, patients who bled during the clinical use of dicumarol after operation had a higher prothrombin time than those who did not bleed.

Correlation between bleeding and prothrombin time was only approximate. Some patients bled when prothrombin time was not greatly prolonged and others failed to bleed when it was markedly prolonged. Although the extent of prolongation of prothrombin time was only a gross measure of the tendency toward bleeding, repeated determinations of prothrombin remain the guide to safe treatment with dicumarol.

Age apparently was not a factor in the incidence of bleeding.

There was maximal bleeding on the eighth day of treatment with dicumarol with a relatively high incidence between the sixth and tenth days.

**REFERENCES**

The Relationship between Prothrombin Time and Bleeding in the Clinical Use of Dicumarol after Operation
C. ADRIAN M. HOGBen and EDGAR V. ALLEN

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