An Evaluation of Replacement Fluids in Laboratory Animals following Control Hemorrhage

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Solutions of Dextran Ph, Plasmod, Periston and isotonic saline were compared with serum albumin and whole blood to determine the efficacy of the former as blood substitutes. Rats, guinea pigs and dogs were used as experimental animals. Dextran Ph, Plasmod and Periston were found to be less satisfactory than whole blood, since 50 to 80 per cent of the rats and guinea pigs survived following their use compared with 100 per cent survival when whole blood was given. There was, however, 100 per cent mortality of the animals when a blood substitute was not given.

In time of war or national emergency, there has usually been urgent need for materials which can be produced in quantity for treatment of shock resulting from trauma or acute loss of blood or plasma, because the supply of blood and plasma may not be adequate or readily available.

It is also recognized that it would be wise to have at hand proper substances for transfusion of patients in small hospitals and in rural areas where blood transfusion service is not adequate. For use in such places the primary considerations for a plasma substitute are availability, stability, relative inexpensiveness, and ease of administration.

The substances which are the subject of this investigation may be produced in large quantities and stored in depots for emergency use with less danger of deterioration or contamination than would be true of blood or plasma. Since these substances have been used clinically and have been found to have a favorable effect in combatting hypotension, it was deemed advisable to compare them in laboratory animals in order to determine whether any one of these substances was significantly superior to the others.

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Materials and Methods

In this study, Dextran Ph (a polysaccharide of high molecular weight), Plasmod (osseous bovine gelatin) and Periston (a synthetic polyvinyl pyrolidine) were compared with isotonic saline solution, human serum albumin, human plasma, and blood in various species of laboratory animals following control or graded hemorrhage.

The Dextran was furnished by the Pharmacia Company, of Stockholm, Sweden, and was manufactured and bottled by them. The Dextran Ph was a 6 per cent solution of Dextran in a 0.9 per cent sodium chloride solution.

The gelatin solution, Plasmod, used was a 5 per cent bovine osseous gelatin in an isotonic solution of sodium chloride. It was furnished by the Upjohn Company. This solution was prepared from the collagen of the long bones of cows by electrodialysis and treatment with steam under pressure.

The Periston was furnished through the Interchemical Corporation by I. G. Farben, of Germany, in a 20 per cent concentration in 50 cc. ampules. This was diluted with Ringer's solution and a 3.5 per cent preparation was made according to the recommendation of Weese, the discoverer. Prior to our investigation with blood replacement, antigenic studies were carried out in guinea pigs and rabbits with this material. Additional tests for pyrogens, toxicity and sterility of the Periston were done by the Interchemical Corporation with negative results.

In evaluating these substances in the laboratory, it was decided that more than one species of animal should be used. Therefore, albino rats, guinea pigs and dogs were used. The effects of these substances under investigation were compared with those of isotonic saline solution and heparinized blood. Observations on the value of human serum albumin and human plasma were also made in some experiments.
Different investigators have used various methods to compare the effectiveness of blood and plasma substitutes. Some have used animals that have had tourniquets applied to their thighs for protracted periods; others have used manipulation of exposed intestines, burns, trauma of thighs and various types of graded hemorrhage.

Since Dextran Ph, Plasmoid and Periston have been used as blood substitutes, they were chosen for this study to replace the blood volume lost by hemorrhage. Guinea pigs were studied first. Several exploratory methods were used to find that method by which blood could be removed most effectively and a replacement agent could be most readily given. Direct cardiac puncture and cannulation of the femoral vein were tried but were found unsatisfactory. For the observations on guinea pigs the right jugular vein was cannulated with the animal under drop ether anesthesia. The right jugular vein was exposed and through a small incision a small caliber polyvinyl plastic tubing was passed down the jugular vein to the region of the right atrium. The tubing was held in position by ligatures, and the distal portion of the vein was tied off. The plastic tubing was attached to a syringe by which blood could be removed rapidly and one of the replacement fluids could be injected with ease. After this procedure, the plastic tubing was removed, and the jugular vein was ligated proximally. The guinea pig was then allowed to recover from the anesthetic. Using this method for bleeding and infusing these fluids, we found a bleeding volume which would be 100 per cent lethal to the guinea pig.

Albino rats were also observed with use of similar methods. The left carotid artery was exposed, and a small plastic tubing was inserted for a few millimeters and held in place with a ligature. A syringe was attached to the plastic tubing, and blood was removed and one of the infusing agents injected through the carotid artery.

In the technics used for guinea pigs and rats, it was found necessary to accomplish the foregoing procedure of hemorrhage and infusion in 10 minutes or less. If a longer period was required, recovery was unlikely to occur. Signs of air hunger were very pronounced after the hemorrhage.

Only those guinea pigs and rats which recovered from the anesthetic and the immediate procedure and assumed an upright position after an infusion were included in the results of these experiments. If these animals survived 24 hours or longer, they were considered survivals.

The evaluation of the replacement fluids was recorded in graphic form. The number of survivals of the 10 experimental animals used for each substance is shown (Figs. 1 and 2).

In the study of these replacement agents in dogs, it was found necessary to use other methods than were used with the guinea pigs and rats. Ivy and associates reported a great variation in survival of dogs undergoing hemorrhages of various degrees. It became quite evident after the initial trials that not all dogs could tolerate the same relative amount of hemorrhage. The method described by Lawson seemed quite adequate for evaluating the replacement fluids and was adopted.

The method of Lawson was modified to the extent that local anesthesia and inhalation of ether were substituted for barbital anesthesia. The dogs were unselected mongrels of both sexes and weighed from 6.5 Kg. to 27.2 Kg. Food and water were withheld for a period of 15 to 18 hours preceding the experiment. Then a hemorrhage of 20 cc. per kilogram body weight was accomplished at the rate of 2 cc. per kilogram per minute. With the animal under 1 per cent procaine hydrochloride infiltration anesthesia, the right jugular vein was exposed and a small polyvinyl tubing was inserted into its lumen and held in place with ligatures. The vein was tied
of distally. The tubing was inserted to a point near the right atrium. Occasionally the tubing passed directly into the right atrium or ventricle. The desired quantities of blood were removed by aspiration with a syringe. The vein was then ligated and could be used again later.

Two hours after this first hemorrhage, the animal was anesthetized in a closed ether chamber. An intratracheal tube was passed into the trachea and attached to an ether can which had inspiratory and expiratory valves in the circuit, so that the animal breathed ether through a one-way system. The carotid artery was exposed, a glass cannula was inserted, and continuous blood pressure readings were recorded by means of a mercury manometer and kymograph. A polyvinyl plastic tubing was again passed down the right jugular vein to the region of the right atrium, and blood was removed by aspiration with syringes. A measured amount of blood, 2 cc. per kilogram, was then removed every three minutes until the blood pressure was less than 60 mm. of mercury. This amount of blood removed was designated as $H_{1a}$. The end point used for this bleeding volume was a blood pressure of 50 to 55 mm. of mercury. Shortly after this point had been reached, one of the substances to be tested was infused through the same jugular vein in a quantity equal to the amount of blood removed. This quantity of replacement fluid was designated as $R$.

The carotid artery and the jugular vein were tied off, and the animal was allowed to recover. Four hours later the animal again underwent hemorrhage under local anesthesia at the rate of 2 cc. per kilogram per 3 minutes until it died. This last bleeding volume was designated as $H_2$. The residual blood volume after $H_{1a}$ had been removed was estimated, using Lawson’s figure of 10.10 cc. per kilogram, and was designated as $H_{1c}$. $H_{1a}$ and $H_{1c}$ were then added together and called $H_1$. The ratio of $H_2$ to $H_1$ was then compared and multiplied by 100, and a percentage value was obtained.

An additional observation was made on 15 dogs during the procedure just described. Electrocardiograms were taken on three dogs of each series. Control electrocardiograms were taken before and after etherization. Electrocardiograms were again taken after the $H_{1a}$ hemorrhage, after the infusion of one of the replacement agents, again before $H_2$, and during the $H_2$ hemorrhage.

In all of the experiments the hemorrhage was done with the animals in a supine position.

Since many of the blood substitutes which have been used in the past have been found to have noxious or deleterious effects, including accumulation in certain organs of the body, the substances under investigation were administered at intervals to a series of guinea pigs over a prolonged period. Twenty male guinea pigs were used for this purpose. The weights of the animals were recorded at the beginning of the experiment and again at its termination. The materials were given into the penile vein. Occasionally it was impossible to make an intravenous injection and the replacement fluid was then given intraperitoneally. Twenty injections were given to 12 guinea pigs over a period of two months. Because of the death of three guinea pigs following injections of contaminated Plasmoid, three additional guinea pigs were substituted and received nine injections intravenously over a period of three weeks. Five guinea pigs were used as control animals.

It was found that contamination of Plasmoid solution with bacterial growth was more prone to occur than contamination of Periston or Dextran after the bottle was opened. Periston and Dextran appeared to be highly resistant to bacterial contamination.

**Results**

Six guinea pigs and three rabbits were used as experimental animals for antigenic tests with Periston. The guinea pigs were divided into two groups. Two solutions were prepared. One solution contained 10 per cent Periston (polyvinyl pyrrolidine) in distilled water; and the second solution contained 10 per cent Periston mixed with egg albumin (20 cc. in 80 cc. distilled water), equal amounts of each. Three guinea pigs were injected with the 10 per cent solution of Periston, being given 1 cc. each; and three guinea pigs were injected with 1 cc. each of the Periston and egg albumin solution, the solutions being given intravenously. Twenty-one days later, all six guinea pigs were given intravenously 1 cc. of 10 per cent solution of Periston. No noticeable effects were seen in any of the guinea pigs. One of the guinea pigs which had received only Periston previously was given 1 cc. of the Periston and albumin mixture without effect. The three guinea pigs which had been given the mixture of Periston and eggalbumin were given 1 cc. of this mixture. In these three guinea pigs an anaphylactic reaction promptly developed and the animals died. From this experiment it appears that Periston is not antigenic.

Three rabbits were used to determine further the possible antigenic properties of Periston. The effects of intravenously infused Periston on blood flow was observed in one rabbit by means of a transparent chamber inserted in one ear. Each of the three rabbits was given 5 cc. of 4 per cent solution of Periston intravenously.
The infused Periston appeared to have no effect on the general condition of the rabbits. The blood flow through the vessels in the transparent chamber was observed for a period of 45 minutes. There was no leukotactic phenomenon exhibited as has been reported by Essex and Graña following the intravenous administration of solutions of Dextran, acacia and other materials.

Three weeks later, 10 cc. of 4 per cent solution of Periston in distilled water was given intravenously to the same three rabbits. There resulted no anaphylactic reactions or other signs of allergy. The circulation of the blood through the rabbit’s ear was again visualized after the administration of Periston, and again there was no leukotactic response. If anything occurred, it was an increase in the rate of the circulation of the blood.

Bleeding volumes were completed in a series of 15 guinea pigs by removal of blood from the region of the right auricle through small plastic tubing. The average amount of blood that could be removed was found to be 3.85 cc. of blood per 100 Gm. of their body weight. All the guinea pigs died after the removal of this quantity of blood. After this, guinea pigs were bled 3.0 cc. per 100 Gm. and 3.5 cc. per 100 Gm. of their body weights. If the blood lost by these hemorrhages was not replaced the guinea pigs died.

With a hemorrhage of 3 cc. per 100 Gm. body weight followed by an infusion of one of the replacement fluids in the quantity of 1 cc. per 100 Gm. of body weight, there appeared to be relatively little difference in the rate of survival, with the exception of the controls that received saline solution. If the blood lost was not replaced or if infusions of isotonic saline solution were given, there were no survivals. The survival rate following the infusion of Dextran 6 per cent, Periston 3.5 per cent, Plasmoid and serum albumin was 100 per cent. The survival rate following the infusion of heparinized guinea pig blood strangely enough was 90 per cent. Ten guinea pigs were used for each comparison.

In another series of guinea pigs from which 3.5 cc. of blood per 100 Gm. was removed, survival rates without replacement and after the infusion of 1 cc. isotonic saline solution per 100 Gm. were the same as the survival rates of those from which 3.0 cc. of blood per 100 Gm. was removed in that there were no survivals. After infusion of Dextran Ph the survival rate was 50 per cent; after infusion of 3.5 per cent solution of Periston the survival rate was 60 per cent; after infusion of Plasmoid the survival rate was 80 per cent; after infusion of human serum albumin or of heparinized guinea pig blood the survival rate was 100 per cent (fig. 1).

A similar type of hemorrhage was carried out on albino rats. The rates of survival following a hemorrhage of 3.5 cc. per 100 Gm. body weight with no replacement or replacement of 1 cc. of the materials per 100 Gm. were: (1) no

<table>
<thead>
<tr>
<th>Replacement fluid</th>
<th>Animals</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>5</td>
<td>94.6 ± 3.6†</td>
<td>8.1</td>
</tr>
<tr>
<td>Plasma</td>
<td>2</td>
<td>78.4 ± 0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Dextran</td>
<td>10</td>
<td>77.1 ± 3.3</td>
<td>10.5</td>
</tr>
<tr>
<td>Plasmoid</td>
<td>9</td>
<td>68.1 ± 3.8</td>
<td>11.5</td>
</tr>
<tr>
<td>Periston 3.5%</td>
<td>10</td>
<td>68.1 ± 4.3</td>
<td>13.6</td>
</tr>
<tr>
<td>Saline solution</td>
<td>7</td>
<td>51.1 ± 7.3</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*Mean percentage ratios:* $H_{1} \times 100$

†The value following the ± is the standard error of the mean.

replacement, 0 per cent; (2) isotonic saline solution, 10 per cent; (3) Dextran Ph, 70 per cent; (4) Periston, 3.5 per cent, 80 per cent; (5) Plasmoid, 80 per cent; (6) human serum albumin, 90 per cent, and (7) heparinized rat whole blood, 100 per cent (fig. 2).

Using the Lawson technic for the comparison of blood and plasma substitutes, with the modification already described, the results of the evaluation of these replacement fluids in the dogs (presented as mean percentage ratios) are as shown in table 1.

In the series of 20 guinea pigs used for infusion of these replacement fluids, before necropsy, the animals were again weighed. Determinations of hemoglobin and complete blood counts, including erythrocytes, leukocytes, lym-
phocytes, heterophils, eosinophils and immature cells, were performed. The results of these blood counts are seen in Table 2. The guinea pigs were killed in a chloroform chamber and necropsies were done immediately. There were no gross changes to be seen in any of the animals. Tissue specimens of the heart, lungs, aorta, blood, spleen, kidneys and bone marrow smears were saved for further examination and comparison with the control specimens.

On microscopic examination of the tissues of the guinea pigs, there were no variations from the normal control tissues observed, in those guinea pigs which had received Dextran Ph and Plasmoid. In the guinea pigs receiving Periston, there were observed bluish vacuolated cells in the liver and spleen. This bluish staining material appeared to have been absorbed by the Kupffer cells and other macrophages in the liver and spleen. The significance of this variation was undetermined.

**Table 2.** Results of Complete Blood Counts in Control and Experimental Guinea Pigs after Protracted Administration of Replacement Agents.

<table>
<thead>
<tr>
<th>Hemoglobin, Gm. per 100 cc.</th>
<th>Erythrocytes, millions per cu. mm.</th>
<th>Leukocytes, thousands per cu. mm.</th>
<th>Lymphocytes, per cent</th>
<th>Heterophils, per cent</th>
<th>Eosinophils, per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control series: no infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.8</td>
<td>4.7</td>
<td>7.6</td>
<td>30</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>13.0</td>
<td>4.7</td>
<td>7.6</td>
<td>44</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>14.8</td>
<td>5.8</td>
<td>9.2</td>
<td>53</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>12.4</td>
<td>3.45</td>
<td>12.8</td>
<td>36</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>13.0</td>
<td>4.95</td>
<td>4.8</td>
<td>54</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dextran Ph infusions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.4</td>
<td>4.25</td>
<td>12.2</td>
<td>80</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>13.2</td>
<td>4.05</td>
<td>4.8</td>
<td>74</td>
<td>26</td>
<td>0</td>
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<tr>
<td>13.6</td>
<td>4.15</td>
<td>8.1</td>
<td>76</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>13.9</td>
<td>3.95</td>
<td>4.8</td>
<td>62</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>11.6</td>
<td>3.50</td>
<td>12.5</td>
<td>80</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td><strong>Periston 3.5 % infusions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.2</td>
<td>3.70</td>
<td>11.5</td>
<td>71</td>
<td>27</td>
<td>4</td>
</tr>
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<td>13.0</td>
<td>3.40</td>
<td>6.0</td>
<td>76</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
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<td>3.55</td>
<td>10.7</td>
<td>48</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td>13.6</td>
<td>3.35</td>
<td>8.5</td>
<td>66</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>14.6</td>
<td>4.35</td>
<td>—</td>
<td>75</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td><strong>Plasmoid infusions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.8</td>
<td>3.45</td>
<td>8.5</td>
<td>66</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>13.2</td>
<td>4.65</td>
<td>14.4</td>
<td>61</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>—</td>
<td>3.00</td>
<td>10.5</td>
<td>56</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
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</tr>
<tr>
<td>12.6</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

**Comment**

The problem of replacing blood lost by hemorrhage is of major importance to the surgeon and the anesthesiologist as well as to other medical practitioners. This is particularly so in the prophylaxis and treatment of operative shock. No one disputes the efficacy of whole blood in these regards. However, we were concerned with evaluating replacement fluids other than blood and blood derivatives. At times blood and blood derivatives may not be readily available. The substances evaluated in this study are readily stored and are relatively inexpensive.

The results of these experiments reveal a definite superiority of the replacement fluids evaluated when compared with isotonic saline solution. In dogs, there was no significant difference between human plasma and Dextran Ph. There appeared to be a superiority of Dextran Ph over Plasmoid and Periston, but it was not statistically significant.

In the guinea pigs treated with human serum albumin, a survival rate of 100 per cent was comparable to that of guinea pigs that had received blood. Plasmoid appeared superior to Dextran Ph and Periston 3.5 per cent.

In the albino rats, serum albumin was found to be superior to Dextran Ph and Periston 2.5 per cent as a blood substitute. Dextran Ph, Periston 2.5 per cent, Periston 3.5 per cent and Plasmoid were about of equal value.

The value of survival rates as a method of evaluating replacement fluids in small animals after hemorrhage may be questioned. The effects of cerebral anoxia and cardiac damage on survival must be borne in mind.

A comparison of the mean percentage ratios obtained in our experiments on dogs with the results obtained by Lawson indicated that our values were consistently higher than his. A possible explanation for this fact may lie in the nature of the anesthetic agents used. In our experiments, ether was used, which causes the
spleen to constrict, and thus the circulating volume of blood is augmented. A barbituric acid derivative was used by Lawson. Dilatation and engorgement of the spleen are known to follow administration of these agents. Further it has been shown by Pender and Essex\textsuperscript{21} that, under the conditions of their experiments on traumatic shock in dogs, those anesthetized with barbiturates lived longer than those anesthetized with ether.

In the efforts to determine whether deleterious effects or pathologic changes followed prolonged intravenous administration to animals of the replacement fluids, nothing of significance was observed, but two findings of interest might be mentioned here. Their significance, however, is undetermined.

There occurred a reversal of the differential count of the lymphocytes and heterophile (table 2). In all but one of the guinea pigs which had received the Dextran Ph, Plasmoid or Periston, the lymphocyte count was greater than the heterophil count. Three of the five animals in the control series showed a higher heterophil count than lymphocyte count.

The second finding of interest was the electrocardiograms taken on the 15 dogs and the response of the animals to the infusion of the replacement fluids. The recovery rate of the electrocardiogram after the original hemorrhage and the subsequent rhythm changes and alterations in the complexes, particularly the T waves, were noted. In this series there was an apparent correlation between the mean percentage ratios and the electrocardiographic changes. The electrocardiographic changes or the lack of them provided a strikingly reliable indication of the probable survival time of these animals and the necessity of a replacement fluid.

**Summary**

An evaluation has been made of the efficacy of certain fluids when used for replacing blood lost by hemorrhage in guinea pigs, albino rats and mongrel dogs.

Hemorrhages of 3.5 cc. per 100 Gm. of body weight were found to produce death in all guinea pigs and rats if one of the plasma substitutes was not used.

The survival rates in guinea pigs after a hemorrhage of 3.5 cc. per 100 Gm. were as follows: without plasma substitute, 0 per cent; with replacement with 1 cc. of the following liquids per 100 Gm. of body weight: isotonic saline solution, 0 per cent; Dextran, 50 per cent; 3.5 per cent solution of Periston, 60 per cent; Plasmoid, 80 per cent; serum albumin or heparinized guinea pig blood, 100 per cent.

The survival rates in albino rats after a hemorrhage of 3.5 cc. per 100 Gm. were as follows: without plasma substitute, 0 per cent; with 1 cc. of the following liquids per 100 Gm. of body weight: isotonic saline solution, 10 per cent; Dextran, 70 per cent; 3.5 per cent solution of Periston, 80 per cent; Plasmoid, 80 per cent; serum albumin, 90 per cent; heparinized rat blood, 100 per cent.

Using the Lawson method for the evaluation of replacement fluids, we obtained the following mean percentage ratios \((H_2/H_1) \times 100\): heparinized dog blood 94.6 ± 3.6, human plasma 78.4 ± 0.5, Dextran 77.1 ± 3.3, Plasmoid 68.1 ± 3.8, Periston 68.1 ± 4.3, saline solution, 51.1 ± 7.3.

Complete blood counts done on guinea pigs after prolonged and repeated administration of the plasma substitutes in question did not reveal alterations of known significance.

Histologic studies of certain organs of guinea pigs after prolonged and repeated administration of the plasma substitutes did not reveal alterations attributable to the replacement fluids when compared with the findings on tissues of normal guinea pigs.

These replacement fluids appeared to have no deleterious effects on the normal growth and development of guinea pigs receiving prolonged and repeated administrations of the fluids under study.

Sensitivity to Periston was not found in rabbits or guinea pigs receiving this substance intravenously.

Utilizing the Clark window in the rabbit’s ear, a leukotactic response was seen after the intravenous administration of Dextran. A leukotactic response was not found after the administration of Plasmoid or Periston.
Conclusions

1. Plasmoid, Dextran Ph and Periston, by the criteria used in this study, have been found to be satisfactory replacement fluids for blood lost by hemorrhage in albino rats, guinea pigs and dogs.

2. Deleterious or noxious effects were not observed after the administration of these replacement fluids in experimental animals.

Acknowledgments

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