CLINICAL PROGRESS

Spontaneous Hemorrhage with Anticoagulants

By Louis B. Jaques, Ph.D., F.R.S.C. (Can.)

ANTICOAGULANTS have been used clinically for the past 25 years, starting with the initial work of Murray and Best,¹ and their use has increased steadily and continuously each year since that time. Fairly early, however, there were reports of spontaneous hemorrhage from the use of anticoagulants. With the introduction and widespread use of the indirect anticoagulants reports of hemorrhage increased and now appear routinely.

The introduction of the use of anticoagulants was based on the experimental work of Murray, Jaques, Perrett, and Best² in animals. In their report that heparin would successfully prevent the formation of a thrombus, these authors did not draw attention to another finding of equal clinical importance. In view of the universal misgivings regarding the possibility of hemorrhage with the administration of anticoagulants, hemorrhage was carefully watched for in all the experimental animals. At that time, it was assumed that if the clotting time was so prolonged that the blood was incoagulable, the subject would die of hemorrhage. However, hemorrhage was not found in any of the several hundred animals used in the study, some of which received very large doses of the anticoagulant. This was also found in the introduction of the indirect anticoagulants (Dicumarol, phenylindanedione, etc.). In many experiments in animals with phenylindanedione, we maintained the prothrombin time at values of 2 to 10 minutes (normal 12 to 15 seconds) for months without hemorrhage.³ These, of course, are values much beyond anything used clinically in anticoagulant therapy.

In the author’s experience from 1934 to 1949, in which the anticoagulants (heparin, Dicumarol, phenylindanedione) were administered to large numbers of animals, spontaneous hemorrhage occurred in only five animals. In 1948 we observed a severe hemorrhagic reaction in two dogs of our colony when on anticoagulants. One of these occurred when the animal suffered an anaphylactic reaction with antistreptolysin vacine, the other occurred from a superficial infection. As soon as anticoagulants were introduced clinically, however, occasional hemorrhagic episodes were reported. In particular, while recommendations were followed regarding safe levels of the prothrombin time, many clinicians observed hemorrhage in a few patients on anticoagulants, when the prothrombin times were only moderately elevated, yet other patients showed very elevated prothrombin times without hemorrhage. This suggested that some hemorrhagic factor was present clinically, which was not present in the animal experiments.

With this record of almost complete freedom from hemorrhage in animals treated with anticoagulants, we were interested to find in 1953⁴ that when rabbits exposed to frostbite were treated with anticoagulants, there was a high incidence of mortality from spontaneous hemorrhage (50 per cent). The hemorrhage was not in the damaged extremity but was generalized hemorrhage into lungs, pleural cavity, subcutaneous tissue, etc. This observation suggested the possibility of identifying...
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Table 1

<table>
<thead>
<tr>
<th>Stress procedure</th>
<th>No Ac</th>
<th>Ac</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0/18</td>
<td></td>
</tr>
<tr>
<td>Frostbite</td>
<td>0/21</td>
<td>11/25</td>
</tr>
<tr>
<td>10% NaCl intraperitoneally</td>
<td>0/24</td>
<td>7/12</td>
</tr>
<tr>
<td>Insulin convulsions</td>
<td>0/24</td>
<td>19/26</td>
</tr>
</tbody>
</table>

Table 1 shows the incidence of death from spontaneous hemorrhage in rabbits receiving an anticoagulant and subjected to stress. The stressful procedures were insulin convulsions, injection of hypertonic saline intraperitoneally, the production of frostbite in the extremities. As recommended by Dr. Hans Selye, the stress procedure was adjusted to give about a 10 per cent mortality. This mortality was not accompanied by spontaneous hemorrhage and is therefore not included in the table. With the anticoagulant used (phenylindanedione) there was no mortality from spontaneous hemorrhage although the dosage (100 mg./Kg. initially and 25 mg./Kg. three times a day for 5 days) was sufficient to give a very prolonged prothrombin time. When the rabbits received both treatments simultaneously, however, there was a very high mortality, which could be clearly ascribed to spontaneous hemorrhage, as judged by the postmortem examinations. Thirty-seven of the 63 rabbits receiving combined treatments died of spontaneous hemorrhage. There was no significant difference in mortality among the treatments. In studies on spontaneous hemorrhage in both rats and rabbits, the following treatments have been investigated as causing spontaneous hemorrhage in animals receiving Dicumarol, phenylindanedione, or heparin: frostbite, 10 per cent sodium chloride intraperitoneally, elec-
The incidence of mortality from spontaneous hemorrhage in rats receiving Dicumarol is shown in figure 1. Dicumarol is a short-acting anticoagulant in rats; so the rats are given Dicumarol in the feed for a week.

A small mortality was observed from Dicumarol alone. However, after addition of stress such as 10 per cent sodium chloride intraperitoneally, there was a 50 per cent mortality. Sodium salicylate, epinephrine, histamine, in the doses used are known to cause a fall in the eosinophil count in the
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Table 2
Mortality of Rabbits from Spontaneous Hemorrhage with Dicumarol Alone

<table>
<thead>
<tr>
<th>Nature of prothrombin-time response</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8/56 = 15%</td>
</tr>
<tr>
<td>Poor</td>
<td>21/324 = 6%</td>
</tr>
<tr>
<td>Good</td>
<td>58/331 = 17%</td>
</tr>
<tr>
<td>Excessive</td>
<td>35/117 = 30%</td>
</tr>
<tr>
<td>All</td>
<td>122/826 = 15%</td>
</tr>
</tbody>
</table>

Dicumarol dose = 5 mg./Kg. body weight.

blood and a marked fall in ascorbic acid in the adrenal cortex, both indicators of marked stimulation of the adrenal. When these were given to dicumarolized rats, there was again approximately 50 per cent mortality from hemorrhage. When dicumarolized rats were given hormones, a high incidence of death from spontaneous hemorrhage was seen with desoxycorticosterone but not with cortisone or hydrocortisone. A high mortality in rats similar to that seen in rabbits was observed with adrenocorticotropin hormone and growth hormone (somatotropic hormone).

Anticoagulants after Adrenalectomy

When heparin was given to adrenalectomized rats, there was an 86 per cent mortality from hemorrhage (fig. 2). There was a significant mortality (36 per cent) in animals receiving heparin that underwent a sham operation. The mortality was even more pronounced (50 per cent) in the animals undergoing sham operation that received Dicumarol. Adrenalectomized rats maintained on 1 per cent sodium chloride when given Dicumarol, all died within a week, but these rats did not show postmortem hemorrhage. Instead, they showed signs of adrenal exhaustion.

Rats receiving desoxycorticosterone did not develop signs of adrenal insufficiency but they still died within 6 days. They died of hemorrhage identical with that of intact dicumarolized rats subjected to stress. This was an important observation, as it demonstrates that we are able to distinguish in these experiments hemorrhage as a specific cause of death.

Experiments with rats permit exploration of many factors. Thus we have demonstrated the prevention of hemorrhagic death by hormones and a vitamin (fig. 3). As stated previously, due to a nonspecific effect, adrenalectomized rats do not survive Dicumarol treatment. However, if the rats are maintained on desoxycorticosterone acetate, then they all die of hemorrhage when given Dicumarol. Further, if maintained on cortisone, they all survive. With hydrocortisone, it can be seen that the mortality decreases as the daily maintenance dose increases. Rats given Dicumarol alone showed 10 per cent mortality, stress (10 per cent sodium chloride alone) no mortality from hemorrhage, and Dicumarol plus stress 50 per cent. When vitamin K1 was given 90 minutes before the stress, the mortality was reduced to 10 per cent in spite of the persisting effect of stress.

Anticoagulants and Platelets

We have also studied the relation of Dicumarol and platelets to hemorrhage (fig. 4). When P32 is given to rats, a considerable number develop thrombocytopenia in 10 days. When given Dicumarol at this time, P32-treated rats had a high mortality from spontaneous hemorrhage (51 per cent). When the rats that received P32, Dicumarol, or both were grouped on the basis of having thrombocytopenia (<9000/mm³) or prothrombinopenia, or both, there was a small mortality in animals with thrombocytopenia alone (20
per cent) or prothrombinopenia alone (16 per cent), and there was 80 per cent mortality with thrombocytopenia and hypoprothrombinemia present in the same animal.

When rats were treated with reserpine, Dicumarol, or heparin, mortality was low (fig. 4). When anticoagulant and reserpine treatments were combined, there was a very high mortality from spontaneous hemorrhage.

**Production of Hemorrhage without Anticoagulants**

In the course of these experiments, spontaneous hemorrhage with high mortality was observed with combinations of treatments that did not include anticoagulants (fig. 5). Rabbits treated with reserpine and subjected to stress showed a 36 per cent mortality from spontaneous hemorrhage without change of prothrombin time. Rats with P\(^{32}\) plus 10 per cent sodium chloride intraperitoneally showed a high mortality. This mortality figure rose to 67 per cent when calculated on the thrombocytopenic animals only. Reserpine in adrenalectomized rats caused 80 per cent mortality. This appeared to be a combination of hemorrhage and effects on gastrointestinal mortality and secretions.

**Relation of Coagulation Changes to Spontaneous Hemorrhage**

How do these treatments lead to hemorrhage in the dicumarolized subject? Is it due to the anticoagulant producing a greater effect on the prothrombin time? Some treatments result in a greater increase in the prothrombin time after Dicumarol while with others it is less. Usually there is no change. Not infrequently, with the same treatment, some individual animals will show a greater response and other animals a decreased response. Thus, the change in prothrombin time of dicumarolized animals under stress is characterized by an increased variability.\(^7\) It is known that adrenalectomized animals are more sensitive to many drugs and in fact adrenalectomized animals show longer prothrombin times with a given dose of Dicumarol than normal animals. However, one can give larger doses of Dicumarol to normal animals so as to get the same prothrombin time yet they still survive; the adrenalectomized animals die.

As originally reported by Link,\(^8\) rabbits vary in their prothrombin-time response to Dicumarol, and in a rabbit colony one can usually find rabbits that are nonreactors to Dicumarol. This is a recessive genetic characteristic. Rabbits for study by us are first tested with an initial dose of 5 mg. of Dicumarol per Kg. Shown in table 2 is the response in prothrombin time to this initial dose and also the incidence of mortality from spontaneous hemorrhage with this dose. The criteria for dose response were as follows. In nonreactors no single prothrombin time was greater than 3 seconds above the initial value (average 10.6 seconds). Poor reactors gave prothrombin times not over 20 seconds. Good reactors showed prothrombin times over 20 seconds and under 200 seconds. Excessive reactors gave several prothrombin-time values over 200 seconds. While there was marked mortality among the 117 rabbits showing an excessive change in prothrombin time, there was a 15 per cent mortality from hemorrhage among rabbits that showed no change in prothrombin time. As shown, Dicumarol can
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Table 3
Poor-reactor Rabbits on Treatment with Corticoids and Dicumarol

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>0.31</td>
<td>21/324 = 6%</td>
</tr>
<tr>
<td>DOCA</td>
<td>0.33</td>
<td>1/26 = 4%</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>0.24</td>
<td>0/25 = 0</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.23</td>
<td>0/25 = 0</td>
</tr>
<tr>
<td>STH</td>
<td>0.44</td>
<td>2/22 = 9</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>0.32</td>
<td>2/23 = 9</td>
</tr>
<tr>
<td>ACTH—single</td>
<td>0.28</td>
<td>6/19 = 32</td>
</tr>
<tr>
<td>ACTH—5x</td>
<td>0.76</td>
<td>5/11 = 45</td>
</tr>
</tbody>
</table>

Dicumarol response expressed as the area under the curve for the log values of prothrombin times after Dicumarol.

cause hemorrhage in a certain percentage of rabbits without additional treatment. This does not occur with phenylindanedione, even when very prolonged prothrombin times are maintained for months. The hemorrhagic effect of Dicumarol by itself is probably due to other toxic effects of Dicumarol.6 Dicumarol accumulates in the liver and affects the concentration of the plasma fibrinogen (the test of a hepatotoxin). Dicumarol apparently reinforces the drug action of other drugs, e.g., the anesthetic action of Dial, tranquilizing effect of reserpine, and increases the requirement for corticosteroids after adrenalectomy. There is a specific uptake of Dicumarol by heart muscle, and the drug is toxic to the isolated rabbit heart, explaining the symptoms of right heart failure observed by the early workers10 in rabbits receiving extra large doses of Dicumarol. The mortality from spontaneous hemorrhage in rabbits treated only with Dicumarol probably represents the combined effect in such animals of the anticoagulant and other toxic actions of the drug.11 The results in table 2 show no correlation between the effect of Dicumarol on the prothrombin time and the mortality from hemorrhage. This is also illustrated in table 3.

Van Cauwenberge and Jaques12 reported that administration of adrenocorticotropic hormone would result in a prothrombin time response in nonreactor rabbits. When nonreactor rabbits were treated with pituitary and adrenocortical hormones, the corticoids had no effects on prothrombin time responses or mortality, but somatotropic hormone and repeated doses of adrenocorticotropic hormone resulted in an increased prothrombin time response. Somatotropic hormone did not cause significant mortality. Adrenocorticotropic hormone in both single and repeated doses caused death from hemorrhage, although only the latter affected the prothrombin-time response.

The bleeding time is another test used to determine the possibility of hemorrhage. Roskam13 showed that heparin did not influence the bleeding time, as did Van Cauwenberge and Jaques12 for Dicumarol. An interesting result of the latter investigation was that while Dicumarol did not cause any change in the bleeding time on the third day after Dicumarol, 40 per cent of these animals were dead next morning of internal hemorrhage (due to the stress of the bleeding time procedure).

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Table 4

Experiments on Spontaneous Hemorrhage

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment used</th>
<th>Nature of action</th>
<th>Hemostatic mechanism affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dicumarol</td>
<td>Anticoagulant</td>
<td>Blood coagulation</td>
</tr>
<tr>
<td></td>
<td>Phenylindandione</td>
<td>Anticoagulant</td>
<td>(fibrin formation)</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td>Anticoagulant</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Reserpin</td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depletion of serotonin</td>
<td>Clot hemostatique</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(platelet plug)</td>
</tr>
<tr>
<td>3</td>
<td>Stress—frostbite, 10% NaCl</td>
<td>Lowers capillary resistance</td>
<td>Vascular integrity</td>
</tr>
<tr>
<td></td>
<td>intraperitoneally</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electroshock, Insulin convulsions, epinephrine, histamine, Salicylates, ACTH, DOCA, Adrenalectomy.</td>
<td>Lowsers capillary resistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mortality from spontaneous hemorrhage*

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

*+ = 30 to 100% mortality.

Relation of Heparin to Hemorrhage with Stress

As reported above, spontaneous hemorrhage with high mortality occurs when heparin is given to adrenalectomized rats or to normal rats receiving reserpin. As shown in figure 6, however, while rabbits show the same high mortality with three different stress procedures when given Dicumarol, this is not seen to the same degree with heparin and stress. Heparin interfeles with various effects of stress and cortisone such as the fall in blood eosinophil level and concentration of adrenal ascorbic acid. It is therefore not surprising to obtain anomalous results with heparin in these experiments. As shown in the lower part of figure 6, spontaneous hemorrhage and resulting mortality depend on when the heparin injections are started with reference to the stressing procedure, for if the heparin injections and effect on blood coagulation are initiated 24 hours before the stress procedure, there is a 37 per cent mortality from spontaneous hemorrhage, similar to the combination of Dicumarol and stress.

Similar anomalies are observed, when Dicumarol and heparin are given together (fig. 6). When heparin injections were started at or after the time when Dicumarol was administered, there was negligible mortality. If heparin was started 24 hours before, so that the coagulation time was markedly elevated at the time Dicumarol was given, there was hemorrhage and mortality. In fact, one animal died of hemorrhage in the first 24 hours before the effect of Dicumarol could have been exerted on the prothrombin time. Finally, when heparin was given in advance of Dicumarol and stress, almost all the animals die. Conspicuous in this was the appearance of large volumes of serous exudate free of blood in the abdominal cavity. It suggests, under these circumstances, a very marked effect on per-

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meability, with leakage of a protein-rich fluid. The results are explainable on the basis that when the anticoagulant effects of heparin and Dicumarol are combined, hemorrhage does not occur but when these are combined with the other effects of these agents (toxic effect of Dicumarol and effect of heparin or permeability) then hemorrhage occurs.

**Multiple Causation of Spontaneous Hemorrhage**

We can now put together these various observations. Spontaneous hemorrhage does not occur simply from administration of anticoagulants. The blood may be completely nonclottable and yet hemorrhage does not occur. In the few animals in which we observed hemorrhage by treatment with anticoagulants alone, there has always been some other factor such as infection or stress. The one exception to this is Dicumarol and, as indicated above, this drug has a number of toxic effects in these animal species separate from its anticoagulant action.

On the basis of the experiments reported, we can see that spontaneous hemorrhage can be produced in 50 to 100 per cent of animals, if another treatment is superimposed on that of the anticoagulant. Table 4 gives a summary of our experiments to date. We have used about 15 different procedures, alone and in combination. These are listed in three groups. The first group consists of the anticoagulants themselves. The second consists of procedures that affect platelets and reserpine. The third group consists of procedures such as stress, injections of hormones and drugs, and adrenalectomy. We have not conducted experiments with all possible combinations of these treatments taken two at a time but we have tested some 40 combinations. The experimental results are summarized in the lower half of table 4. If we take as our criterion a mortality from spontaneous hemorrhage of 30 to 100 per cent then we find that any of the treatments in groups 1, 2, or 3 alone does not cause hemorrhage. Even when several treatments in the same group are given, provided the treatments have no other actions, hemorrhage of this order of severity does not result. However, if two procedures that appear in different groups are given simultaneously, the result is fatal, i.e., 1 + 2, 2 + 3, or 3 + 1.

How is this to be explained? For some years Roskam, Tocantins, MacFarlane, and myself have emphasized that hemostasis involves more than the coagulation of blood. Equally important are the coagulation of the blood, the platelets, and the blood vessel wall. The clumping together of platelets gives a sticky mass that is very effective in plugging holes in blood vessels and producing a seal. This process is best described by the French technical term "clou hémostatique." The status and response of the blood vessel itself are more complex. The normal response of the blood vessel wall is constriction, reflex constriction of the smooth muscle in the walls so as to narrow the lumen. This can be so effective as to completely occlude the vessel, and this in itself is a very effective hemostatic mechanism. Aside from this vasoconstriction, variations in the state of the vessel wall appear to be involved. When this is abnormal, there is leakage of blood into the tissue. If there is leakage of fluid alone, this is spoken of as increased permeability. If it is fluid plus a sufficient number of red cells, we speak of it as decreased capillary resistance, and this can be tested by applying a negative pressure or suction to the skin. Under various conditions, then, leakage of blood occurs. In recent years Kramár reported a very interesting and valuable series of investigations using capillary resistance measurements. He has shown that stress of any type or lack of corticosteroid hormones such as in the adrenalectomized rat, results in marked decrease in the capillary resistance. While Kramár's results are essential to understand our findings, they are not sufficient to explain them. Under our conditions we can have a decrease in capillary resistance without hemorrhagic death. It appears that with severe stress the damage to blood vessels is much greater than that indicated by a decrease in capillary resistance. Our results can be explained on the basis that simultaneous interference with more than one hemostatic mechanism is required to produce...
severe spontaneous hemorrhage. Dicumarol interferes with blood coagulation, stress impairs the blood vessel wall. Together (interference with 1 and 3) they cause severe hemorrhage. P₃₂ produces thrombocytopenia. This with Dicumarol (interference with 1 and 2) causes severe hemorrhage. Apparent exceptions are due, in the case of two treatments failing in combination to give spontaneous hemorrhage (e.g., heparin and stress) to mutual interaction and neutralization, in the case of single treatment (e.g., Dicumarol) causing spontaneous hemorrhage, to the single treatment having multiple effects. These are discussed above.

Further, death from hemorrhage usually occurred when stress and Dicumarol were given simultaneously 7 to 8 days after beginning treatments in rats, but in 48 to 60 hours in rabbits. Time of death was clearly related to the hemorrhage, and this could be related to the development of maximum interference with hemostatic mechanisms. Depending on the time schedule adopted and the procedures used, death from hemorrhage could be produced consistently in a few hours (reserpine to dicumarolized rats, heparin in adrenalectomized rats, stress from determining bleeding time in dicumarolized rabbits) or several weeks (frustration in dicumarolized rats, hormones in Dicumarol-treated rabbits).

Nervous and Humoral Factors in Hemostasis

Hemostasis depends on blood coagulation, platelets, and blood vessels. Nervous and hormonal factors chiefly affect the blood vessels. Hence, they are not easy to measure but often one or more of these is the factor precipitating hemorrhage when the first or second factor is deranged. Various measures have been used to detect changes impairing the hemostatic effectiveness of vessels: resistance to pressure differential (capillary resistance or fragility), permeability, endothelial stickiness (or electrostatic charge?), vasoconstrictor response, bleeding time. Roskam, measuring the bleeding time, first showed that a significant hemorrhagic tendency required simultaneous defects in several mechanisms and demonstrated the influence of the autonomic nervous system and sympathomimetic amines. Spontaneous hemorrhage, measured by mortality from hemorrhage when superimposed on defects of coagulation or platelets provides a new procedure for the quantitative evaluation of nervous and humoral factors in hemostasis. The integrity of the blood vessels in hemostasis appears to be affected by physical or chemical stressors, psychic trauma, menstruation, deficiency of vitamins C and P; anesthesia, anaphylaxis; histamine-liberators, sympatholytic and sympathomimetic agents; the Arthus phenomenon, convulsions, etc. The elucidation of the nervous and humoral pathways involved is of great importance to the clarification of many clinical problems.

The results described indicate the equal importance of all three components of hemostasis and the resulting great reserve of this important physiologic process. It is obvious that this gives a very useful operational procedure—the simultaneous application of two or more treatments gives an easily measured indicator, death from spontaneous hemorrhage. This makes possible for the first time, the assessment of physiologic factors governing hemostasis, including hormonal and nervous components. Further, it provides a means of quantitative testing of the contribution of a specific body component to hemostatic efficiency. Finally, as already shown, this procedure provides pharmacology and experimental therapeutics with a means of testing the action and effectiveness of a drug or procedure in stopping hemorrhage.

Summary

When dicumarolized animals are subjected to various types of stress, a high mortality from spontaneous internal hemorrhage occurs. This phenomenon is observed with various combinations of the treatments—Dicumarol, phenylindanedione, heparin, frostbite, insulin convulsions, hypertonic saline intraperitoneally, adrenalectomy, adrenocorticotropic hormone, corticosteroids, histamine, adrenaline, salicylates, P₃₂, reserpine. Hemostasis depends on blood coagulation, platelets, and vascular integrity. Experimental results demonstrate that spontaneous hemorrhage results

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when any two of these mechanisms are de-
ranged simultaneously. Hormonal and neural
factors affect the blood vessels and in this
way determine spontaneous hemorrhage with
anticoagulants. Spontaneous hemorrhage has
a multiple causation.

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