Impending Hemorrhagic Shock and the Course of Events following Administration of Dibenamine

By Harold C. Wiggers, Ph.D., Harold Goldberg, M.A., Frank Rokmhold, M.A., M.D., and Raymond C. Ingraham, Ph.D.

By blocking sympathogenic vasoconstrictor mechanisms with dibenamine, a dog’s tolerance to severe hemorrhagic hypotension states is definitely improved. New evidence is presented that partial release from vasoconstriction achieved by giving small doses of dibenamine during the impending shock state seems to provide animals with even greater tolerance to this standardized form of stress. Although the use of dibenamine clinically for this purpose seems contraindicated, the dangers of administering vasoconstrictor drugs to patients in impending shock are emphasized.

During and following the severe reduction of the circulating blood volume which results from extensive hemorrhage, sympathogenic vasoconstrictor mechanisms appear to be greatly activated.1, 2 As a consequence, the diminished blood volume is partially compensated. The reduction in the capacity of the total vascular bed renders more efficient the accommodation of the remaining blood volume, to the extent that the blood supply to the heart and brain are the best possible under these hemorrhagic conditions. Hence, the initial beneficial though temporary effects of vasoconstriction, providing the interval between the cessation of hemorrhage and the restoration of blood volume to normal is not unduly prolonged, must be recognized.

It is equally obvious, however, that the reasonably adequate blood supply to the heart and brain is maintained at the expense of a marked reduction in blood flow to such organs as the liver, kidney, intestines and skin where vasoconstriction becomes intense. If, therefore, either by experimental intention or clinical impracticality, the period of hemorrhagic hypotension is prolonged, the existing impending shock state progresses rather rapidly to one of irreversibility, in which repeated transfusions prove futile.3

It is recognized, furthermore, that hypotension, per se, reduces greatly the peripheral circulation. When superimposed vasoconstriction is not a factor, however, the period of severe hypotension (after histamine) which can be withstood without the development of irreversible shock, is many times greater than that seen in hemorrhagic hypotension.4 Whereas there is probably no significant redistribution of flow from the less vital to the more immediately vital organs in histamine hypotension, hemorrhage and its attendant vasoconstriction lead to severe reductions in peripheral blood flow. Since vasoconstriction leads to ischemia in many regions, it is reasonable to assume that the auto-infusion of tissue fluids in the capillaries of these ischemic areas is greatly impaired, thus reducing the net compensatory fluid replacement volume.

With the thought in mind that severe, prolonged vasoconstriction hastens the rate of transition from impending to irreversible shock, studies were carried out on dogs whose sympathogenic vasoconstrictor mechanisms had been functionally blocked prior to the onset of bleeding.5 It was observed that dogs given 15 to 20 mg. per Kg. doses of dibenamine hydrochloride some twenty hours prior to the onset of hemorrhage tolerated the standardized hemorrhagic hypotension procedures better than untreated control dogs. Not being satisfied...

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with the conclusiveness of the evidence obtained, the studies were extended to the series reported in this paper. It seemed advisable, in this series, to permit a group of animals to endure the impending shock state for about 45 minutes before administering the adrenergic blocking agent. Most control animals at the end of 45 minutes of hemorrhagic hypotension have been found to be just at the point of transition from impending to irreversible shock. It was also decided to reduce the dosage of dibenamine, in an attempt to provide only partial rather than complete inhibition of the vasoconstrictor mechanisms.

**Procedure**

Forty healthy mongrel dogs, varying in weight from 7.7 to 23.2 kilograms, were used. All were subjected initially to the same operative and hemorrhagic procedures. Under local procaine hydrochloride anesthesia, (a) a femoral artery was cannulated for rapid hemorrhaging and for the continuous registration of mean arterial pressure with a mercury manometer, (b) the other femoral artery was exposed for repeated blood sampling, and (c) a femoral vein was cannulated for the eventual reinfusion of the blood withdrawn during the hemorrhagic period.

After adequate control measurements had been made, each dog was rapidly hemorrhaged until arterial pressures reached a level of 35 to 38 mm. of Hg. The bleeding rate varied between 50 to 75 ml. per minute and the onset of the hemorrhagic-hypotension period was attained within a bleeding period of 7 to 10 minutes. The blood withdrawn to induce this degree of hypotension was collected in a graduate cylinder, which contained adequate quantities of the anticoagulant, Liquaemin*, and was measured. This volume, referred to as the *initial bleeding volume* (IBV), averaged about 37 ml. per Kg. in control dogs, although considerable variation was noted (see table 3).

During the ensuing 90 minutes, the hypotensive level was constantly maintained by means of an automatic pressure stabilizer device (after the method of Lamson†). A calibrated reservoir bottle, partially filled with a known quantity of the withdrawn heparinized blood, was connected to the side arm of a femoral arterial cannula. This reservoir was then elevated to the level required to maintain the established hypotension level (35 to 38 mm. of Hg). Thus, as compensatory mechanisms were mobilized following the initial rapid hemorrhage, any consequent tendency for arterial pressure to rise above 35 to 38 mm. of Hg was abruptly arrested by automatic bleeding from the dog into this reservoir. Contrarily, in the later stages of the 90 minute hypotension period if compensatory mechanisms became exhausted, any tendency for arterial pressure to decline below the established level was prevented by immediate automatic infusion of withdrawn blood from the reservoir into the animal. Reservoir blood volumes were carefully observed and recorded at 5 to 10 minute intervals or more frequently when necessary.

The maximal quantity of blood which slowly accumulated in the reservoir during hypotension plus the IBV is referred to as the *maximal bleeding volume* (MBV). Subtracting the IBV from the MBV yields that amount of blood which was slowly and automatically withdrawn from the animal to sustain the 35 to 38 mm. of Hg blood pressure level. This is referred to as the *secondary bleeding volume* (SBV). It was quite variable in volume (see table 3) and was always considerably less than the IBV. The volume of withdrawn blood which remained to be reinfused at the termination of the 90 minute hypotension period is called the *net-total bleeding volume* (N-TBV). Though occasionally identical, especially in control dogs which survived, the N-TBV was usually less than the MBV. This discrepancy signifies the amount of blood which was automatically reinfused during the late stages of the 90 minute hypotension period. This *automatic reinfusion volume* (ARV); that is, the MBV minus the N-TBV, was of considerable diagnostic significance in the control dogs.

After 90 minutes of hypotension, the remaining blood (N-TBV) was filtered through cotton gauze and reinfused via a femoral vein. Following this replacement of all withdrawn blood, the wounds were carefully sutured and the dogs were returned to their quarters. They were observed for 72 to 96 hours or until irreversible shock intervened. Animals in good condition after 72 hours were considered to have recovered completely. Those succumbing within that interval usually did so within 12 hours and were considered as shock fatalities.

Twenty dogs served as untreated controls. The other 20 dogs were "test" animals which received dibenamine. Since complete inhibition of sympatho- vasoconstrictor mechanisms was not desired, preliminary tests were conducted to ascertain the dose of dibenamine which would afford partial inhibition or release from vasoconstriction. As an arbitrary criterion, a dose was selected which, when injected during hemorrhagic conditions, most constantly prevented large elevations of arterial blood pressure in response to pressor doses of adrenaline (3-5 μg. per Kg. intravenously) and which would not induce the profound "adrenaline reversal" commonly obtained with doses yielding complete block-

* We are sincerely indebted to Roche-Organon, Inc. for their generosity and cooperation in supplying us with the quantities of Liquaemin required to execute this study.
ing. As might be expected, this dose varied from animal to animal. It was decided that our purpose could best be accomplished if the dibenamine was given in doses of 3 mg. per Kg. to all test dogs. It was administered in 15 to 20 ml. of 0.9 per cent saline via femoral vein just 30 minutes after the onset of the 90 minute hypotension period. This moment for the injection of dibenamine was selected (a) because it was desired to induce partial reduction of existing vasoconstriction at the midpoint of the 90 minute hypotension period and (b) because it generally requires about 15 minutes for dibenamine to approach maximal effectiveness as an adrenergic blocking agent. Unfortunately, it was impractical to employ the adrenaline test as a measure of dibenamine action during the course of the hypotensive period. It was noticed, however, that 15 minutes after dibenamine injection, previously dilated pupils constricted to less than prehemorrhage dimensions. An attempt was made to test the effectiveness of the dibenamine by comparing the blood pressure response to 3 µg. per Kg. doses of adrenaline given intravenously before and after the hypotension period. In table 1 the results are tabulated such that comparisons may be made between pre- and posthemorrhagic responses to identical doses of adrenaline among the dogs which received dibenamine. A few of the prehemorrhagic responses in the early experiments were inadvertently omitted.

Pre- and posthemorrhagic responses to adrenaline among control dogs were not significantly different. In general, the authors believe that the desired partial inhibitory influences of dibenamine were obtained, if the response to adrenaline is accepted as a satisfactory criterion. There were obviously quantitative differences in the individual animals which were beyond control.

**Results**

The results show that the dibenamine, in the amounts given, did alter the course of events during the second half of the hypotension period. It altered them to the extent that in most of the dogs, the transition from impending to irreversible shock did not occur as it did in 70 per cent of the untreated control dogs. The comparative survival rates are presented in table 2. It is seen that, following reinfusion of the N-TBV at the end of the hypotension period, only 6, or 30 per cent, of the untreated control dogs recovered. The post-reinfusion survival times among the 14 who died in shock varied from 1 to 36 hours, 12 of these succumbing within a 12 hour period.

In striking contrast, only 2 of the 20 dogs which received dibenamine entered the irreversible state and succumbed; within 4 and 36 hours after reinfusion, respectively. This indicates that the transition from impending to irreversible shock did not occur in 90 per cent of these dogs.

The question arises as to whether the dibenamine group were subjected to as intense a degree of impending shock as the untreated controls. From the comparative data on bleeding volumes presented in table 3, it would seem that one could argue for or against such a belief without conclusive proof in either case. Inasmuch as the number of recoveries among the controls was small and the number of fatalities in the dibenamine group was even

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**Table 1.—Blood Pressure Response to Adrenaline**

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Prehemorrhagic response to adrenaline 3 µg./Kg.</th>
<th>Posthemorrhagic post-dibenamine response to adrenaline 3 µg./Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm. Hg</td>
<td>mm. Hg</td>
</tr>
<tr>
<td>1</td>
<td>-20</td>
<td>+10, then -20</td>
</tr>
<tr>
<td>2</td>
<td>+50</td>
<td>+15</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>10</td>
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<td>12</td>
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<td>17</td>
<td>+50</td>
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</tr>
<tr>
<td>18</td>
<td>+10</td>
<td>-10</td>
</tr>
<tr>
<td>19</td>
<td>+70</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>+70</td>
<td>0</td>
</tr>
</tbody>
</table>

* These represent the 2 fatality dogs. See text for discussion.

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**Table 2.—Survival Rate following Hemorrhage**

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Dogs</th>
<th>C.R.</th>
<th>F.</th>
<th>% C.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>20</td>
<td>6</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Dibenamine 3 mg./Kg</td>
<td>20</td>
<td>18</td>
<td>2</td>
<td>90</td>
</tr>
</tbody>
</table>

C. R. = complete recovery dogs.
F. = fatality (irreversible shock).
less, median values are used for presentation. It will be noted that there is a wide variability in the range of bleeding volumes in each category.

Particular attention is directed to a comparison of the bleeding volumes for the dogs which recovered in the control and “test” series. (a) The IBV values in the two groups are essentially identical. This indicates the close approximation of the intensity of impending shock developed in both groups. It was noted that the control survival dogs generally continued to bleed into the reservoir bottle during the first 70 minutes of the hypotension period as their hematocrits progressively decreased.

Consequently the SBV was considerable in these 6 dogs (15.9 ml./Kg.). During the final twenty minutes, the bleeding volume tended to remain at status quo, any significant exchange of blood between the dog and the reservoir being an exception rather than the rule. Hematocrit values remained at status quo during this interval. The ARV (2.7 ml./Kg.) in these 6 dogs was small. (b) SBV trends among the dibenamine group were far more variable. This may be related partially to the variable effectiveness of the dibenamine in the different dogs. That the SBV trend should be different from that seen in control dogs would be anticipated, since dibenamine influences vascular mechanisms which ultimately influence bleeding volumes. Hence the SBV among these “test” dogs is definitely less amenable to group consideration. It may be said that in these 18 dogs, bleeding into the reservoir bottle occurred during the first 40 minutes of the hypotension period. Then a 30 minute period of status quo or negligible interchange of blood between the animal and the reservoir was usually observed. During the remaining 20 minutes, blood began to be slowly (automatically) reinfused into the animal from the reservoir. In fact, the ultimate degree of reinfusion, as indicated by the ARV values, parallels or exceeds that seen in the fatalities of the control series (7.1 and 6.8 ml./Kg., respectively). In

<table>
<thead>
<tr>
<th>Table 3.—Bleeding Volumes in ml./Kg.</th>
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<tr>
<td>Control</td>
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<tr>
<td></td>
</tr>
<tr>
<td>IBV</td>
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<tr>
<td></td>
</tr>
<tr>
<td>MBV</td>
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<td></td>
</tr>
<tr>
<td>N-TBV</td>
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<tr>
<td></td>
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<tr>
<td>SBV</td>
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<td></td>
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<tr>
<td>ARV</td>
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C. R. (6) = 6 complete recovery dogs.
F. (14) = shock fatalities.
C. R. (18) = 18 complete recovery dogs.
F. (2) = 2 shock fatalities.
For discussion of IBV, MBV, N-TBV, SBV, and ARV, consult the text.

previous studies, an ARV of 4.0 ml. per Kg. or above in untreated dogs appeared to afford a reliable criterion for the diagnosis of existing irreversible shock. Such a value is obviously not prognostically significant in dibenamine treated dogs.

It is not surprising to observe a considerable ARV in these dibenamine animals. In fact, an ARV in excess of the one obtained (median) was anticipated, since any diminution in the degree of vasoconstriction must entail a considerable enlargement of the total vascular capacity. A priori, the established hypotensive arterial pressure level could presumably only be maintained by proportionate augmentation of the circulating blood volume. Though un-
likely, this increment could be achieved solely by automatic reinfusion of a sufficient volume of blood. It does not seem likely that this was the case with the small and late reinfusion noted. The possibility should not be overlooked that part of the compensatory increment in blood volume was achieved through increased auto-infusion of tissue fluids, through the opening up of previously constricted vascular areas. Such a translocation of tissue fluid should be reflected by further reduction in the hematocrit. In several instances, the hematocrit changes provided support for this possibility. In most of the “test” dogs, however, such a tendency for a reduction in hematocrit was masked or balanced by the automatic reinfusion which tended to elevate hematocrit readings. In general, hematocrit changes were too variable to provide a means of estimating trends. It seems worth emphasizing that any augmentation of the blood volume through reduced vasoconstriction and the establishment of more favorable conditions for autoinfusion of tissue fluids must lessen the volume of blood which had to be automatically reinfused to maintain arterial pressure at a constant hypotensive level.

Inasmuch as previous studies by others as well as by the authors have indicated that liver function is greatly impaired by prolonged hemorrhagic hypotension, an attempt was made to measure liver function before and after the hemorrhagic hypotension period. At the time these experiments were performed (1946) liver function tests for the measure of hepatic metabolism in intact animals were even less satisfactory than they are at present. The bromsulfalein test was selected as most practical for these experimental conditions. It was reasoned that any severe deficiency in hepatic excretory performance in this instance would be suggestive of simultaneous impairment of hepatic metabolic functions. These tests did not prove very satisfactory but they did suggest a trend deemed worthy of mention. Control bromsulfalein tests were usually run the day previous to the hemorrhagic experiment. These proved uniformly normal. The test was again run immediately upon completion of reinfusion. Also, if the animals survived they were repeated during the succeeding 2 to 3 days.

Among the dogs in both groups which entered irreversible shock and died, the findings were consistent in that they indicated high retention of the dye 45 to 60 minutes after its injection (32 to 63 per cent retention). Among the dogs which recovered in both groups, the pattern was definitely less consistent. Many survivals exhibited insignificant retention of dye. In others it ranged from 5 to 38 per cent, falling off to almost no retention when tests were repeated on succeeding posthemorrhage days. From these studies, the impression was gained that in the dibenamine treated dogs, the degree of hepatic impairment achieved was certainly less than among control dogs and small enough to prevent the onset of extensive irreversible liver damage during the hypotension period. It is recognized, however, that the degree of hepatic congestion and excretory insufficiency cannot be conclusively estimated on the basis of dye retention tests.

**DISCUSSION**

In two previously reported investigations, using the same standardized hemorrhagic hypotension procedures for inducing the shock state, large doses of dibenamine (15 to 20 mg. per Kg.) were administered (a) 30 minutes and (b) 20 hours prior to the onset of hemorrhage.

In the former group, the mortality rate was as great as that seen among untreated control dogs. In the latter series, in which more time was allotted for compensation of the cardiovascular influences of the dibenamine before hemorrhage was begun, tolerance to the hemorrhagic stress was greatly enhanced. In this situation, 70 per cent of the untreated control dogs as compared to 40 per cent of the dibenamine treated dogs entered the irreversible shock state and succumbed. In the present study it was demonstrated that when small doses of dibenamine (3 mg. per Kg.) were administered after impending shock was well advanced, even greater tolerance to the bleeding procedure was achieved. This is demonstrated by the fact that 70 per cent of the untreated control dogs entered irreversible shock as compared to only 10 per cent mortality among the dibenamine treated animals. This small mortality rate occurred in spite of the fact that the bleeding volumes among the dibenamine treated dogs in this present series
were considerably greater than those obtained in the dibenamine treated dogs of the two previous studies in which mortality rates were quite high.

In seeking to answer why greater protection and percentage survival were afforded the dogs in the present series, one can only speculate. It would seem reasonable to assume that the smaller doses of dibenamine did not burden compensatory vascular mechanisms as severely as did the larger doses employed in the earlier studies. This would provide a greater margin of compensatory reserve for counteracting the effects of hemorrhagic hypotension. Undoubtedly, any toxic manifestations of dibenamine were less severe in the animals which received the smaller doses.

It is of even greater interest to attempt an explanation for the fact that only 10 per cent of the dibenamine treated dogs in the present series as compared to 70 per cent of the untreated controls succumbed in irreversible shock. The authors are convinced that both groups of animals were exposed to impending shock of the same degree of intensity. There was considerable reason for believing that the dibenamine reduced the degree of existing vasconstriction shortly after it was administered. Automatic bleeding from dog to reservoir ceased about 10 to 15 minutes after dibenamine was administered, whereas it continued for approximately 70 minutes in the control animals. Following about 20 minutes of status quo, there was considerable automatic reinfusion into the dibenamine animal as indicated in the ARV and the reduction of the MBV and the N-TBV. This was presumably necessary to maintain the hypotensive level in the face of diminution of the peripheral vasoconstriction and the accompanying increase in the capacity of the total vascular bed. The further decrease in the hematocrit seen in a few dogs following dibenamine administration would further substantiate the belief that previous nonpatent vascular channels had been reopened to the circulation. Remington and his co-workers' in a somewhat similar series of hemorrhagic shock studies, found the beneficial influences of dibenamine upon survival rates to be associated with lower vasmotor resistance values and higher blood flow values. These are not strictly comparable since the studies were conducted on anesthetized dogs and no attempt was made to sustain any fixed degree of hypotension. Finally, the partial reduction of the blood pressure response to strong pressor doses of adrenaline with occasional small adrenaline reversals obtained in our dibenamine treated dogs adds further strength to the belief that the much greater survival rate is definitely related to improved peripheral blood flow at the given hypotensive blood pressure level. The improvement in blood flow could only be attributed to reduced vasoconstriction, since arterial pressure was maintained at a constant level.

The long accepted belief that severe exsanguination induces intense and widespread vasconstriction has been conclusively demonstrated by Zweifach and Chambers.1-2 It was learned from Freeman and his associates8-9 that total sympathectomy affords protection against prolonged vasocostrictive reduction in tissue blood flow. Considerable emphasis has been placed upon disturbances in renal and hepatic function following severe hemorrhage.10-12 More recently Chambers, Zweifach and Shorr13,14 supplied specific evidence that the kidneys and liver release vasotropic substances when, as a result of hemorrhage, the blood flow to these structures is impaired. As the severity of impending shock increases, greater releases of VEM from the kidneys into the circulation render metarterioles more and more hyperresponsive to vasocostrictor influences of both humoral and neurogenic origin. Perhaps one effect of dibenamine was to reduce the degree of vasoconstriction in renal arterioles, thus permitting a reasonable degree of renal blood flow at blood pressure levels which ordinarily abolish renal blood flow completely. Under such conditions, less VEM would be released by the kidneys, which would tend to reduce the overall degree of vasoconstriction in the peripheral vascular system and thus permit more satisfactory peripheral blood flow during the drastic hypotensive period. It is also possible of course that the dibenamine may have afforded protection to the metarterioles of large peripheral vascular beds against sympathogenic vasocostrictor influences of either neurogenic or humoral origin.

The possible improvement in blood flow af-
forded at hypotensive blood pressures by dibenamine action is probably not restricted to any one vascular area such as the kidney. One would expect that hepatic flow, for instance, might be equally improved. Selkurt’s studies revealed that hepatic flow is greatly reduced in hemorrhagic states, leading to severe portal congestion. Also, the direct relation between the impairment of liver flow and function and the onset of irreversible shock has been clearly demonstrated by Frank, Seligman and Fine. According to Shorr and Zweifach, such impairment leads to progressively greater release of VDM from the liver, which renders the metarterioles hyporeactive or unresponsive to sympathogenic vasoconstrictor agents. The ultimate and terminal consequences are widespread dilatation of metarterioles and precapillaries with consequent pooling of blood within the many now patent capillaries. Any improvement in hepatic flow through reduction of arterial or even hepatic vein constriction would mitigate against the production and release of VDM.

From the more practical, clinical viewpoint, however, several points should be stressed. It is difficult to visualize the clinical condition of hemorrhagic shock in which it would be safe or advantageous to employ dibenamine. Rapid restoration of blood volume in itself relieves a situation of prolonged compensatory vasoconstriction. It is felt, however, that this study emphasizes the advisability of preventing the existence of severe prolonged vasoconstriction prior to such time as infusion measures can be instituted. It certainly renders clear the dangers inherent in the prescription of vasoconstrictor drugs for patients in the impending shock state. Such a procedure may be just enough to initiate the transition from the impending to the irreversible shock state.

SUMMARY

Near the middle of an experimental impending hemorrhagic shock period, dogs were given small doses of dibenamine, calculated to be just sufficient to produce partial block of sympathogenic vasoconstrictor mechanisms. It was noted that the animals so treated tolerated the standard experimental hemorrhagic hypotension period far better than a series of untreated control dogs. The possible explanations for the improved tolerance has been discussed.

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Impending Hemorrhagic Shock and the Course of Events following Administration of Dibenamine
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