Effect of Dicumarol on Blood Vascular Integrity in the Rabbit

By Thomas E. Nelson, Jr., Ph.D.

The simplicity and relative economy of administration of the coumarin anticoagulant drugs are important considerations in the management of thromboembolic diseases. But, the tendency toward spontaneous hemorrhage, associated with coumarin therapy, presents a definite hazard.

Assuming that the hemorrhagic effects are side reactions not related to hypoprothrombinemia, there has been an extensive search for structurally related compounds which would induce hypoprothrombinemia with less hemorrhagic risk. On the other hand, the view that prothrombin depression is directly related to the development of the hemorrhagic state is supported by observations in the vitamin K deficient new born infant, sprue, patients with hepatic disease or obstructive jaundice, as well as the Dicumarol-treated individual. But in view of reports that Dicumarol interferes with the production of other clotting factors, proconvertin (clotromboplastin or factor VII) and factor X, which may also be depressed by hepatic injury, such hemorrhage as occurs with the coumarin drugs or liver injury cannot be accredited to hypoprothrombinemia alone.

In addition to interference with the coagulation factors, Jaques et al. have recently demonstrated that Dicumarol treated rats and rabbits subjected to various forms of stress showed a mortality rate significantly above that of anticoagulant treated non-stressed controls. Stress alone was observed to increase prothrombin time. Also, Dicumarol elevated the prothrombin time of adrenalectomized rats above that of control animals given only Dicumarol, causing 100 per cent fatality. Thus, several factors may play a role in the prothrombin and hemorrhagic responses of animals given Dicumarol and the possibility remains that the coumarin drugs interfere with intermediate mechanisms which are essential to both the elaboration of hemostatic factors and the maintenance of the vascular wall. Evidence suggesting this possibility was reviewed by Spaet. However, the actual cycle of events resulting in Dicumarol hemorrhage has never been defined.

In the course of experiments to determine the effects of Dicumarol in rabbits, we have observed changes in both the disappearance of labeled plasma protein from the bloodstream and the appearance of labeled protein in the peritoneal cavity. Observations made on the transvascular transfer of T-1824 labeled plasma protein after Dicumarol administration were previously reported, but at that time we were unable to establish any direct relationship between this effect and the loss of label from the blood. However, further experiments have helped to show a relationship between protein leakage and whole blood loss, the effect on protein leakage of administering vitamin K to the previously Dicumarol treated animal, and the possible relation of hypoprothrombinemia to the increased protein leakage.
Table 1
T-1824 Disappearance Rates After Dicumarol

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Dicumarol injected (hours before dye)</th>
<th>T-1824 Prothrombin disappearance rate (%/min.)</th>
<th>Пурпурра</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(% initial value)</td>
<td></td>
</tr>
<tr>
<td>A. INTRAVENOUS—25 mg./Kg. body wt./day (gelatin suspension)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>X X</td>
<td>0.346</td>
<td>7 +</td>
</tr>
<tr>
<td>2</td>
<td>X X</td>
<td>0.269</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>X X</td>
<td>0.324</td>
<td>&lt;5</td>
</tr>
<tr>
<td>4</td>
<td>X X</td>
<td>0.285</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>X X</td>
<td>0.316</td>
<td>12 +</td>
</tr>
<tr>
<td>6</td>
<td>X X</td>
<td>0.300</td>
<td>?</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>0.307±0.025</td>
<td></td>
</tr>
<tr>
<td>B. ORAL—60 mg./Kg. body wt./day by stomach tube</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>X X</td>
<td>0.221</td>
<td>12 +</td>
</tr>
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<td>2</td>
<td>X X</td>
<td>0.308</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>X X</td>
<td>0.311</td>
<td>9</td>
</tr>
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<td>4</td>
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<td>0.384</td>
<td>&lt;6 ++</td>
</tr>
<tr>
<td>5</td>
<td>X X</td>
<td>0.305</td>
<td>&lt;5 0</td>
</tr>
<tr>
<td>6</td>
<td>X X</td>
<td>0.396</td>
<td>&lt;5 0</td>
</tr>
<tr>
<td>7</td>
<td>X X</td>
<td>0.360</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>X X</td>
<td>0.448</td>
<td>7</td>
</tr>
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<td>9</td>
<td>X X</td>
<td>0.355</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>X X</td>
<td>0.307</td>
<td>30</td>
</tr>
<tr>
<td>11</td>
<td>X X</td>
<td>0.281</td>
<td>89</td>
</tr>
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<td>0.323</td>
<td>7 ++</td>
</tr>
<tr>
<td>13</td>
<td>X X</td>
<td>0.565</td>
<td>7 ++++</td>
</tr>
<tr>
<td>14</td>
<td>X X</td>
<td>0.412</td>
<td>49 ++++</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>0.431±0.106</td>
<td></td>
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<tr>
<td>C. CONTROL—Mean and S.D. of 9 untreated animals</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td>0.300±0.024</td>
<td></td>
</tr>
</tbody>
</table>

Methods

Female rabbits, anesthetized with pentobarbital, were used for all experiments. Blood samples were drawn from an exposed femoral artery into heparin-rinsed tuberculin syringes and centrifuged. In all experiments, the plasma samples were treated similarly except for the volume dilution used. Samples taken for dye disappearance were diluted 1:9 and the dye density determined in a Coleman colorimeter. The data were corrected and plotted as described by Paldino et al.8 Some animals used for this measurement were sacrificed at the termination of the experiment and the degree of purpura and hemorrhage observed were rated 0 to 4+.

The protein transfer rate across the peritoneal and vascular membranes was estimated by a previously described technique.7 However, in the course of these experiments, it was noted that in a few animals an effective osmotic imbalance existed between the body fluids and the injected artificial ascitic fluid. This resulted in a small but measurable water shift requiring a simple correction of the colorimeter readings prior to calculating the transfer rate. For this correction, variations in the specific gravity of the ascitic fluid samples were obtained with a falling drop densitometer. The percentage change in protein concentration was then used to estimate more accurately the ascitic fluid dye concentration theoretically obtainable had there been no water exchange.

Dicumarol was administered by one of several different methods: in water suspension by stomach tube; injected intravenously in a gelatin suspension,7 or as the water soluble di-sodium salt prepared according to the method of Overman et al.,9 or it was injected intraperitoneally as a concentrated suspension prepared in a vehicle of 2 ml. of diluted rabbit serum. In order to maintain solubility of the di-sodium salt of Dicumarol, it was necessary to inject this preparation at approximately pH 9.

Plasma prothrombin levels were determined by the method of Ware and Stragnell10 and expressed as per cent of the individual animal's own control value.

Results

Effect of Dicumarol on T-1824 Disappearance from the Blood

Intravenous Dicumarol in Gelatin Suspension

Previous observations in rabbits with "artificial ascites"7 indicated that the effect of intravenous Dicumarol (gelatin suspension) on the rate of T-1824 disappearance from the blood stream is negligible. It was possible, however, that the presence of a large volume of serum in the peritoneal cavity in these animals might interfere with, or mask slight changes in, the rate of removal of dye from the blood stream, thereby producing false disappearance values. The disappearance rates obtained in animals given similar dosages of Dicumarol (25 mg./Kg./day for 2 days) with no artificial ascites (table 1A) do not support this theory. Though the prothrombin values were depressed to extremely low levels, sufficient to cause at least mild purpura in the peritoneal cavity, none of the animals demonstrated a statistically significant increase in the disappearance rate above that obtained in control animals (table 1C).

Oral Dicumarol

Somewhat similar results were obtained when twice as much Dicumarol was given per day by stomach tube over periods of 24, 48,
DICUMAROL AND VASCULAR INTEGRITY

Table 2

T-1824 Disappearance Rates After Intravenous Di-Sodium Dicumarol or Sodium Hydroxide

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>mg./Kg. B.W.</th>
<th>Dicumarol injected hours before dye</th>
<th>T-1824 disappearance rate (%/min.)</th>
<th>Prothrombin level (% initial value)</th>
<th>Purpura</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>72</td>
<td>48</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>A. DI-SODIUM DICUMAROL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>X</td>
<td>0.400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>X</td>
<td>0.396</td>
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<td>3</td>
<td>22</td>
<td>X</td>
<td>0.430</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>X</td>
<td>0.550</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>X</td>
<td>0.493</td>
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<tr>
<td>6</td>
<td>22</td>
<td>X</td>
<td>0.490</td>
<td></td>
<td></td>
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<tr>
<td>7</td>
<td>25</td>
<td>X</td>
<td>0.420</td>
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<td>8</td>
<td>25</td>
<td>X</td>
<td>0.345</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>X</td>
<td>0.422</td>
<td>&lt;5</td>
<td>+++</td>
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<tr>
<td>10</td>
<td>25</td>
<td>X</td>
<td>0.400</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Mean:</td>
<td></td>
<td></td>
<td>0.435±0.057</td>
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<td></td>
</tr>
</tbody>
</table>

B. SODIUM HYDROXIDE TREATED (Equivalent of 25 mg./Kg. B.W. di-sodium Dicumarol)

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>mg./Kg. B.W.</th>
<th>Dicumarol injected hours before dye</th>
<th>T-1824 disappearance rate (%/min.)</th>
<th>Prothrombin level (% initial value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>X</td>
<td>0.215</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>X</td>
<td>0.227</td>
<td>100</td>
</tr>
</tbody>
</table>

The erratic prothrombin response is to be expected with oral administration of Dicumarol, but if the increase in disappearance rates obtained in this series is related to the extent of prothrombin depression, one would expect to find better correlation between these 2 sets of values. On the other hand, it is quite apparent from observations in sacrificed animals of this group that the increased dye disappearance rates do show a correlation with the incidence and severity of purpura.

Intravenous Di-sodium Dicumarol

A third group of animals given Dicumarol intravenously as the di-sodium salt (table 2A) responded quite differently from those given the suspension. All of these animals had high dye disappearance rates. It is unfortunate that not all animals were sacrificed at the termination of the experiments. However, in those found to be hemorrhagic one can observe a correlation between the increased loss of dye from the blood and the severity of interstitial bleeding. Why this group of animals showed only irregular increases, is not clear. However, it is quite certain that this is not the result of an increase in blood pH from injection of the basic di-sodium salt, since administration of sodium hydroxide alone in amounts equal to that used to dissolve 25 mg. of Dicumarol had only a depressant effect upon the rate of dye disappearance (table 2B). In addition, it was observed that the administration of the drug in this form does not immediately increase the rate of removal of dye from the blood stream, but instead, appears to depress it (fig. 1). In this experiment a control disappearance was obtained over a 120 minute period. Following this, 25 mg. di-sodium Dicumarol/Kg. body weight were injected and the dye disappearance, prothrombin, and plasma protein concentrations were determined over a similar period of time. From this experiment we see that the administration of the drug in this form immediately depresses the plasma prothrombin but, instead of producing an immediate increase in loss of dye from the blood stream, it actually decreases the disappearance rate. This latter observation agrees with the change in protein concentrations as measured densiometrically.
Figure 1

Effect of di-sodium Dicumarol on the dye disappearance rate, plasma protein and prothrombin levels. Di-sodium Dicumarol injected 150 minutes after injection of dye. Disappearance rates are expressed in per cent per minute. Prothrombin and plasma protein concentrations are expressed in per cent of the animals' own control value.

These experiments indicate that Dicumarol enhances the loss, or removal, of dyed protein from the blood and this action seems to be related to the increased red cell leakage. However, this type of disappearance measurement is relatively insensitive to the early changes occurring in the vascular wall of the Dicumarol treated rabbit. Therefore, in order to study the early phase of vascular breakdown after Dicumarol and its relation to prothrombin and vitamin K metabolism, the following experiments were carried out using the "artificial ascites" animal.

Effect of Dicumarol on Artificial Ascites

Preparation

In none of the above experiments was it possible to establish a relationship between the plasma prothrombin level and the disappearance of dye from the blood, in agreement with previous studies on the rate of transfer of dye into the peritoneal cavity. One explanation might be that Dicumarol has a direct damaging action on the vascular wall independent of its effect on prothrombin. If this assumption is true, it should be possible to separate these 2 actions of the drug by chemical or physical means. Though vitamin K is known to inhibit the prothrombin depressing action of Dicumarol, its effect on the transvascular protein exchange induced by Dicumarol is not established. To test this possibility 2 types of experiments were devised.

Observations with Dicumarol and Vitamin K:

In one procedure, 10 rabbits were given an intravenous injection of Dicumarol 48 and 24 hours before making the dyed protein transfer measurements. These animals previously were given 4 or 8 mg. of vitamin K, (Mephyton, Merck Sharp & Dohme) intravenously 1 hour before each injection of Dicumarol. The results obtained (table 3A) indicate quite clearly that when vitamin K inhibits the prothrombin depressant action of Dicumarol it also inhibits the increased dyed protein transfer. Although there is no apparent correlation between the degree of hypoprothrombinemia and the extent of increase in protein transvascular exchange, it is clear that Dicumarol did not cause an increased protein exchange in those animals which showed no prothrombin depression.

Effect of Intraperitoneal Dicumarol

If Dicumarol exerts 2 unrelated actions, one on the prothrombin elaboration mechanism of the liver, and one on the vessel wall, injection of the drug into the blood stream would rapidly distribute it to the entire body and both actions might proceed in parallel and appear as one. In a further attempt at separating these 2 possible mechanisms, it was assumed that intraperitoneal deposition of crystalline Dicumarol suspension should permit any direct action on the surrounding blood vessels to proceed for a short time prior to appreciable absorption into the blood stream. If the peritoneum was subjected directly to Dicumarol in high concentration, before the arrival of the drug in the liver one might observe an independent action on the vascular endothelium. Six rabbits were given intraperitoneal injections of Dicumarol (25 mg. crystalline Dicumarol/Kg. suspended in 2 ml. of diluted normal rabbit serum). Figure 2 illustrates the results obtained from...
such an experiment. At intervals following intraperitoneal administration of the drug, the dye transfer rates and the plasma prothrombin levels were determined in the 3 pairs of animals. In contrast to the other experiments described here, these results do indicate a truly inverse relationship between the transfer rate and the prothrombin values.

When animals given Dicumarol intraperitoneally in this manner were first given vitamin K₁ 1 hour before the Dicumarol injection the increase in protein transfer rate again appeared to be in some way related to the prothrombin depression (table 3B).

Discussion

The nature of the vascular defect in the hemorrhagic diseases is yet unknown. According to Spaet, impaired hemostasis and purpura have separate though related pathogeneses. Other investigators have expressed the view that vascular integrity may be more closely associated with the hemostatic system. Copley, et al. have recently shown that fibrin films have anticoagulant properties, thus strengthening an hypothesis of Copley, Zweifach, and others, that the endo-endothelial protein surface may be composed in part at least of precipitated fibrin. Observations such as this give credence to the theory that an unimpaired blood coagulation mechanism is required for efficient blood vessel maintenance and function.

Increased vascular fragility and permeability may be associated in certain conditions. From the experimental results described in this report, it seems quite likely that purpura produced by Dicumarol may very well be such a condition. As shown in this, and previous communications, Dicumarol may not only induce hemorrhagic phenomena but it appears also to increase transvascular dye labeled protein transfer, or leakage, in measurable amounts prior to the appearance of purpura. Since the dye T-1824 is firmly bound to plasma protein, it may be assumed that its disappearance from the blood stream measures movement of protein across the vascular membrane. However, it is not altogether clear what mechanisms are involved. We could not show histologically that this increase in disappearance of dye labeled protein was the result of increased active removal by phagocytosis. A significant increase in the amount of dye in the Kupffer cells would suggest activation of this mechanism. However, a negative result does not preclude increased phagocytosis since it can be argued that the amount of dye observed in the Kupffer cells represents dyed protein in transit being continuously released into some extravascular pool or destroyed. These dye disappearance experiments alone indicate only increased protein loss from the blood, but give no indication of the actual mechanisms by which this is accomplished.

Table 3

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Initial protein transfer rate</th>
<th>Vitamin K₁ dose (mg/Kg. B.W.)</th>
<th>Dicumarol dose (mg/Kg. B.W.)</th>
<th>Prothrombin level (%)</th>
<th>Initial values</th>
<th>Transfer rate (mg dye/hr.)</th>
<th>mg dye/ml conc. diff.</th>
<th>Beginning</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. INTRAVENOUS VITAMIN K₁ AND DICUMAROL. Vitamin K₁ injected 1 hour prior to each gelatin-Dicumarol injection of 22 mg. Dicumarol per Kg. B.W.</td>
<td>1.40</td>
<td>6</td>
<td>48</td>
<td>24</td>
<td>135</td>
<td>0.204</td>
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<td>48</td>
<td>24</td>
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<td>48</td>
<td>24</td>
<td>105</td>
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<td>9</td>
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<td>94</td>
<td>0.290</td>
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<tr>
<td>B. INTRAVENOUS VITAMIN K₁ AND INTRAPERITONEAL DICUMAROL. Vitamin K₁ injected 1 hour prior to single intraperitoneal injection of 25 mg. Dicumarol per Kg. B.W. suspended in 2 cc. serum. Prothrombin levels were measured before and after dye transfer measurements.</td>
<td>1.50</td>
<td>4</td>
<td>20</td>
<td>120</td>
<td>102</td>
<td>0.267</td>
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<td>1.80</td>
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<td>98</td>
<td>89</td>
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<td>3</td>
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<td>20</td>
<td>67</td>
<td>48</td>
<td>0.331</td>
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<tr>
<td>C. CONTROL. Mean and S.D. of 10 untreated animals.</td>
<td></td>
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</table>
In all of the disappearance experiments cited, there is an obvious lack of correlation between the dye disappearance rate and the plasma prothrombin level. However, a comparison of the disappearance rates with the incidence and severity of purpura shows a fairly good correlation. This is more obvious in animals given Dicumarol intravenously.

The vascular reactions in rabbits to the 2 different forms of Dicumarol given intravenously (di-sodium salt or gelatin suspension) suggest that the di-sodium salt induces a more severe hemorrhagic response as well as greater plasma protein leakage. One can only speculate as to the reason for this difference. It seems fairly certain that neither of these effects of the drug in this form are the result of the sodium hydroxide per se, (table 2B). Furthermore, the decrease in the vascular integrity due to Dicumarol occurs only after a reduction in the blood prothrombin level (fig. 1). It is noteworthy that Dicumarol in this experiment does not immediately increase but actually temporarily decreases the disappearance rate of dyed protein. The hypoprothrombinemic effect however, was observed within 90 minutes after injection of the di-sodium Dicumarol. If the protein bound to Dicumarol in some way becomes more susceptible to phagocytosis, this effect should be reflected in the disappearance rate very soon after injection. The fact that Dicumarol does not immediately increase the disappearance rate of dye labeled plasma proteins suggests that accelerated removal of the dye-protein complex by the reticuloendothelial system is not a contributing factor in these experiments. Therefore, it seems reasonable to assume that when Dicumarol increases the disappearance rate, it does so by actually disrupting normal vascular integrity sometime after the manifestation of hypoprothrombinemia. As we have reported previously,7 one can measure an increase in the transperitoneal transfer of labeled protein occurring as early as 3 hours following intravenous injection of Dicumarol. However, we have not been able to observe such a change in less than 90 minutes following intravenous administration of this drug. Interestingly enough, though there is no immediate rate increase, Dicumarol, at least administered as the di-sodium salt, may affect the plasma protein or the reticuloendothelial system in such a way as to reduce temporarily the normal uptake or leakage of plasma protein. That this effect is not specific for dye labeled plasma protein is suggested by the lessened rate of decrease in total plasma protein measured densiometrically.

It is conceivable that there are 2 effects of Dicumarol on vascular integrity. In all experiments in which Dicumarol was administered intravenously, and probably those where oral administration was used, the blood Dicumarol level was much higher than would be required to inhibit prothrombin elaboration. This might cause a direct injury to the vascular wall which would conceivably completely mask any indirect action Dicumarol might demonstrate as the result of prothrombin depression. Though the mechanism of the reversible Dicumarol-vitamin K inhibition is not yet established, it is known that prothrombin elaboration may be inhibited or enhanced depending upon which substance is present in excess.
If Dicumarol acts directly on the vascular wall, independently of prothrombin depression, it might be possible to maintain the prothrombin level in a normal range in the presence of a high blood Dicumarol level and possibly separate these 2 effects of Dicumarol. Assuming this reasoning is correct, it appears from the results in experiments where both drugs were given (table 3A) that Dicumarol only indirectly affects protein transfer after depressing the prothrombin level. An increased dyed protein transfer was observed only in experiments where vitamin K\(_\text{I}\) failed to inhibit completely the hypoprothrombinemic effect of Dicumarol. This idea also receives support from the last group of experiments (fig. 2 and table 3B) where Dicumarol was given intraperitoneally. In this procedure, absorption into the blood stream was undoubtedly very slow, since the major portion of the injected Dicumarol was recovered undissolved from the peritoneal cavity after each experiment. Again with this series of animals, we found a definite correlation between the severity of hypoprothrombinemia and the transperitoneal protein transfer rate or with the incidence of purpura. We could find no gross signs of direct irritation of the blood vessels in the peritoneal cavity which could be related to the presence of Dicumarol.

It appears, therefore, that the "capillary permeability" increasing action of Dicumarol is at least indirectly related to the coagulation mechanism. This is supported by both the close correlation between the prothrombin response and the transperitoneal protein transfer rate observed with intraperitoneal injection of Dicumarol and the findings when vitamin K\(_\text{I}\) was administered with Dicumarol.

Of course these results do not rule out a possible dual mechanism by which Dicumarol may disrupt blood vascular integrity. A fairly convincing argument for 2 parallel reactions can still be presented if one assumes that vitamin K can block another, possibly cytotoxic, action of Dicumarol in addition to blocking the Dicumarol-inhibition of coagulation factor production.

It is conceivable also that vitamin K or some other substance inhibited or destroyed by Dicumarol is required for the maintenance of the normal blood vessel wall. At present, however, our failure to detect a direct action of Dicumarol on the blood vessels and lack of experimental evidence in support of a specific intermediate mechanism related to both vascular and coagulation defects associated with Dicumarol suggest that the coagulation factors are necessary for preservation of normal vascular integrity.

**Summary**

Results of experiments in rabbits in which the disappearance of Evans Blue labeled plasma proteins was used as a measure of vascular integrity, indicate that Dicumarol does increase the rate of loss of plasma proteins from the blood stream. This action does not occur immediately after the introduction of Dicumarol into the blood stream but requires a latent period of between 90 and 180 minutes. During this time there may actually be a decreased rate of loss from the blood.

The degree of increase in the dye disappearance rate, although not directly correlated with the degree of hypoprothrombinemia, can be roughly correlated with the extent and severity of internal hemorrhage. These results tend to confirm the idea that vascular fragility, usually considered independent of vascular permeability, may in this instance be the preliminary manifestation of Dicumarol hemorrhagic diathesis.

In experiments where the effect of Dicumarol on exchange of protein between plasma and the peritoneal cavity was measured, it has been found that the presence of vitamin K\(_\text{I}\) in the blood in sufficient amount to completely block the hypoprothrombinemic action will also block the tendency toward increased protein exchange. Also, if Dicumarol is introduced into the peritoneal cavity rather than directly into the blood stream, the increase in transperitoneal protein exchange rate appears to be fairly proportional to the degree of hypoprothrombinemia.

It is concluded that although the possibility of several independent actions of Dicumarol exists, one effecting vascular permeability and another inhibiting the elaboration of coagula-
tion factors, it is more likely that the changes seen in vascular integrity are related to the effects of the drug on the coagulation mechanism by way of vitamin K inhibition.

Acknowledgment

These experiments were performed in laboratories provided through the courtesy of the Alan Hancock Foundation.

The author is extremely grateful to Dr. Chester Hyman for his assistance in the procurement of funds and guidance in carrying out this research.

Summario in Interlingua

Le resultatos de experimentos con conilios, con le disparition de proteinas plasmatic marcate per blau de Evans acceptate como mensura del integritate vascular, indica que Dicumarol resulta in un accelerate perdita de proteinas plasmatic ab le circulation del sanguine. Iste effecto non occurre immediatemente post le introductio de Dicumarol in le circulation sed require un periodo de intento de 90 a 180 minutas. Durante iste intervallo le perdita potes de facto esser realizata.

Le grado del acceleration in le disparition del co-

fornata, ben que illo non es correlatioitmente directly-

mente con le grado del existente hypoprophrombi-

nemia, pote esser correlatioitmente plus o minus precise-

mente con le grado e con le severitate del hemor-

rhagia interne. Iste resultatos tende a confirmar le

idea que fragilitate vascular, usualmente considerate

como independente de permeabilitate vascular, pote—
in iste caso—representar un manifestatio preliminari

del diathese hemorrhagic causate per Dicumarol.

In experimentos measurante le effecto de Dicumarol

super le excambio de proteina inter le plasma e le
cavitate peritoneal, il essero constatata que le pre-

scia de vitamina K en le sanguine in quantitato

sufficiente a bloccar completemente le effecto hypo-

prothrombinemia sufficet etiam a bloccar le tendantia a

un augmento del excambio de proteina. In plus, si

le Dicumarol es introducite in le cavitate peritoneal

plus tasto que directamente in le circulation del san-
guine, le acceleration del excambio de proteina pare

esser satis proportional al grado del hypoprophrombi-
nemia.

Es conclusioit que—ben que il non es impossiibile

que Dicumarol ha plure non independente actiones:

le un effectuant permeabilitate vascular, un alte-

r inhibitorie le elaboratio de factores de coagulation—

il es plus probable que le alteratioit observate in

le integritate vascular es relationate al effectos del
droga super le mecanismo coagulatori via le inhibi-
tion de vitamina K.

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Circ Res. 1960;8:889-896
doi: 10.1161/01.RES.8.4.889

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/8/4/889

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