EFFECTS OF INTRAVENOUS INJECTIONS ON THE HORSE WITH SPECIAL REFERENCE TO THE CIRCULATORY SYSTEM

by

STEPHEN JAMES ROBERTS

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TABLE OF CONTENTS

INTRODUCTION

Slight knowledge of intravenous therapy was shown by the Egyptians and Romans. In 1492 the first known attempt at blood transfusion was made, but it was not until the seventeenth century that Doctor Gabets of Paris invented and used the first transfusion canula. Even with such early experiments in intravenous therapy it did not become practical and possible until the twentieth century. Indeed, in veterinary medicine the last ten years have seen rapid strides in intravenous medication and transfusion which is now commonly used by every up to date veterinarian with excellent results in many diseases afflicting livestock including horses.

Many drugs and biological products are now injected into the jugular vein of the horse in the treatment of disease. This type of therapy has several important advantages:

1. Therapeutic agents injected into the blood stream result in quicker and more rapid distribution to the cells throughout the body.

2. Intravenous injections allow certain drugs such as chloral hydrate, and calcium chloride, which if administered subcutaneously or intramuscularly would cause severe tissue reaction, to be given safely.

3. Intravenous therapy is the most efficient as well as the most rapid method of giving the horse full benefit of the material injected.

4. Anesthetics may be given intravenously and thus the veterinarian is saved the worry present when an inexperienced person gives inhalation anesthesia.

5. The physiological effect of intravenous anesthesia on the veterinarian's client is desirable as it impresses on the client the professional procedures being used and tends to discourage lay treatment of disease.

There are also certain disadvantages in intravenous medication which should be considered:

1. Many intravenous medicants are rapidly excreted and thus they exert their influence for only a short period.

2. Shock is a danger accompanying intravenous therapy especially when administering biological serums; therefore intravenous medicants should be administered slowly and observations of the pulse, respiration, and physical reactions should be carefully noted.

Many of the common intravenous medicants used on horses were adapted to veterinary practice from human medicine; others were first used in veterinary medicine. Because of the relatively high value of horses and the difficulty of securing and maintaining them in rather large numbers, very little actual experimental work has been done on the effects of intravenous injections of certain drugs. Most of the experimental work has been done on smaller animals and then has been transferred to horses after a few trial injections with results that have not been recorded. Following this procedure the general practitioner and clinical

veterinarian found the practical and satisfactory doses of the product by trial and error methods, without publishing any scientific work on the drug. As a result there is a wide breach in veterinary knowledge as to the specific effects of many of the more common drugs injected intravenously in the horse. It was with a desire to lessen this breach of knowledge that this experimental work was undertaken.

In the subsequent experiments calcium gluconate, chloral hydrate, formalin, gelatin, Lang's solution, sodium iodide, magnesium sulphate, air, oxygen, sodium citrate, hypertonic and isotonic saline solution, ammonium oxalate, sodium cacodylate, tap water, distilled water, oxalic acid, blood, dilute hydrochloric acid solution, and sodium bicarbonate were injected intravenously. A common drug, dextrose, was omitted because Link (46) had previously reported on this therapeutic agent in the horse.

EXPERIMENTAL METHODS

The physical reactions of the horses were noted following the intravenous injections. The pulse and respirations were checked before and after the experiments; the pulse by palpation of the external maxillary artery; the respirations by observing the lifting of the ribs on inspiration and the contraction of the abdominal muscles and fall of the ribs on expiration. The body temperature was checked by a six inch Fahrenheit rectal thermometer. Abnormal symptoms occurring during and after the injections were carefully noted and recorded.

The effects of the intravenous injections on the circulatory system were especially noted. The hemoglobin determinations were, in practically all cases, made by the Haden-Hauser method. This method was checked by the Photoelectric method and was found to be accurate. Hemolysis of the blood was observed by examination of the serum after drawing the blood into a clean dry test tube and allowing the red cells to settle. The specific gravity and total protein determinations of the blood serum after collecting the blood in clean dry test tubes and allowing it to clot were made by the Kagan proteinometer. Calcium determinations on the blood serum of the horse were made by the Kramer-Tisdall method. Red cell and white cell counts were made by the accepted pipette and counting chamber technique. Recognition was made of the fact that this test is subject to an approximate ten percent error even in the hands of a trained technician.

Coagulation time, the time required for withdrawn blood to coagulate in vitro, was checked in these experiments by the capillary pipette method. It was recognized that there is no absolutely accurate clinical or laboratory test of the coagulation time since so many factors are involved. Howell's method (32) said to be the most accurate, consists of drawing a definite amount of blood into a clean dry test tube, allowing it to stand and clot, and noting the time. This method was used in the experiments immediately before and after the intravenous injection in conjunction with the capillary pipette method. It was observed that they were consistently in agreement. Withdrawing

blood from the jugular vein of the horse was accomplished by using a thoroughly cleaned and dried 14 guage needle. The blood was allowed to run freely from the needle into a regular size test tube and the capillary pipette was filled by suction from the stream of blood as it flowed from the needle. The capillary pipettes were clean, dry, and fine, and were broken in a good light to observe the clotting.

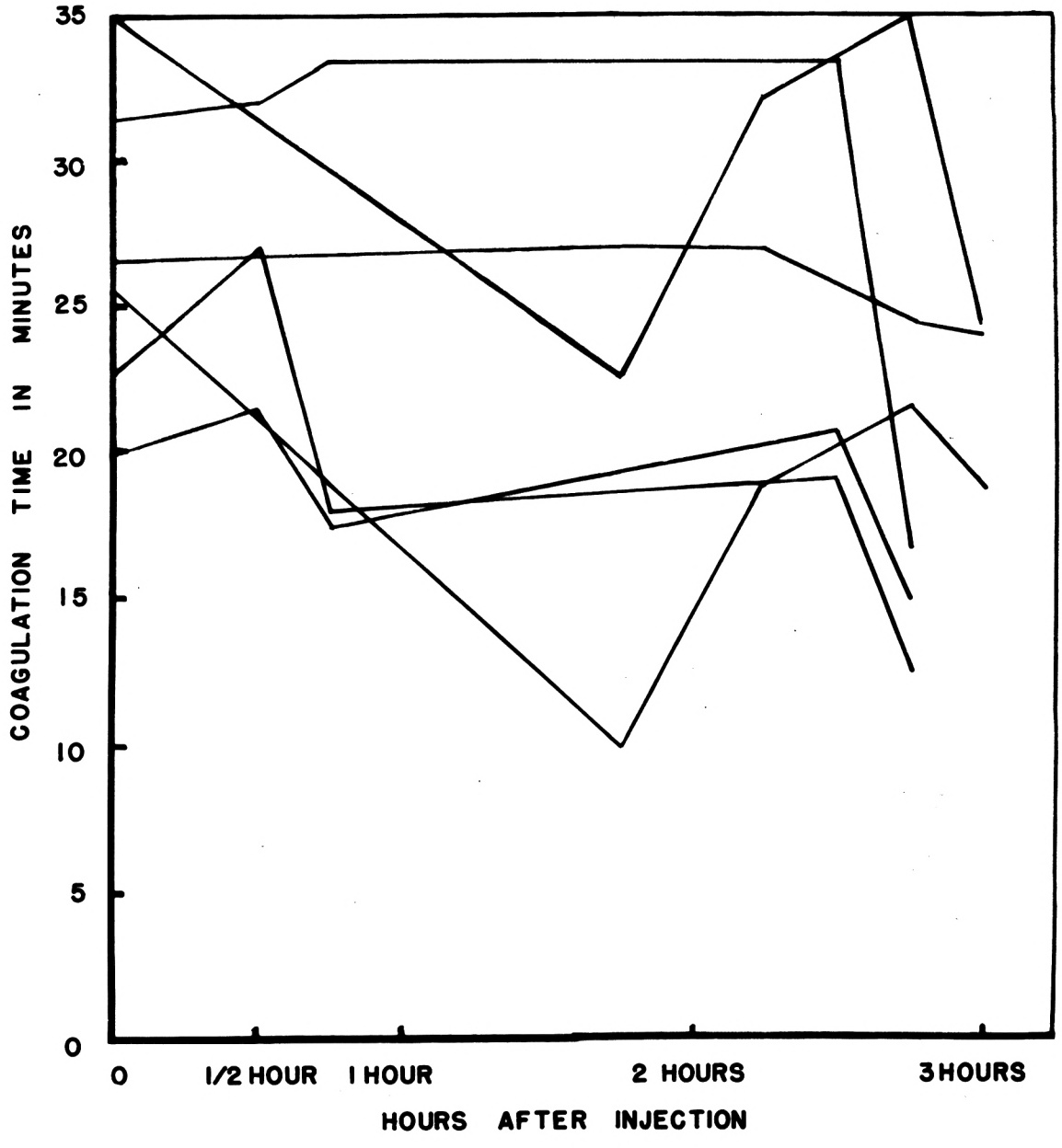
Since many factors influence clotting time, a series of control experiments were run. Five coagulation times on each of six horses of various ages and types were recorded. The average percent greatest decline in coagulation time was 37.3. This was based on the average coagulation time before the injection and the average coagulation time after the injection (Plate I). The coagulation time did not follow a regular course and the range in percent varied from 9.42 to 61.9 in the six horses used as controls. Thus the average percent of greatest error in the normal coagulation time computed by the capillary pipette method was determined to be 37.3.

Samples of urine for examination conducted in some of the experiments were collected from the horses either naturally or by means of a catheter. The urine examinations consisted of: the specific gravity determination by the Urinometer method; the reaction determined by litmus paper; albumin determination by the Fish-Picro-aceto-glycerol test; sugar determination by the Benedict test; and the microscopic examination of the sediment in a tube of centrifuged urine.

EXPLANATION OF PLATE I

Graph of the course of the coagulation times of the six control horses.

PLATE I


35
30
25
20
15
10
5
0
COAGULATION TIME IN MINUTES
0
1/2 HOUR
1 HOUR
2 HOURS
3 HOURS
HOURS AFTER INJECTION

The following experiments all of the intravenous injections except isotonic saline, tapwater, distilled water, air, and oxygen were given through a clean Norden simplex intravenous gravity flow outfit with a 2½ in. 14 guage needle. In the exceptions mentioned above the injections were given through a 12 or 14 guage, 2 to 4 in. needle by means of gravity or pressure from clean flasks or gallon jugs. All of the intravenous injections were made into the jugular vein of the horse.

The observations and results of tests made during and after the intravenous injections were recorded on a separate clinical sheet (Form 1, Appendix). These forms were later combined and tabulated together in an outline or chart form which was easily interpretable and from which comparisons and conclusions could be drawn. A sample chart may be studied on page 15, (Table 1).

The horses used in these experiments were obtained by the clinic for use in operative surgical exercises. They were generally aged or were incapacitated due to incurable lameness, blindness, or were afflicted with some chronic incurable condition. The majority, however, were quite strong and vigorous and made good experimental subjects.

AIR AND OXYGEN

Numerous articles have mentioned the danger of allowing even small amounts of air to gain entrance to the circulatory system. The air emboli thus produced have been blamed, in many cases erroneously, for certain sudden and unexplained deaths

in animals. It was in an effort to determine the effects of air and oxygen on the body and on the circulatory system that this phase of the study was undertaken.

According to Richardson, Cole, and Hall (64) and Jones and Lockart (37) small amounts of air, oxygen and carbon dioxide introduced into the peripheral veins had no effect as they were rapidly absorbed in the lung tissue with no evidence of cardiac and respiratory distress. The gas emboli were completely filtered out in the vascular system of the lungs. They lodged in the arterioles of a caliber of not more than thirty microns in diameter and were readily absorbed by the blood and eliminated in the alveoli of the lungs. The emboli were never found in the arterial circulation except when some defect such as a persistent foramen ovale or ductus arteriosus was present. It was also noted that both air and oxygen were absorbed by the blood at about equal rates. Carbon dioxide was absorbed more rapidly than either air or oxygen.

The injection of larger amounts of air either rapidly or slowly caused slight to severe cardiac and respiratory distress with complete recovery in a relatively short time. Individual variations were evident and were due to the influence of blood pressure; individuals with a higher blood pressure survived larger doses of air than individuals with a lower blood pressure.

When excessively large doses were injected, dyspnea and cardiac distress became so severe that death frequently occurred. Occasionally partial recovery occurred following the intravenous

injection of large quantities of air but death resulted in several hours due to pulmonary edema or several days later due to bronchial pneumonia. The fatal dose of air intravenously for a 150 pound man was computed to be approximately 525 cc. If the injections were given very slowly more air could be given. For example, a dog was given a total of 3910 cc of air over a period of 87 hours before death occurred. The cause for death was due to a drop to zero of the aortic blood pressure due to a lack of sufficient blood in the pulmonary veins, thus a cerebral anemia and asphyxia were produced. Pine (59) stated that the blood-air mixture occluded the arterioles of the lung causing a secondary passive congestion of the right side of the heart resulting in heart failure.

Howell (32) stated that air introduced intravenously had the same effect as air in vitro and resulted in a reduction in coagulation time.

According to Jones and Lockhart (37) Moore and Braselton and Wever stated that minute quantities of air injected into the arterial circulation produced a severe reaction often resulting in death. In man the lethal dose of air injected intra-arterially was determined to be approximately 37.5 cc depending on the rapidity of the injection and the location of the emboli either in the cerebral or coronary vessels. In humans apparently cerebral embolism is more common, while in cats coronary embolism is seen more often. Injections of small amounts of air intraarterially in small experimental animals resulted in mild

reactions such as tremors, to severe reactions such as cardiac and respiratory distress and death. The symptoms closely resembled pleural shock in humans following the production of artificial pneumothorax.

The method employed in injecting air and oxygen into the peripheral venous circulation was by displacing the air into the jugular by means of water. This was accomplished by two flasks equipped with air tight rubber stoppers, glass tubes, and rubber tube connections. The oxygen was introduced into one flask by attaching the tube holding the needle to the oxygen tank and displacing water into the second flask. Then by reversing the flasks the water forced the oxygen into the vein.

In the experiments tabulated in Table 1 there was noted a close similarity to the statements by the other workers. There was an increase in the cardiac and respiratory rates as the larger amounts of air were given intravenously; the rise with oxygen was slightly less than the rise for similar amounts of air. No deaths occurred when 500 cc of air was injected and in many horses no or very slight reactions to the injection were noted. When 1000 cc of air was injected intravenously more severe cardiac and respiratory distress resulted than in the previous group, and one horse died. In the group given more than 3000 cc of air deaths were frequent and all cases were characterized by symptoms of lowered aortic blood pressure including wobbliness, colicy pains, falling due to muscular weakness, and death apparently due to asphyxia. However, it was

noted that there was a great individual variation in response to injections of like amounts of air. The approximate fatal dose of air for a 1000 pound horse was 4000 cc, which corresponds relatively to the figure given for man. Probably if the intravenous injections had been given more slowly the horse could have been given more air.

In four cases the coagulation time was noted and in all four a definite decrease in coagulation time was observed following the injection of air. It was also noted in these experiments that air or oxygen given intravenously had no effect on the specific gravity, or the total protein in the serum or on the hemoglobin in the blood. It was seen that in most cases there was a very slight rise of several tenths of a degree in body temperature, probably brought on by the restlessness of the horse following the injection.

The reaction of horse number seven to the intrajugular injection of 1000 cc of air was interesting and unusual. After slight restlessness and colicy symptoms the horse became normal in 30 minutes. In one hour cerebral symptoms developed, starting with muscular tremors and spasms, progressing to paralysis of the lips, leaning first to one side and then to the other against the wall, development of a dummy like attitude, and apparent amaurosis. The horse fell several times but each time regained his feet. In 24 hours the horse was depressed and still blind and in 48 hours the horse died due to rupture of the stomach.

During the experiments two cows were given air intravenously.

The first cow was suffering from a severe lymphocytoma involving the base of the heart and the thoracic cavity; only 1000 cc of air was necessary to cause death apparently due to heart failure. The second cow was normal and 4000 cc of air caused a marked rise in pulse and respiration rates. For ten minutes after the injection air could be palpated in the jugular vein. The cow was nearly normal in one and one half hours, at which time she was given 7500 cc of air when death occurred due to asphyxia. Thus inside of two hours this cow was given 11,500 cc of air intravenously.

During the experiments air was injected into the carotid artery of two horses to see what symptoms would result. The first horse was under deep chloral anesthesia and 200 cc of air was injected by a hypodermic syringe through an 18 guage needle into the isolated right carotid artery. The only reaction observed was a marked acceleration of the pulse. The second horse was given 60 cc of air into the left carotid artery isolated after local anesthesia had been administered. The following reactions occurred: the horse staggered and fell; dyspnea and severe distress were evident; he arose in ten minutes with some difficulty. It was noticed that there was a ptosis of the left eyelid and a drooping of the left ear. Nystagmus was evident, the left eye rotating medially. A marked ataxia was present, the right side of the body being most severely affected. In approximately three and a half hours the horse was apparently normal.

Summary

1. Small amounts of air or oxygen up to approximately 500 cc injected intravenously in horses were not fatal, were rapidly absorbed into the blood and were eliminated, at least in part, in the lungs with no ill effects.

2. The approximate amount of air or oxygen injected rapidly into the jugular necessary to cause death in the horse was 4000 cc.

3. Small amounts of air injected into the arterial circulation produced severe reactions.

4. A definite drop in coagulation time occurred in a limited number of experiments when air was injected intravenously.

5. Oxygen injected intravenously did not give as severe a reaction as did the same amount of air.

6. The symptoms produced by the intravenous injection of air caused primarily cardiac and respiratory embarrassment together with symptoms associated with a marked drop in the aortic blood pressure.

7. There was a marked individual variation of symptoms in horses injected with like amounts of air.

8. Amounts of air that may accidentally enter the venous circulation during routine intravenous therapy in the horse are harmless.

Table 1. Tabulation of experimental results of intravenous injections of air and oxygen in horses.

Horse No.	Amount of air injected	Rate of injection	Pulse rate Before	Pulse rate After (15 min.)	Respiration rate Before	Respiration rate After (15 min.)	Body temperature (Fahrenheit) Before	Body temperature (Fahrenheit) After (15 min.)	Coagulation time Before	Coagulation time After	Coagulation time Time	Clinical observations
Air												
16	500	166.6	48	60	18	42	99.5	100.0				Restless, normal in 1½ hours.
15	500	166.6	28	36	12	20	99.4	99.5				No reaction.
13	500	500	36	54	12	76	98.6	99.4				Restless, wobbly, down in 20 minutes, up and normal in 1½ hours.
15	500	500	36	60	16	20	98.2	98.8				Restless, normal in 1½ hours.
12	500	500	36	56	10	24	97.4	98.6				Slightly restless, defecated, normal in 45 minutes.
12	500	250	39	56	13	28	99.1	99.1				Restless, normal in 1 hour.
15	500	250	45	58	9	24	99.0	100.0				No reaction.
21	500	250	36	48	16	16	99.2	100.2				No reaction.
18	500	250	54	60	12	32	102.0	102.6				Restless, normal in ½ hour.
28	1000	333	48	48	18	38	101.7	101.6				No reaction.
4	1000	500	60	60			99.4	99.6				Slightly restless, normal in ½ hour.
6	1000	500	42	60	10	44	99.8	99.6				Distress, colic, down in 10 minutes, up in 1 hour, normal in 2½ hours.
7	1000	400	36	52	12	54	99.0	99.4				Normal in ½ hour, later incoordination, blind, leaned to right, in 24 hours blind, depressed, dead in 43 hours, ruptured stomach.
4	1000	250	48	66	16	44	99.6	99.9				No reaction.
20	1000	250	40	54	20	48	98.0	100.0	20	5	20 min.	Restless, normal in 1 hour.
										10	50 min.	
16	1000	500	60	60	27	52	99.7	100.0	20	9.5	5 min.	Restless, normal in 45 minutes.
										10.5	50 min.	
										10.5	60 min.	
										9	2½ hrs.	
										15	7½ hrs.	
11	2000	400	40	78	24	52	98.9	98.0				Restless, wobbly, down and still down in 1 hour, horse weak.
3	3700	528.5	68		32		100.8					
15	4000	500										
1	4000											
Oxygen												
29	1000	500	40	40	24	52	99.9					Restless, slight colic, normal in ½ hour.
28	2000	500	48	54	21	33	100.0	99.9				Slightly wobbly, sweat, restless, normal in 1 hour.
29	2000	250	36	40	16	36	100.0	100.2	20	5	20 min.	No reaction.
										10	50 min.	
28	4000	400	48	66	12	36	99.2	99.5	16	7.5	5 min.	Restless, wobbly, down at 30 minutes, acted peculiar.
										4.0	30 min.	

ISOTONIC SALINE SOLUTION

Physiological saline or an .85 percent sodium chloride solution is a common solution frequently injected intravenously following severe hemorrhage to raise blood volume and pressure. It has also been used in many other conditions such as toxemia, collapse, heat prostration, and other diseases producing severe dehydration. Other physiological solutions have been used such as Ringer's solution which is claimed to be superior to an .85 percent sodium chloride solution because it also contains other salts. In the experiments undertaken, an .85 percent sodium chloride solution was used.

According to Bastedo (5), Sollmann (71), and Milks (51) the administration of physiological saline intravenously in normal animals resulted in a temporary rise in blood pressure due to the increased blood volume, hydremic plethora. The volume tended to return to normal usually in about one half an hour as the blood regulatory mechanisms eliminated the excess volume by storing blood in the splanchnic areas; by excretion through the kidneys; and by the escape of fluid into the tissues, edema. After excessively large doses there was a tendency for pulmonary edema to occur, occasionally resulting in death due to respiratory failure.

Saline injected at reasonable rates and temperatures had no effect on the pulse or the body temperature. However, other authors (11), (79) state that cold or hot solutions may cause

vein block. A rapid injection rate had a tendency to increase the rate and depth of respirations. According to Munson (57) "speed shock" as seen in human medicine and characterized by a fall in blood pressure, irregular respirations and incoagulability of the blood due to the too rapid administration of isotonic saline solutions does not occur in veterinary medicine.

It was noted by Milks (51) that in moderate hemorrhage saline injections caused a lowering of the coagulation time. Numerous reports in human medical literature report the occasional occurrence of chills with a rise in temperature following intravenous saline medication. Siebert (69) showed that this condition was due to pyrogens or toxins from certain bacteria growing in the distilled water or saline solutions resulting from a lack of careful and frequent preparation of the physiological saline solutions.

The saline solution was injected at rates varying from 89 cc to 333.3 cc per minute (Table 2). These rates are in general much faster than those employed in human medicine but no untoward symptoms or results occurred in the 13 injections made. It was noted that an increase in the rate and depth of respirations followed some of the injections but this was not constant.

The temperature of the saline solution injected included the extreme as well as the reasonable ranges. It varied from 37.4° to 160° F. Clinical symptoms were noted only in the horse given saline at 160°. This animal was slightly nervous

during the injection. When the saline was given at 37.4° F. there was a drop of .4° in the body temperature five minutes after intravenous administration. In six horses given saline at a temperature above 110° F. there was an average rise in body temperature of .71° F. with a range from .2° to 1° F. This artificially produced slight rise of temperature when warm to hot saline was injected would be of value in practical therapeutics when the patient's body temperature is subnormal. In the intravenous use of saline, extremes of temperature of the solution had no marked clinical effects on the animal.

The injection of 4000 cc of physiological saline solution had a mild, temporary but noticeable diluting effect on the blood. In blood determinations taken before and five minutes after the injection, the specific gravity decreased in six of seven horses with an average decrease of .000957; and the average total protein values decreased .3343 g per 100 cc of serum. In six horses the red blood cell count showed a decline of 16.8 percent and the white cell count showed a decline of 6.63 percent. The hemoglobin values also declined in each horse with an average decline of 14.7 percent.

It was noted that a drop in coagulation time occurred following the injection of normal saline. The average greatest decline in coagulation time for all eleven injections was 43.1 percent. Apparently the heated saline infusions caused an increase in the tendency of the blood to clot, for in six injections where the temperature of the solution was above

120° F. the coagulation time was decreased an average of 54.4 percent.

No chills or marked temperature rises as is observed in humans occurred in any of the horses used in the experiments.

Summary

1. Extremes in rates of injection and in temperatures of physiological saline solutions injected had slight clinical effects on the horse.

2. A gallon of physiological saline, heated above or cooled below the normal ranges of temperature had a slight but constant effect on body temperature for a short period either raising it or lowering it.

3. A gallon of physiological saline injected intravenously in the horse caused a temporary slight hydremia and a lowering of the blood hemoglobin value, specific gravity and total protein values, and red and white cell counts.

4. Physiological saline had a definite lowering effect on the coagulation time of horse blood which was especially noted after the heated solutions had been injected.

Table 2. Tabulation of experimental results of intravenous injections of physiological saline in horses.

Horse No.	Amount of solution injected (in cc)	Rate of injection (rate per min.)	Temperature of solution (Fahrenheit)	Coagulation time		Hemoglobin		Pulse rate		Respitation rate		Body temperature degrees Fahrenheit		Specific gravity		Total protein		Red blood count (cells per cc)		White blood count (cells per cc)		Reaction
				Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	
1[1]	4000	186.0	77.0	14.5	12.0	14.0	13.0	47	72	28	50	99.4	99.6									none
1[1]	4000	167.0	98.6	16.0	16.5	13.8	10.4	42	52	24	30	99.0	98.8									none
1[1]	4000	160.0	37.4 to 47.3	18.5	14.5	12.5	9.2	48	60	28	30	99.6	99.2									none
1	4000	200.0	81.5	20.0	12.5	12.2	12.2	48	46	26	25	99.8	99.7									none
2	4000	143.0	110.0	20.0	6.5	10.0	9.5	40	78	18	28	100.0	100.2	1.0277	1.0251	6.94	6.04	6,850,000	6,300,000	4,400	3,800	none
3	4000	89.0	120.0	10.0	8.5			42	68	35	32	99.8	100.8	1.0291	1.0290	7.42	7.38					none
9	4000	333.3	130.0	20.0	13.0	8.0	7.5	36	36	28	24	99.4	100.3	1.0284	1.0272	7.18	6.76	7,250,000	5,300,000	9,700	8,400	none
10	4000	266.6	140.0	12.0	7.0	11.0	10.0	36	38	20	36	98.9	99.4	1.0285	1.0263	7.22	6.46	6,500,000	6,550,000	16,000	14,000	none
12	4000	190.5	150.0	8.75	6.0	9.75	8.5	28	28	16	12	97.0	98.0	1.0285	1.0281	7.22	7.08	5,250,000	3,000,000	6,400	8,000	none
14	4000	200.0	160.0	35.0	6.5	11.0	9.5	44	40	15	15	99.2	99.4	1.0250	1.0235	6.00	5.49	5,740,000	4,100,000	8,160	6,000	slightly nervous
14	4000	100.0	150.0	13.0	4.0[2]	8.0	8.0	48	48	24	40	100.1	100.8	1.0275	1.0288	6.87	7.31	5,250,000	5,650,000	5,500	6,800	none
22	1000	100.0	160.0	14.5	11.0			28	36	16	18	99.3	99.4	1.0300	1.0297	7.73	7.63					
12	3000	115.0	120.0 to 150.0	16.5	15.5	7.5	7.5	40	44	16	16	100.8	99.2	1.0244	1.0266	5.80	6.56	5,350,000	5,650,000	5,500	6,800	

All readings after the injection were made five to 15 minutes after the injections except where otherwise noted.

1. Injections at 24 hour intervals.
2. This reading was made two hours after the injection.

HYPOTONIC SOLUTIONS, TAPWATER AND DISTILLED WATER

Experimental intravenous injections of hypotonic solutions, distilled water and tapwater, were undertaken with horses because the diluent of most of our intravenous solutions is hypotonic. Even some of our regularly used intravenous solutions are hypotonic. It was desired to check the effect of unsterilized tapwater on the blood stream and body, as several practitioners reported that they regularly used tapwater in preparing their solutions and also on occasion gave tapwater intravenously in certain diseases such as heat stroke.

According to Dukes (18), Bastedo (5), Sollmann (71), and Edmunds and Gunn (19) hypotonic solutions injected intravenously into the blood stream caused a decrease in the osmotic pressure of the blood which tended to cause fluid to pass from the blood into the tissues. It produced a temporary increase in venous and capillary pressure that also favored the loss of fluid into the tissues. Thus small amounts of hypotonic solutions injected slowly acted much the same as did small injections of isotonic solutions. When hypotonic solutions were mixed with blood hemolysis of the red cells occurred. However, the extent to which the osmotic pressure of the plasma may be lowered without causing complete hemolysis is considerable and it varies among the species. In horses complete hemolysis of the blood cells mixed with saline in a test tube does not occur until the sodium chloride concentration of the

solution is lowered to .42 percent. This explains why the blood of the horse can tolerate considerable amounts of tapwater or distilled water without signs of hemolysis. Following large and rapid hypotonic injections hemolysis of the blood occurred and hemoglobin appeared in the urine.

The respirations were slowed; the blood pressure was lowered; and a marked increase in the pressure and volume of cerebro-spinal fluid occurred. Immediate diuresis did not occur as would be expected for two reasons: the tissues, mainly muscles and liver, take up large quantities of water; and renal circulation is slowed by the swelling of the kidney cells. Water excretion occurred by other channels, causing excess salivation and a serous diarrhea. Excessively large doses caused the rather late appearance of paralysis of the central nervous system and convulsions. The fatal intravenous dose of tapwater was somewhat smaller than the fatal dose of normal saline solution. Distilled water was again somewhat more toxic than tapwater as it was free of even traces of inorganic salts.

Munson (57) and other medical men have stated that hypotonic solutions are dangerous because they produce hemolysis of the blood accompanied by symptoms of chills and fever. It has been noted frequently with certain distilled water, even when it has been made isotonic and sterilized in an autoclave, that chills and fever follow the injection. Nelson (58) and Siebert (69) have shown the reason for this to be that toxins of bacterial origin in the water persist even after autoclaving.

In the experiments with the intravenous injections of distilled water and tapwater there were eight injections of tapwater given to eight horses. The amounts of tapwater varied from 4000 cc to 24,000 cc given by gravity flow at rates from 192 cc to 266 cc per minute. The temperature of the tapwater was approximately 80° F. Eight horses were given eight injections of distilled water. The amounts varied from 2000 cc to 12,000 cc given at the same temperature as the tapwater and at rates from 190 cc to 285 cc per minute. The tabulation of figures of the experiments will not be given here as in the previous discussions; they were inserted previously to give the reader an idea of the procedure followed.

After the injections of the hypotonic solutions there were no significant changes in the hemoglobin, pulse rate, respiration rate, or temperature. In most injections there was a slight increase in the pulse rate. In half of the injections there was a slight decrease in the respiration rate and in several the respirations were much deeper. In seven of nine injections in which the red blood cell count was taken before and five minutes after the injection, there was noted a slight to a definite decrease in red blood cells. This decrease was most marked in the horses given 12,000 cc of distilled water and 16,000 cc of tapwater. In five of eight injections the white blood cell count also declined after the intravenous injections of hypotonic solutions.

The changes in the total protein and specific gravity

readings before and after the injections were interesting. In 12 injections in which the specific gravity and the total protein were checked before and after the injection, six cases showed an increase in specific gravity and total protein and six cases showed a decrease. The reasons for these rather odd results could be explained in the following manner, always considering the individual differences in the horses. The hydremia produced would tend to cause a passing of the serum proteins into the tissue, thus causing a drop in specific gravity and total protein. Hemolysis releases hemoglobin from the red blood cells into the serum and this in turn tends to raise the specific gravity and total protein. Thus it was noted that in all cases where an increase resulted there was also an hemolysis of the red blood cells and where a decrease resulted either no hemolysis occurred or an excess of water had been injected.

There was in general a definite decline or drop in the coagulation time after the injections of hypotonic solutions. The decline in coagulation time based on the coagulation time before the injection and the greatest drop in coagulation time after the injection was 46.27 percent for distilled water and was 54 percent for tapwater occurring on the average about 40 minutes after the injection. Hemolysis of red cells and hemoglobin in the urine was noted after all injections of water over 4000 cc and was accompanied in all cases that were noted by an amber to a dark red colored urine, which was positive to the albumen test. This red color of the urine, due to hemoglobin, usually disappeared 24 hours after the injection.

In only one horse did it persist for 48 hours. Outside of an increase in the amount of phosphate, urates, and cellular debris noted on microscopic examination of the urine, no significant changes were noted in the specific gravity, reaction, sugar, ketone, odor or bile tests on the urine. No immediate diuresis occurred in any of the horses injected with large amounts of hypotonic solutions.

In general the clinical symptoms occurring during and after the injections were mild. In a few horses slight nervousness and deep respirations developed. In four horses there was frequent defecation with the feces becoming progressively more fluid. One horse had fluid profuse defecations, a diffusely pink mucous membrane, depression, and red colored urine lasting for 48 hours. Only one horse died. In this horse 3500 cc of distilled water was given soon after an injection of 4000 cc of isotonic saline solution; convulsions occurred and the horse died in several minutes. On post mortem examination a passive congestion of the lungs and edema around the base of the heart were found; the diagnosis was heart failure. In another horse given 8000 cc of distilled water immediately after a 4000 cc injection of saline a definite attack of spasms of the diaphragm or hiccoughs resulted and lasted for 15 minutes.

Chills and a rise in temperature were not noted in any of the horses. Horse number 11 was given intravenously 4000 cc of water distilled 68 days previously and not resterilized with only a slight .2° F. rise in temperature. The amount of

tapwater which may be given intravenously to a normal horse is enormous. Two horses were given 20,000 cc and 24,000 cc of tapwater respectively. According to Dukes (18) the blood volume of a horse is 9.7 percent of his body weight or for a 1200 pound horse about 116.4 pounds. Since six gallons of water weighs approximately 48 pounds, the amount of fluid introduced into the blood stream inside of one and one half hours was equal to about 41 percent of the total blood volume. The only marked clinical symptom was a red colored urine that persisted for 12 to 24 hours.

Summary

1. Hypotonic solutions caused a definite lowering of the coagulation time; the greatest decline occurring about 40 minutes after the injection and lasting for two to four hours.

2. In the normal horse hypotonic solutions up to 2000 cc or 4000 cc rarely caused hemolysis; more than 4000 cc commonly produced hemolysis. This hemolysis resulted in the presence of hemoglobin in the urine lasting about 24 hours.

3. Immediate diuresis did not follow the large intravenous injections of hypotonic solutions but loose and frequent defecations often occurred.

4. The normal horse can tolerate large doses of hypotonic solutions given intravenously.

5. No chills or fever were noted in any of the horses given

intravenous injections of unsterilized tapwater or distilled water.

6. Large intravenous injections of distilled water usually produced more severe reactions than did the injections of like amounts of tapwater.

HYPERTONIC SODIUM CHLORIDE SOLUTION

Experiments with hypertonic salt solutions were undertaken after it was noted that Lang's intravenous colic solution had a marked effect on coagulation time and peristalsis. According to Milks (51) hypertonic saline solution when injected intravenously raised the osmotic pressure of the blood which in turn caused a withdrawal of fluid from the body tissues into the blood stream greatly increasing its volume, hydremic plethora. Since the hypertonic solution abstracts fluid from body tissues it would also abstract fluid from the red blood corpuscles and injure them to some extent. According to Sollmann (71), Robertson stated when a hypertonic solution such as a 33 percent sodium chloride or a 50 percent glucose solution was injected intravenously in cats in the amount of 5 cc per kilogram there occurred an enormous increase in blood volume. This increase took place rapidly; after the injection the blood volume fell rapidly and in one half an hour it was normal. Sollmann (71) stated that this excessive increase in blood volume might if severe enough cause circulatory embarrassment. Therefore he advised that large injections of hypertonic solutions be given

very slowly.

Experimental dehydration produced in the human body by injection of a hypertonic solution caused a marked drop in cerebral spinal pressure lasting for six to seven hours, Bastedo (5), Edmunds and Gunn (19), and Sollmann (71). But according to Sollmann, following the shrinking effect the brain swelled to even larger proportions than before because of the great increase in blood volume that must be absorbed by the tissues. Thus there were two periods following the injection of a hypertonic solution, first, fluid absorption into the blood and then a second period of fluid transudation and excretion. Occasionally injections of hypertonic solution caused fever by producing dehydration of the body tissues. Hypertonic solutions were more markedly diuretic than were isotonic solutions. Sollmann (71) on this point stated that prolonged injection of hypertonic solutions might diminish both the body weight by ten to 11 percent and the plasma volume 20 percent in two hours. Bastedo (5) suggested that for the above reasons combining hypertonic intravenous injections with large amount of water intake would be good treatment under suitable conditions to combat toxemia.

Large amounts of hypertonic salt solution injected intravenously caused a violent stimulation of the central nervous system and might even be fatal due to withdrawal of fluid, Sollmann (71), and Edmunds and Gunn (19). The symptoms exhibited were progressively: lassitude, weakness, increased

reflex excitability, tremors, and finally convulsions. Blood pressure fell before death, red cells were crenated and hemorhages were found in different organs. The lungs and intestinal mucous membranes were edematous.

In perusal of the literature it was noted in Bastedo's text (5) that Hughson and Scarff found that intravenous injection of a 30 percent solution of sodium chloride caused an active peristalsis in normal as well as in paretic intestines. This active peristalsis was produced even after section of the vagus and splanchnic nerves. Jones and Hewitt (38) stated that in experiments on dogs the quantity rather than the concentration of the solution appeared to be the significant factor. Thus the response of the intestine varied in proportion to the amount of salt injected. Large amounts of hypertonic salt solution given intravenously were relatively non toxic to the circulatory and respiratory systems. The sodium ion was responsible for the stimulation of intestinal musculature. Hover (31) mentioned the use of hypertonic salt solutions for impactions in horses.

In the experiments on horses ten intravenous injections of 30 to 120 g of sodium chloride in 15 percent to 30 percent solutions with distilled water were given to nine horses. The injections were made at room temperature at rates varying from 66.6 cc to 100 cc per minute. It was found that no significant changes occurred in the pulse rate, respiration rate, body temperature, hemoglobin value, or in the red and

white blood cell counts as a result of the above injections.

In a few of the horses clinical symptoms of restlessness occurred. One horse after the injection of 300 cc of a 30 percent sodium chloride solution developed a pronounced sweating from the entire body surface which lasted for approximately nine hours. No hemolysis of the red blood cells was observed in any of the ten experiments with hypertonic solutions. It was noted however that there was a definite decline in the specific gravity and total protein values of the serum after each injection. The average decrease of specific gravity was .00157 and of total protein .541 g per 100 cc. These were collected five to 15 minutes after the injection. This decline was attributed to the hydremia produced in the blood following intravenous injections of hypertonic salt solutions.

In the experiments undertaken no accurate method of checking the increase in peristalsis was possible other than by auscultation of the abdomen before and after the injection; the author and several colleagues auscultated these horses and in all of the cases where this was done before and after the injection there was a marked increase in peristalsis, with several horses defecating at frequent intervals after the injection.

It was also noted in the ten experiments with hypertonic salt solutions on horses that there was a uniformly marked decline in the coagulation time following the injection. This decline reached its average lowest point approximately 45 minutes

after the intravenous injection. The greatest decline in coagulation times were noted in the horses given two ounces of sodium chloride in a 30 percent solution. The average greatest decline after all of the ten injections was 57 percent. This value was based on the average coagulation times before the injection and the greatest drop in coagulation time after the injection. The reduction in the coagulation time lasted from two to four hours after the injection.

Summary

1. Increased peristalsis was noted in the horse after the injections of 30 percent solutions of sodium chloride.

2. There was a slight hydremia produced with a slight but definite decline in specific gravity and total proteins of the serum.

3. There was a definite decline in coagulation time that lasted for approximately two to four hours.

4. Hypertonic saline solutions containing up to four ounces (120 g) of sodium chloride in a 30 percent solution were not harmful to horses, producing only slight restlessness and sweating in some horses.

SODIUM CITRATE

Sodium citrate has long been used as an anticoagulant in indirect blood transfusions. It has been combined with sodium chloride to make Lang's solution. Recently it has been advanced

by Druillet (17) as an agent that will hasten the coagulation of blood in vivo. According to Sollmann (71) and Bastedo (5) sodium citrate is considered an excellent anticoagulant and has been used extensively in solutions with blood from .2 percent to .5 percent. It affects this action by combining with the calcium of the serum to form a double salt that does not liberate calcium ions essential for coagulation. Sollmann (71) mentioned that about one half of the citrated blood transfusions in humans are followed in one half an hour by a fairly severe chill and rise in body temperature to 2.5° F. and returning to normal in four to eight hours. This reaction is of little importance and is apparently due to alterations produced in the corpuscles. The advantages of citrate transfusions is their relative simplicity. Sodium citrate causes relatively slight if any alterations in normal blood and is rapidly excreted or is changed to the carbonate in the recipient's body. Sodium citrate in small doses when injected slowly intravenously causes slight physical symptoms and it rapidly disappears from the circulation. Relatively little of it escapes through the kidneys into the urine. Only in larger doses of more than .5 g of sodium citrate per kilogram of body weight is any excreted in the urine.

Bastedo (5) further stated that moderate intravenous injections caused a shortening of both the coagulation and bleeding times; for humans the dose was six grams (90 grains) in a ten percent solution. Druillet (17) stated that sodium

citrate may be used for its antihemorrhagic effect in race horses in doses of 20 to 25 g in a 30 percent solution injected intravenously. Sollmann (71) and Jones and Hewitt (38) stated that small to moderate doses of sodium citrate injected intravenously in dogs caused an increased tonus of the intestines and a moderate increase in intestinal motility. The effect seemed to be due to the sodium ion.

Jones and Hewitt (38) recorded that large intravenous doses of sodium citrate depressed intestinal motility, and weakened the heart by taking the calcium ions from the circulation. In dogs large doses caused a bradycardia and a slowing of the respirations. Sollmann (71) noted that in animals the intravenous toxicity varied with the rate of injection. When giving large doses of sodium citrate they should be given slowly or they would produce symptoms of calcium deprivation. According to Bastedo (5) the symptoms are as follows: cerebral and cerebellar excitation, muscle twitchings, tetany, respiratory and circulatory collapse, the last due to depression of the heart muscle and a stimulation of the vasomotor system. Druillet (17), however, believes this is not an acute calcium deprivation but is of the nature of an anaphylactic shock.

Eleven intravenous injections were given to ten horses. These were given at room temperature, at rates varying from 50 cc to 150 cc per minute. Sodium citrate in amounts from one ounce (30 g) to three ounces (90 g) were given in solutions of 15 to 30 percent.

The pulse and respiration rates increased slightly after the one ounce injections and markedly after the two to three ounce injections nearly trebling the normal rates after the larger injections. There was a slight indefinite rise in the body temperature five minutes after the injection, but in several cases this rise was more definite 30 to 60 minutes after the injection. The hemoglobin values showed a slight but gradual increase after the injection of sodium citrate in amounts of one to three ounces with the greater increases occurring after the larger injections.

The specific gravity and total protein values showed a very slight decrease in all of the one ounce injections of sodium citrate, but in the two and three ounce injections there was a marked increase in the specific gravity and total protein values of the serum. The values returned to normal in approximately 30 minutes. There were no significant changes in the red blood cell or in the white blood cell counts. No hemolysis of the blood occurred after any of the injections.

It was noted in the experiments on the horses that there was a definite to a marked increase in the calcium level five minutes after the injection of sodium citrate. This might, however, be due to the rapid mobilization of calcium from the tissues into the blood stream to restore the calcium ions removed but probably still present in combination with sodium citrate in an unionized form. The calcium level returned to normal within 30 minutes after the injection.

The coagulation time was markedly reduced after the injection of the sodium citrate solutions. On the basis of the average coagulation time before and the average greatest drop in coagulation time after the injection, there was a decline of 59.21 percent in the coagulation time. This lowest drop occurred from 30 minutes to two hours after the injection. The decline in coagulation time was not in a regular curve, but nevertheless the decline was obvious and lasted for approximately two hours after which it gradually rose to normal in 24 hours.

The marked symptoms produced in those horses given two or more ounces (60 to 90 g) most closely resembled an acute calcium deprivation. The horses became restless, wobbly and incoordinated, fell down and showed marked signs of tetany with extension of limbs and head. Increased pulse and respiration rates developed with salivation, and in some cases sweating. In five to ten minutes most of the horses had regained their feet,and in 30 minutes seemed perfectly normal. To prevent this reaction the injection had to be given very slowly. The horses given one ounce (30 g) showed no clinical symptoms. No marked increase in peristalsis was noted in any of the horses, but mild increases could easily have been missed as no attempt to accurately determine an increase in peristalsis was undertaken.

Summary

1. A definite decline in the coagulation time that lasted

for several hours was produced by 100 cc to 200 cc of 15 to 30 percent sodium citrate.

2. Large injections, two ounces or more, given rapidly to horses caused marked clinical symptoms of calcium deprivation, including excitement, incoordination, prostration, tetany, and rapid pulse and respirations.

3. A marked rise in the specific gravity, total protein and calcium of the serum occurred five minutes after the injection of more than two ounces of sodium citrate.

4. These experiments with sodium citrate on horses conformed closely with the findings of workers with other species of animals.

LANG'S INTRAVENOUS SOLUTION

Lang's intravenous solution consisting of two ounces each of sodium chloride and sodium citrate in 1000 cc of distilled water was proposed by W. W. Lang of England (43) in 1936 as a successful treatment for cecal impaction in the horse. According to Lang it resulted in the horse drinking large quantities of water, improving the appetite and attitude with a stimulation of peristalsis and the elimination of large amounts of fecal material within 24 hours. In this country it has been used with variable success and a weaker solution of one ounce each of sodium chloride and sodium citrate in 500 cc of distilled water has been adopted. Practitioners are using this solution as an adjunct to the regular treatment

of impaction. It was noted in our previous experiments with hypertonic salt solution and sodium citrate solutions that definite lowering of the coagulation time occurred and it was desired to check this with the effect of Lang's solution.

According to both Lang (43) and Rose (66) the solution, either the stronger or the weaker, should be injected slowly and in weak patients a heart stimulant should be given. Jones and Hewitt (38) and Lang (43) described an increased intestinal tonus and motility after intravenous injections of Lang's solution. The former in their experiments stated that this solution was slightly toxic to anesthetized dogs.

Seven intravenous injections of Lang's solution were given to seven horses. Two injections were of the original Lang's solution strength of two ounces each of sodium citrate and sodium chloride in 1000 cc of water, while the other five were of the modified weaker solution, one ounce each of sodium chloride and citrate in 500 cc solutions. They were given into the jugular vein at room temperature and at rates varying from 100 cc to 200 cc per minute. No significant changes occurred in the hemoglobin value, respiration rate, body temperature, specific gravity, total protein values, and red and white blood cell counts; no hemolysis occurred. There was an increase in the pulse rate after the injection. The weaker solution increased the pulse 8.2 beats per minute, and the stronger solution 35.5 beats per minute. This corresponds closely to the effects of sodium citrate solutions. However, both the pulse

and the respiration rates were less affected by the injection of Lang's solution than by sodium citrate solution alone.

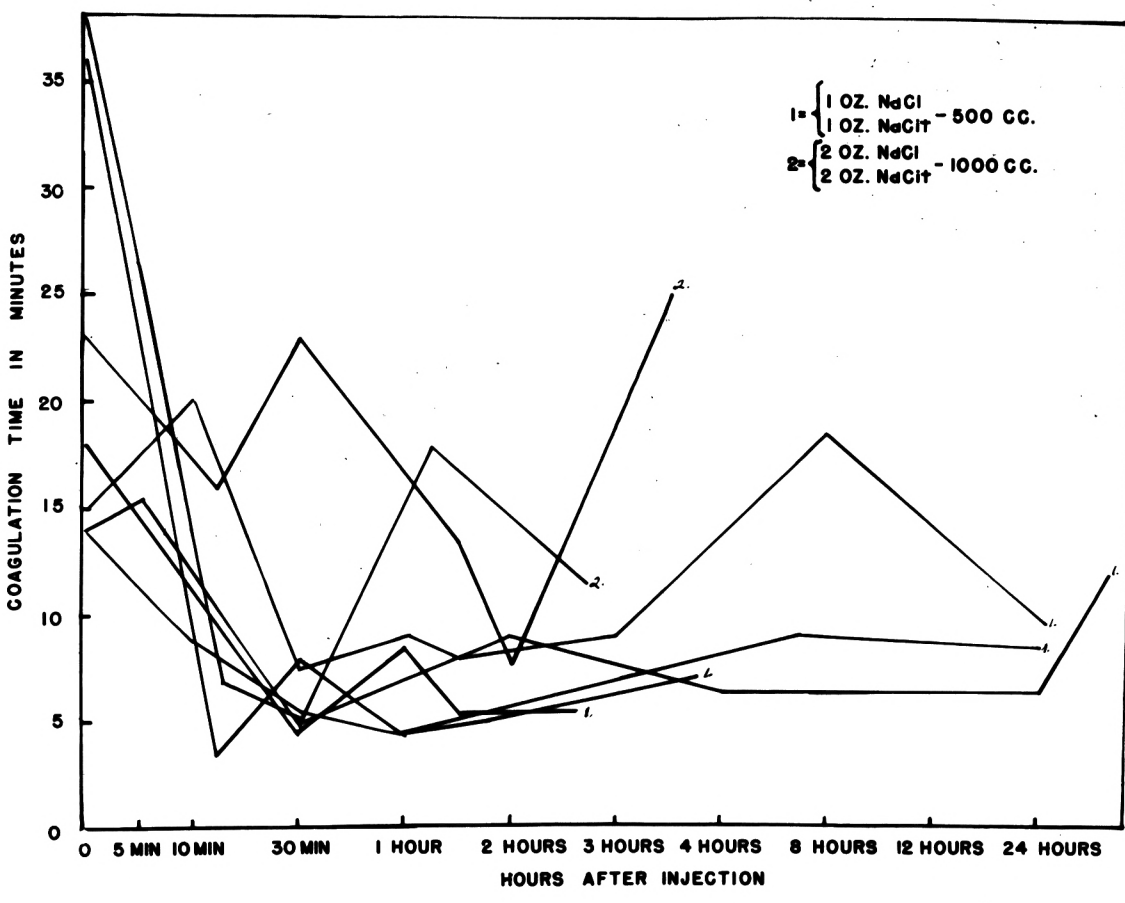
In the experiments with horses using Lang's intravenous solution it was noted that the solutions of one ounce each of sodium chloride and sodium citrate in 500 cc had slight clinical effects even when given rapidly. The symptoms consisted of slight restlessness, salivation, slight signs of thirst, and a definite increase in peristalsis. The stronger solution containing two ounces of sodium citrate and sodium chloride when injected rapidly caused a marked reaction typical of an acute calcium deficiency described in the previous discussion of sodium citrate and consisting of restlessness, staggering, falling down, rising in five minutes, increased peristalsis, defecation, and abdominal pain, with a return to normal in 20 to 30 minutes. Very slight clinical symptoms were noted when the solutions were given very slowly.

Intravenous injection of Lang's solution caused a more marked drop in coagulation time than did either the hypertonic sodium chloride solutions or the sodium citrate solutions. The percent of decline in coagulation time based on the seven average times before the injections and the greatest decline in coagulation time after the injection was 78.28. The greatest decline occurred about 40 minutes after the injection. (Plate II). This decline in coagulation time persisted for about three or four hours before it began to rise toward normal. Thus it appeared that in Lang's solution the sodium chloride and sodium

EXPLANATION OF PLATE II

Graph of the course the coagulation time followed in seven horses after the injection of Lang's solution.

PLATE II


1= 1 OZ. NaCl / 1 OZ. NaCit - 500 CC.
2= 2 OZ. NaCl / 2 OZ. NaCit - 1000 CC.
COAGULATION TIME IN MINUTES
0
5
10
15
20
25
30
35
0
5 MIN
10 MIN
30 MIN
1 HOUR
2 HOURS
3 HOURS
4 HOURS
8 HOURS
12 HOURS
24 HOURS
HOURS AFTER INJECTION

citrate enhanced each other's effect on the coagulation time. The sodium chloride apparently tended to make the sodium citrate in the solution less toxic.

Summary

1. Lang's solution caused a marked drop in the coagulation time.

2. Lang's solution was more effective in lowering the clotting time than was either hypertonic sodium chloride solution or sodium citrate solution.

3. Lang's solution caused a definite increase in peristalsis.

4. The horses' desire for water after the injection was variable.

5. Lang's solution is non toxic for the horse if injected very slowly. Toxic effects after rapid injection were the same as those exhibited by hypertonic sodium citrate solutions.

SODIUM IODIDE

Sodium iodide is a drug commonly used in veterinary practice for treating actinomycosis and fistula of the withers. The common dose is one ounce (30 g) in 250 cc or 500 cc of water given intravenously. It was used in these experiments with horses to check its effect on the blood stream and the body and also in concentrated solutions to determine if markedly hypertonic solutions of sodium iodide had any effects not noted in weaker solutions.

According to Sollmann (71) the immediate toxicity of sodium iodide injected intravenously was low although it disturbed the colloidal equilibrium more profoundly than did doses of physiological saline, as was shown by an increased sedimentation rate. Like other neutral salts, sodium iodide is diuretic and expectorant, with 50 percent to 75 percent of the sodium iodide being eliminated in the urine within 24 hours and the rest being eliminated in three or four days.

Farquharson (20) stated that less than five percent of his cases showed a reaction during the injection. In those rare cases restlessness, increased respirations, and heart action occurred and occasionally lacrimation and apparent vertigo appeared. In large doses, .8 g per kilogram, a delayed toxicity to intravenous sodium iodide injection occurred, according to Sollmann (71), with symptoms of central paralysis, pleural exudations, pulmonary edema, and pericardial effusions followed by death in 12 to 36 hours. Continuous use of iodides lead to iodism characterized by nasal discharge, lacrimation, loss of appetite, and scaly skin eruption. Farquharson (20) stated that sodium iodide was much less toxic than potassium iodide because the sodium ions were less toxic to the heart than are potassium ions. He also mentioned the observation that many of the pregnant cattle treated with intravenous injections of sodium iodide aborted. However, it has been noted by the author in numerous unrecorded cases of pregnant cattle treated with sodium iodide that no

abortions resulted even though they were treated until iodism occurred.

In these experiments nine horses were given ten intravenous injections of one ounce (30 g) of sodium iodide each in from 30 cc to 500 cc of distilled water, or concentrations of from six percent to 100 percent. The injections were given at room temperature at rates varying from 60 cc to 166 cc per minute. No significant changes were noted in the pulse rate, respiration rate, body temperature, specific gravity and total protein values. None of the above mentioned acute or chronic symptoms appeared in any of the horses injected in the experiments.

The hemoglobin values decreased ten minutes after the injection. A range of .5 to 1.5 grams of hemoglobin per 100 cc of blood was noted with an average decrease of .7 grams. These returned to normal in one and a half hours. It was noted after several of the injections the blood was bright red instead of the usual dark red venous blood. The red blood cell count decreased after six of the injections with an average decrease of 2,071,333 cells per cc of blood. The white blood cell count also showed an average decrease 15 minutes to five hours after the injection of 2,102 cells per cc. The coagulation time noted after eight injections was markedly lowered. The injection was followed in several horses by a brief temporary rise in the coagulation time but then in all cases a marked drop was evident in 30 minutes, persisted for about two hours after the injection and then slowly rose toward normal. In general

it was noted that more marked declines in coagulation times occurred after the injection of the more concentrated solution. The percent of decline in coagulation time based on the average time before the injection and the greatest decline in coagulation time after the injection was 67.35.

Summary.

1. A marked lowering of the coagulation time occurred 30 minutes after the injection of sodium iodide and lasted for approximately one and a half hours before slowly rising to normal.

2. A marked decrease occurred in the red blood cell and white blood cell counts from 15 minutes to five hours after the injection. Also a slight decrease in hemoglobin was present after ten minutes.

3. One ounce doses of sodium iodide given intravenously in solutions from six to 100 percent had no clinical effects on the horses.

SODIUM BICARBONATE

The bicarbonate present in the blood and tissues is essential to the acid-base balance in the body. According to Dukes (18), Van Slyke and Milks (51) the bicarbonate of the blood is termed the "alkali reserve". Sodium bicarbonate is probably one of the most useful drugs, but the intravenous use in man and in animals has been rather limited.

According to Sollmann (71), since sodium bicarbonate is

so readily absorbed from the digestive tract, the advantages of intravenous injections are considered doubtful. However, sodium bicarbonate has been used intravenously in humans to combat acidosis in amounts of 500 cc of a five percent solution. In shock it has been said to give better results than plain saline as the rise in blood pressure is more sustained and the respirations are deeper. According to Bastedo (5) following the intravenous injection of sodium bicarbonate there was an increased oxygen consumption, carbon dioxide elimination, and diuresis as most of the bicarbonate is eliminated in the urine making it alkaline. The above authors also stated that giving sodium bicarbonate by any means and thus increasing the alkalinity of the body improved the tone of the arteries and resulted in an increase of lymphocytes and a heightening of the bactericidal power of the serum and tissues; this latter point needed further experimentation. Jones and Hewitt (38) stated that sodium bicarbonate given intravenously to the dog caused a more marked stimulation of the intestinal tonus and motility than any of the other salts such as sodium chloride, sodium citrate, and calcium gluconate used in their experiments. Excessive intravenous doses produced an alkalosis and large repeated daily doses of sodium bicarbonate might lead to water retention and edema.

Sodium bicarbonate has been widely used intravenously in animal diseases such as azoturia, uremia, ketosis, and tetanus to combat the acidosis usually present in these conditions.

But the success of the alkaline treatment has been variable. The intravenous injection of 2000 cc of an eight percent sodium bicarbonate solution has been advocated by Hixson (30) for combatting the acidosis occurring in the influenzal types of diseases, mainly so-called "shipping fever" commonly seen in feeder calves. In a series of 4500 cases in cattle where sodium bicarbonate solutions were given, he recorded a reduction in death losses from an average of 20 to 30 percent to less than one percent when treatment was given early.

Because intravenous injections of sodium bicarbonate had seldom been given to horses, two injections of 2000 cc of a ten percent sodium bicarbonate solution and one injection of 4000 cc of an eight percent solution were given to three horses. These solutions were given at room temperature into the jugular vein. Distilled water and U.S.P. sodium bicarbonate were used and no attempt was made to sterilize the solution as heating would have altered the sodium bicarbonate, producing sodium carbonate. These solutions were given at rates of 125 cc to 166 cc per minute.

The hemoglobin showed a marked drop after the 2000 cc injections with an average drop of 2.5 grams per 100 cc of blood; however, this value returned to normal in 30 minutes. The red blood cell count showed an average increase of 525,250 cells per cc five minutes after the injection, returning to normal in 24 hours. The white blood cell count, however, showed a slight decrease of 966 cells per cc after five minutes, but

in 24 hours the white cell count had increased 1916 cells per cc above the normal. This latter rise might have been due either to the impurities and organisms in the solution injected or to the presence of the alkali, resulting in a rise in the number of the lymphocytes as suggested by Bastedo (5). No hemolysis occurred after any of the injections.

There was noted a slight decrease in the specific gravity and total protein values after the injection, probably due to the dilution effect of the injected solution. No significant changes occurred in pulse rate, respiration rate, and body temperature. No increase in peristalsis was noted in any of the horses.

The coagulation time was lowered following the intravenous injection of sodium bicarbonate. The percent of reduction based on the coagulation time before the injection and the greatest drop after the injection was 38.11. This greatest decline as compared with the control horses indicates that the effect of sodium bicarbonate on the coagulation time is not significant. In one horse a marked diuresis occurred with the urine becoming much clearer 105 minutes after the injection and with the specific gravity reduced from 1.029 to 1.012. Other than in this case no unusual clinical symptoms were noted during or following the injections.

Summary

1. The intravenous injections of large amounts of hypertonic sodium bicarbonate solutions into horses resulted in a

moderate increase in the white blood cell count in 24 hours and a temporary reduction in hemoglobin values.

2. A definite diuresis occurred in one of the horses.

3. No clinical symptoms were observed during or following the intravenous injection of sodium bicarbonate in the horse.

SODIUM CACODYLATE

Sodium cacodylate was the earliest organic arsenic compound used in medicine. It has been sporadically used in treating anaplasmosis, influenza, pneumonia, chronic skin diseases, and anemias in animals with only questionable success. Experiments were undertaken to check its effects on the circulation and body of the horse.

According to Milks (51), Sollmann (71) and Edmunds and Gunn (19) the action and uses of sodium cacodylate are similar to those of other arsenic compounds. However, it has a feeble action because only small amounts of arsenic ions are released into the tissues. It is not easily dissociable; it contains less arsenic which is liberated more slowly and therefore sodium cacodylate is less toxic than other arsenic compounds. Sodium cacodylate is eliminated, mainly unchanged, in the urine but also in the sweat and breath giving both a garlic like odor. The recommended therapeutic dose for the horse is 45 to 90 grains, Milks (51), Ingmand (35). However, in anaplasmosis in the bovine as much as 200 grains are given in a single dose. Since sodium cacodylate gives a more prolonged but feeble and

non toxic reaction in the body more efficient arsenic compounds have practically eliminated the use of sodium cacodylate in clinical veterinary medicine.

Excessive doses were toxic due to the excess ionic arsenic released and produced typical symptoms of arsenic poisoning. In humans large doses have been reported to cause albuminuria and hematuria due to the production of an acute nephritis. Sollmann (71) stated that given intravenously in the human it produced fibrosis of the vein in nearly every case. Sodium cacodylate is generally given intravenously in horses as it is rapidly reduced in the alimentary tract.

Eight intravenous injections of ten grams (150 grains) of sodium cacodylate in 50 cc to 150 cc of distilled water, 6.6 percent to 20 percent concentrations, were given to five horses at room temperature and at rates of from 50 cc to 100 cc per minute. No hemolysis and no reaction occurred in any of the horses after the injection except for one horse which developed a phlebitis that persisted for several days. No significant changes were noted after the injection in the pulse rate, respiration rate, body temperature, hemoglobin value, white blood cell count, specific gravity and total protein values. One horse received four daily injections with no untoward symptoms except a marked decline of 42 percent in the red cell count, with a decrease in the red cells from 8,250,000 to 4,710,000 per cc in five days.

No significant trend or decline in the coagulation time

was noted except in the horse developing the phlebitis. The coagulation time in this animal was nine minutes before the injection and dropped to one and one fourth minutes 30 minutes after the injection with a markedly abnormal rise in 24 hours. The percent of drop in coagulation times based on the average coagulation time before the injection and the greatest decline after the injection was 43.44. This greatest decline occurred on an average 55 minutes after the injection.

Summary

1. Sodium cacodylate in 150 grain doses had little if any effect on the circulatory system or on the body of the horse. In one horse a marked phlebitis developed, in another given four daily injections of ten grams of sodium cacodylate the red cell count dropped 42 percent by the fifth day.

OXALIC ACID AND AMMONIUM OXALATE

Oxalic acid which previously had no use in therapeutics has been described by Steinberg and Brown (73) and Miller and Davies (52) as an agent which when injected intravenously would produce a marked lowering of the coagulation time. Experiments were undertaken to check their results and to check further the effect on the body of the horse. A few experiments with the related drug, ammonium oxalate, were also undertaken to check its effect.

Howell (32) stated that a .1 percent or more concentrated

solution of sodium, ammonium or potassium oxalate with blood in vitro would prevent coagulation by precipitating calcium as insoluble calcium oxalate. Except for this use and that effect on coagulation mentioned above no further therapeutic uses for the oxalates or oxalic acid are known. Oxalic acid and the oxalates have an acid action in the body causing symptoms of poisoning; this action being due to the power of these agents to precipitate calcium from the tissues. Intravenously these agents in large doses affect the central nervous system by stimulation causing nervous twitching, tetany, convulsions and finally paralysis, Sollmann (71), Bastedo (5), and Edmunds and Gunn (19). The medullary centers are especially affected producing a rise in the body temperature, rapid deep respirations, salivation, incoordination, vomiting and nausea. Death is usually due to respiratory paralysis except in large doses when a paralysis of the heart muscle may occur. If death does not occur, practically all the oxalates are excreted in the urine in the form of calcium oxalate. This compound may and often does precipitate in the tubules of the kidney, producing congestion and inflammation; in severe cases due to the nephritis an anuria may result. Sollmann (71) stated that oxalates increase the tone and pendulum movements in excised intestines.

Steinberg and Brown (73 (44) found that various plant extracts accelerated the rate of coagulation of blood after intravenous injections in 500 patients. Further work showed that the active agent causing this reaction was oxalic acid.

Following this finding over 1000 persons were injected with small amounts of oxalic acid, three milligrams, to hasten the coagulation time of their blood. It was found to be non toxic and effective inside of five minutes to both normal patients and to those suffering from hemophilia, purpura, gastric ulcers, hemorrhage following childbirth or surgery, lung and kidney infections, obstructive jaundice, and vitamin K deficiency. They also showed that normal human blood had approximately 5.5 to 7.5 mg of oxalic acid per 100 cc. If this concentration fell, a longer coagulation time resulted but if this value rose the coagulation time was shortened. The reason or theory for its action was not advanced. Miller and Davies (52) reported on the use of a five percent oxalic acid solution in horses and dogs and they recorded a marked reduction in coagulation time in a limited number of cases. Stapleton (72) reported marked reductions of coagulation times using one grain of oxalic acid to 100 cc of distilled water in small animals and a five percent oxalic acid solution in large animals. Foster (23), 1940, reported on work with oxalic acid and stated that over a wide range of dosage oxalic acid had no effect on coagulation time until a sufficiently high dosage had been reached at which point clotting was delayed. This report, together with the fact that few if any reports by other workers have entered the literature since 1939, tends to indicate that the value of oxalic acid was possibly overrated by Steinberg and Brown (73). Moreover it is rather difficult to envision how the addition of

such a small amount of oxalic acid as three milligrams or one grain is going to have any effect on the coagulation time of blood when the blood already contains 5.5 to 7.5 mg of oxalic acid per 100 cc.

Ten injections of 100 cc to 200 cc of the five percent oxalic acid solution as recommended by Miller and Davies (52) were administered intravenously to nine horses at rates varying from 75 cc to 125 cc per minute. Four injections of five grams of ammonium oxalate in 150 cc to 200 cc of distilled water were given to four other horses. Only slight reactions including restlessness, excitement, slight salivation, and defecation occurred in most of the horses given the 100 cc of five percent oxalic acid and the ammonium oxalate solutions. The larger injections of 200 cc of five percent oxalic acid solutions produced in general more severe reactions including: excitement, quivering, distress, colicy pain, pale mucous membranes, staggering, falling down, rising in ten to 30 minutes, sweating, fast deep respirations, increased peristalsis, and defecation with a return to normal in one to two hours. In several cases a moderate phlebitis developed in the injected vein, probably due to the corrosive irritating action of the oxalic acid. In one weak emaciated horse having a red blood cell count of 2,250,000 and a coagulation time of 78 minutes an injection of 100 cc of a five percent oxalic acid solution produced death in two to five minutes due to apparent heart failure. Evidence of a mild nephritis appeared in the urine of one horse with

oxalates, albumin, and lowered specific gravity. Another case developed bilateral nasal hemorrhage after the injection of 200 cc of five percent oxalic acid.

Following the intravenous injections of oxalic acid and ammonium oxalate there was a marked rise in the pulse rate and a definite rise in the respiration rates.

The red blood cell count was decidedly increased ten minutes after the injections of both solutions, so much so that the increased proportion of red cells to serum could be observed in the test tube. The white blood cell count was also increased after the injection of the ammonium oxalate solution. These red and white cell counts usually returned to normal 30 minutes to two hours after the injection. Injection of ammonium oxalate solution caused a slight increase in hemoglobin values after the injections; this effect was not noted after the injection of oxalic acid. Injections of the latter caused a moderate general rise in temperature noted ten minutes after the injection. No significant changes were observed in the specific gravity and total protein after the injection of either agent. No hemolysis was observed.

In the experiments with ten horses injected with five percent oxalic acid there was a decline of 56.6 percent in the coagulation time based on the coagulation time before the injection and the greatest drop in coagulation time after the injection. This occurred on an average one hour after the injection. A decline of 51 percent in the coagulation time

occurred after the injection of the ammonium oxalate solution. The coagulation time curves especially of the ammonium oxalate solutions were rather irregular. The trend of coagulation time for oxalic acid was more regularly downward than ammonium oxalate with a gradual rise after two to four hours reaching normal in 24 hours or more. Occasionally 24 to 72 hours after the injection the coagulation time experienced an abnormal rise.

Summary

1. Oxalic acid is irritative and corrosive if injected into the tissues around the vein and occasionally caused a local phlebitis when injected intravenously.

2. Oxalic acid in 100 cc to 200 cc doses of a five percent solution recommended by Miller and Davies (52) is often toxic especially to weak subjects.

3. Oxalic acid solutions caused a lowering of the coagulation time for approximately four hours after the injection but it was not as efficient and was more toxic than other intravenous agents that lower the coagulation time.

4. Ammonium oxalate caused a brief rise and then a sudden drop in coagulation time with little indication of a general trend in the coagulation curve.

5. Injections of oxalic acid frequently caused increased peristalsis and defecation, more pronounced after larger, more toxic doses.

6. Both oxalic acid and ammonium oxalate produced a

temporary rise in the number of red cells per cc of blood immediately after the injection.

7. Oxalic acid in doses recommended tended to produce varying degrees of nephritis.

MAGNESIUM SULPHATE

Magnesium sulphate solutions have been used intravenously as a sedative and narcotic especially in tetanus. Lately it has been combined with chloral hydrate and has been used as a general intravenous anesthetic and narcotic. The experiments with horses were undertaken to check the effect of moderate and large doses of magnesium sulphate on the circulatory system and the body.

Magnesium is essential to life and is closely related to calcium metabolism. It is normally present in blood serum to the extent of one to three milligrams per 100 cc. Magnesium, as is calcium, is closely associated with nerve and muscle responses. Magnesium sulphate is a common magnesium salt used mainly for its purgative action when given orally. After intravenous injection magnesium sulphate is eliminated mainly in the urine and therefore it is contraindicated in kidney diseases. According to Milks (51), Meltzer and Auer in 1905 discovered the anesthetic action of magnesium salts and advocated magnesium sulphate solutions for nerve blocking, and general anesthesia either by intravenous or subcutaneous injection. Magnesium salts have a "curare like" or paralytic

action on the motor nerve and plates in the muscles. They have a marked depressant action on the central nervous system but the salts do not penetrate the brain and act as volatile anesthetics. Sollmann (71) stated that due to this direct central depression a complete loss of consciousness and surgical anesthesia could occur with incomplete motor paralysis; however, this state was difficult to obtain. Magnesium sulphate has not been in general use as an intravenous anesthetic as the effective dose for general anesthesia is near the fatal dose. It has proven useful in treatment of tetanus to cause a relaxation of muscles which effect lasts for 24 hours, Milks (51). Magnesium sulphate has also been used in other conditions such as eclampsia, grass tetany, and chorea in animals. Magnesium sulphate has been combined with chloral hydrate and given intravenously as a general narcotic and anesthetic (12). The dose as advised in this abstract was ten grams of each per kilogram of body weight in a five to ten percent aqueous solution. This mixture was claimed to hasten the appearance of anesthesia, to increase its depth and to reduce to a minimum the toxicity of chloral hydrate by its "decongesting" properties that favored diuresis, elimination of toxins and in particular the prevention of pulmonary complications. It was also held that this anesthetic combination did not provoke any harmful modification of the pulse, respiration, coagulability of the blood or leucocytic defense.

Magnesium sulphate injected intravenously in moderate

doses was claimed to have a diuretic effect, Milks (51). Hypertonic solutions caused a slight but definite drop in cerebral spinal fluid pressure, Bastedo (5). In rabbits, according to Sollmann (71), the injection of magnesium sulphate lowered the body temperature and caused renal irritation as evidenced by hyaline casts in the urine. In the dog intravenous injections caused a lowering of blood pressure and a dilation of the splanchnic organs and vessels, Haury (28).

Toxic intravenous doses of magnesium sulphate were manifested early by depression of respirations, analgesia, anesthesia, and curare like paralysis of motor end plates. A rapid injection rate caused death due to direct paralysis of the heart rather than to paralysis of the respiratory muscles.

Five injections of 500 cc of ten and 20 percent solutions of magnesium sulphate were given at room temperature to four horses at rates of 100 cc to 125 cc per minute. There was noted a decrease in the hemoglobin value following the injection of the ten percent solution and a definite increase in hemoglobin value following the 20 percent solution. In two injections there was an increase in red blood cells and white blood cells five minutes after the injection, which was probably due to a concentration of the blood because of a loss of fluid into the tissues. The hypertonic salt solution first caused a hydremia which then rapidly resulted in a secondary loss of fluid from the blood into the tissues. The specific gravity and total protein of the blood serum were definitely increased

after the injection of the 20 percent magnesium sulphate solution but there was no significant change after the ten percent solution was injected. No hemolysis occurred after any of the injections.

The pulse rate was slightly increased after the ten percent injections of magnesium sulphate but markedly increased after the 20 percent injections. The respiration rate was only slightly increased after the ten percent solutions were injected but decreased and were deeper after the 20 percent solutions. This seemed to indicate that the toxic or anesthetic dose was being reached in these latter solutions. The temperature was only slightly elevated five minutes after the intravenous injections of magnesium sulphate solutions. Only slight nervousness and elevation of the tail followed by a mild depressant action occurred in the horses given 500 cc of a ten percent magnesium sulphate solution, while those given the 20 percent solution staggered and fell down, rested quietly, had deep respirations and regained their feet in 20 to 30 minutes but remained lethargic for several hours. In the experiments it was attempted on several occasions to produce surgical anesthesia in horses by the intravenous injection of 20 percent magnesium sulphate solution, but the dose proved fatal due to respiratory paralysis before anesthesia had occurred. In one case 1300 cc of a 20 percent solution was given in a period of one and a half hours before death occurred. Thus it seems improbable that magnesium sulphate can have a beneficial effect

in preventing pulmonary complications when combined with chloral hydrate.

Hypertonic solutions of magnesium sulphate in a limited number of cases showed a definite tendency to lower the coagulation time of the blood. The percent of decline in coagulation time based on the coagulation times before the injection and those taken after the injection at the point of their greatest decline was 66.29. This greatest drop occurred approximately 85 minutes after the injection. This decline lasted for two to three hours before beginning to rise to normal.

Summary

1. Hypertonic solutions of magnesium sulphate injected intravenously caused a marked decline in the coagulation time of blood, the effect lasting for two to three hours.

2. Horses readily tolerated 500 cc of ten percent or 300 cc of 20 percent magnesium sulphate solutions without showing any marked depressant symptoms. Injections of 1000 cc of 20 percent solutions were very near the toxic or fatal dose.

3. Satisfactory surgical anesthesia with magnesium sulphate solutions was not obtained.

CHLORAL HYDRATE

Chloral hydrate is one of the most common drugs used intravenously in horses to produce narcosis or anesthesia for surgical operations. It is also used as a narcotic in tetanus,

strychnine convulsions, and painful colics. The experiments undertaken were to check its effect on the circulatory system and the body of the horse.

According to Milks (51) chloral hydrate was introduced as a narcotic by Liebreich in 1869. Since the drug has irritating properties it cannot be injected subcutaneously or intramuscularly and one must rely on the oral, rectal, or intravenous route. The first is most popular in human medicine, the last with horses since the rate and depth of narcosis or anesthesia can be easily controlled.

In moderate doses the use of chloral hydrate is considered safe, Alstead (1), Milks (51), and Bastedo (5). It acts by depressing the cerebrum without appreciably affecting the respiratory or circulatory systems and produces a prompt deep sleep lasting for several hours. Narcosis by chloral hydrate is strictly physiological in that there is a diminished attention to external stimuli and the animal awakens with no depressant effect. However, in these moderate amounts there is no marked abolishment of pain. A profound narcosis must be reached before there is any diminution of painful stimuli. According to Bastedo (5) the horse can tolerate in proportion to its size more chloral than can man.

The average moderate intravenous dose for the horse is considered to be about one to two ounces in a seven to ten percent solution given slowly, Krill (42) and Ingmand (35). Fowler (24) stated that the average horse can be given two

ounces orally and then two to four ounces intravenously to produce deep narcosis. Krill (42) and Ingmand (35) stated that chloral is contraindicated in old debilitated horses. Sollmann (71) mentioned that in cats a sudden stoppage of the heart may occur from relatively small doses of chloral under the influence of excitement. This condition has also been noted in humans. According to Milks (51), Sollmann (71), and Bastedo (5) fairly large doses of chloral hydrate depressed all centers including motor centers, caused deep narcosis, lessened reflex excitability, and depressed respiratory and vasomotor centers in the medulla. In this dose it served as an anesthetic for operations. There was no effect on the peripheral nerves. Often these large doses caused irregular feeble respirations, and depressed the heart so that the pulse became slower, softer, and weaker. The peripheral arteries were dilated due to depression of the arterial muscles. Peripheral arterial dilation together with decreased muscular movements and depression of the heat producing center caused chloral to be a marked antipyretic. Chloral hydrate was eliminated chiefly by the kidneys as non toxic urocholic acid. Sollmann (71) stated that excised intestines developed slow but strong contractions following immersion in a fairly strong solution of chloral hydrate. Fowler (24) noted that an occasional phlebitis and distention of the vein occurred following intravenous injection of chloral hydrate in horses.

Bastedo (5) stated that chloral is contraindicated in

humans suffering from failure or threatened failure of the circulatory system, depressed states of respiration as in pneumonia, and in uremia or acute nephritis. As mentioned previously the toxic dose of chloral varied with the individual animal. For the horse Fowler (24) stated the maximum dose to be six ounces divided into a two ounce dose orally as a basal narcotic and four ounce dose given very slowly intravenously to prevent cardiac failure. Milks (51) stated the fatal dose for the horse varied from five to eight ounces. The margin of safety with chloral was narrow and a toxic dose caused paralysis of the respiratory center and death due to respiratory failure. Artificial respiration was usually of no avail as the circulatory centers were also severely depressed and the circulation was feeble. Toxic doses lowered blood pressure by direct depression of the heart muscle, of the vasomotor center, and of the arterial muscles, Amadon (3) and Milks (51). The toxic symptoms closely resembled chloroform poisoning.

In the experiments with chloral hydrate, 11 horses were given 12 intravenous injections of one half to three ounces of chloral hydrate in 100 cc to 1000 cc of distilled water. The strength of the solutions varied from six to 24 percent and were given at rates of 66 cc to 200 cc per minute. A slight average increase in the hemoglobin value of .61 g per 100 cc of blood occurred after the injection. This rise was more marked in the horses given the larger amounts of chloral. Only two of the injected horses showed slight degrees of hemolysis;

these two received two and three ounces of chloral respectively. After each of four injections the red blood cell and white blood cell counts showed a definite rise that lasted for several hours. No significant changes were noted in the specific gravity or the total protein values after the injections.

The coagulation time in all of the horses except in those given three ounces of chloral showed a definite decline. The average decline based on the average coagulation time before the injection and the average greatest drop in coagulation time after the injection was 68 percent. This greatest drop occurred approximately 60 minutes after the injection. The decline lasted for nearly eight hours after which the coagulation time gradually rose to normal in 24 to 48 hours.

It was noted in two of the 11 horses in the experiment that several hours after the injection of two ounces of chloral the struggling and effort associated with rising produced apparent heart failure and death. One subject was an aged but strong mule and the other a strong five year old horse. Possibly certain horses or animals are more susceptible to chloral hydrate than others. This fact was also suggested by Bastedo (5). In normal horses it was noted that the larger the dose of chloral the longer was the period of narcosis and the greater was the reduction in the body temperature. Also it was noted that the pulse was accelerated immediately after the injections and the respirations were definitely slowed. In the experiments two horses that were given three ounces of chloral hydrate defecated

frequently for 30 minutes after the injection with the feces becoming progressively more fluid. One pony given one ounce of chloral in 250 cc of distilled water developed a marked phlebitis with distention of the vein.

Summary

1. The tolerance of horses to chloral hydrate varied depending on age, condition, and afflictions, being more toxic for the old debilitated horses with degrees of heart weakness. Struggling or excitement of these horses under chloral produced heart failure in several cases.

2. Chloral hydrate in moderate doses of one to two ounces in 250 cc to 500 cc of distilled water caused a definite decrease in the coagulation time of the blood.

3. Chloral hydrate solutions injected intravenously caused an increase in hemoglobin, red and white blood cell counts, and pulse rate; and a decrease in respiration rate and body temperature most noticeable in the two to three ounce injections.

4. Following anesthetic doses of chloral hydrate there was a definite reduction in body temperature.

CALCIUM GLUCONATE

Calcium gluconate is one of the most common drugs used intravenously in veterinary medicine. Since its introduction as a specific cure for milk fever in cattle by Greig in 1930,

it has been widely used for this and for other conditions in cattle and horses such as hypocalcemia, tetany, eclampsia, acetonemia, and purpura hemorrhagica. It is commonly prepared in a 20 percent solution with four percent boric acid forming in reality calcium di-boro-gluconate and mono-boro-gluconate which in the body readily reverts to calcium gluconate and boric acid, Stewart and MacPherson (74). Calcium gluconate was used in these experiments instead of calcium chloride because it is less apt to produce heart block, Krill (42), Jones and Hewitt (38) and is less apt to produce sloughing if injected outside the vein. Therefore calcium gluconate has been universally adopted by veterinarians in the field.

Calcium is essential to life and is normally present in all tissues of the body. In the horse the concentration of calcium in the serum is nine to 14.8 mg per 100 cc and the ionic portion of this calcium plays an important part in the coagulation of blood, Dukes (18), Ferguson (21). In the tissues calcium decreases the irritability of nerves, the permeability of cells and capillaries, and favors dehydration. According to Sellmann (71) and Milks (51) slight decreases in the amount of calcium caused a mild increase in the irritability and a slight decrease in the strength of all neuromuscular tissues; thus a decrease of calcium in the muscles may lead to spontaneous fibrillary twitchings, jerkings, or convulsions. As the amount of calcium approaches zero the irritability of the neuromuscular tissues disappears and complete paralysis

that may produce death results.

A slight increase in calcium lessens the irritability of neuromuscular tissues but increases the strength of contraction. Following intravenous injections of calcium the systolic blood pressure falls, a slowing of the heart occurs, but shortly the rate becomes accelerated and the blood pressure rises. Its action is somewhat like that of digitalis with acceleration and strengthening of the heart beat, Bower and Mengle (8), Bastedo (5). Calcium gluconate should not be given to digitalized animals as it is quite toxic to them. Larger intravenous doses of calcium gluconate may produce, due to its depressant effect on nerve and muscle tissues, toxic symptoms such as cardiac weakness, tachycardia, extrasystloes, fall in blood pressure, atrioventricular block, paralysis of respiration, and death due to ventricular fibrillations, Bastedo (5), Sollmann (71).

The average dose of 20 percent calcium gluconate for the cow is 250 cc to 500 cc, Milks (51). Calcium gluconate should be injected slowly especially to patients affected with heart weakness or a lowered blood pressure, as rapid administration brings on toxic symptoms from doses that when given slowly are harmless, Krill (42), Bastedo (5). Bower and Mengle (8) stated that when calcium gluconate was given at the rate of $\frac{1}{2}$ cc per minute about nine to 12 times as much could be given as when the drug was injected at the rate of 60 cc per minute. The hypercalcemia produced by injection of calcium gluconate lasted for several hours. Bastedo (5) stated that in humans the intravenous injection was accomplished by a momentary intense feeling

of heat over the body and occasionally nausea and vomiting. This latter symptom was also noted in the dog. Most of the calcium gluconate injected intravenously is eliminated in the urine. It produces an acidosis of the blood and thus produces a secondary diuretic effect by displacing the sodium chloride and water and eliminating them through the kidneys, Bastedo (5), Edmunds and Gunn (19). Because of this diuretic effect, usually achieved only in large doses, it has been advocated as a treatment for edema, pleural effusions, and ascites. However, according to Sollmann (71) it is contraindicated in certain types of nephritis. Morris and Rogen (56) stated that the therapeutic doses in humans have little diuretic effect; in excessively large fatal doses anuria may result, Edmunds and Gunn (19).

According to Jones and Hewitt (38) calcium gluconate caused a definite stimulation of the intestinal musculature in therapeutic doses in dogs. Bastedo (5) also stated that calcium salts increased the tone and peristalsis of the intestines and reduced the irritability of the bowel. Sollmann (71) stated that calcium gluconate stimulated phagocytosis. Calcium also plays a very important role in decreasing the permeability of cells and capillaries in the body. Because of this property calcium gluconate had been advocated in treating purpura hemorrhagica, Udall (78), on the theory that purpura was of the nature of an anaphylaxis and calcium has the antianaphylactic action of decreasing the permeability of capillaries.

Also because of this action calcium gluconate has been used in urticaria, eczema, skin rashes, and other allergic conditions but according to Bastedo (5), Edmunds and Gunn (19), and Lewitus (45), with questionable results as it is difficult to evaluate the effect of calcium in these latter rather transient conditions. During the experiments one case of urticaria in a horse was treated with 500 cc of calcium gluconate with recovery in 12 hours.

The ionized calcium in the blood is the small portion of the total amount of calcium in the blood serum that is essential for the production of clotting, Dukes (18). However, recent work has tended to show that clotting may occur in the absence of calcium under certain conditions, McLeod (48), Mellanby and Pratt (50). According to Bastedo (5) in wasting diseases such as obstructive jaundice, the lowering of the protein in the serum also caused a lowering of the ionic calcium with an increase in the coagulation time of the blood even though the total calcium may have been in the normal range. Thus he claimed that intravenous injections of calcium gluconate in certain conditions would produce a lowering of the coagulation time; however, he stated that it had no effect in hemophilia or purpura hemorrhagica. Sollmann (71) also cited Velden who stated that the coagulability of blood is increased for a short time after calcium injections. However, Crane and Sanford (15) and Milks (51) questioned whether an excess of calcium would cause an increased coagulability of the blood. Edmunds and Gunn (19) stated that the viscosity of blood was increased

in hypercalcemia. It is generally considered among many veterinary practitioners and clinicians that calcium gluconate has a favorable effect on increasing the rate of coagulation of blood. Possibly this effect is not due to the calcium entirely, but may be due to other factors. Occasionally intravascular clotting of blood in the jugular vein has been noted in extremely weak patients, especially bovines, and the cause for death in a very small number of these cases one to two hours after treatment might be attributed to blood thrombi loosening and passing into the pulmonary arteries.

Eleven intravenous injections of 250 cc to 1000 cc of 20 percent calcium gluconate were given at room temperature to ten horses. The rates of the injections varied from 62.5 cc to 150 cc per minute. In general the smaller injections of 250 cc to 500 cc of calcium gluconate produced no observable reactions and only slight changes in the blood, whereas the larger injections of 1000 cc to 3000 cc produced mild to marked physical reactions consisting of trembling, muscle tremors, yellow mucous nasal discharge, restlessness, slight colicy pains, lacrimation, protruding penis, and tenesmus. Most of these horses given the larger injections exhibited a marked increase in urination both in frequency and in quantity, and two-thirds of them defecated often, indicating a possible increase in peristalsis. One horse given 3000 cc of calcium gluconate showed symptoms as above with apparent anuria instead of diuresis. Also in these horses given the larger amounts the hemoglobin value, pulse rate, respiration rate, specific gravity and

total protein values, and red cell counts showed much greater increases than did those of the horses given the 1000 cc injections of calcium gluconate. The temperature changes and the white blood cell counts were not significantly changed in any of the horses.

The average increase of the pulse rate after all of the injections with calcium gluconate was 16.5 beats per minute; of the respiration rate 5.5 respirations per minute. Only relatively slight average increases occurred in the specific gravity or total protein values, with an average increase of 560,000 cells per cc in the red blood cell counts. The urine of one horse showing a marked diuresis after the intravenous injection of 3000 cc of calcium gluconate became acid in reaction, pale and clear in color, low in specific gravity, and was positive to Benedicts sugar test due to the gluconic acid present in the urine. The other horse given the same amount developed an anuria. The calcium value of the serum of the horse given 2000 cc of calcium gluconate before the injection was 10.04 mg per 100 cc, five minutes after the injection this value was 28.60 mg, and in 50 minutes it was 25.7 mg per 100 cc of serum. In a horse given 3000 cc of calcium value before the injection was 11.21 mg and five minutes after the injection it was 33.0 mg per 100 cc of serum.

The coagulation time in all of the horses following the intravenous injection of calcium gluconate decreased. This decline was generally more noticeable after the larger injections

of 500 cc to 3000 cc. The average percent decline of all injections based on the coagulation time before the injection and the greatest drop in coagulation time after the injection was 66.9. This greatest drop occurred approximately 45 minutes after the injection. The lowered coagulation time lasted for two to three hours and then rose gradually and in 24 hours had returned to normal coagulation time.

Summary

1. A definite drop in coagulation time occurred in all cases, lasting two to three hours and rising to normal in 24 hours.

2. Amounts of calcium gluconate up to 2000 cc given at the average rate of 108 cc per minute had little clinical effect on the circulatory system of the horse except for mild increases in the pulse and respiration rates, and trembling and slight diuresis in some cases.

3. Excessive amounts, 2000 cc to 3000 cc of calcium gluconate, injected intravenously in the horse given at the average rate of 108 cc per minute tended to produce more severe and slightly toxic reactions. The calcium concentration reached 25 to 33 mg per 100 cc of serum without dangerous or extremely toxic symptoms developing.

4. Rapid intravenous injections of calcium gluconate, from 60 cc to 150 cc per minute, produced no clinical symptoms in normal horses.

FORMALIN SOLUTIONS

Formalin solutions have been used intravenously in horses rather empirically for treating purpura hemorrhagica, and septicemia. These experiments were undertaken to check the effect of formaldehyde solutions on the bloodstream and the body. In these experiments fresh formalin solution which is a 40 percent solution of formaldehyde in water was used and it in turn was diluted by distilled water to various concentrations.

Formaldehyde combines chemically with an exceptionally large number of organic substances including proteins causing a coagulation of the protein. Because of this characteristic, formalin solutions are very irritating to mucous membranes and other tissues with which it comes in contact, making its use on the body in general inadvisable, Sollmann (71). Formaldehyde prevents or retards the coagulation and spontaneous laking of blood in vitro in proportions of 1:200 or 1:400 with blood. Sollmann (71) stated that intravenous injections of this drug in concentrations of 1:5000 had no physiological effect on the body, and experiments by Maquire in 1900 with the intravenous use of dilute formalin solutions were abandoned. In the body formaldehyde is mainly oxidized in the tissues to formic acid or methenamine, and only in excessively large doses is formaldehyde, as such, eliminated in the urine. Also according to Sollmann (71) the fatal dose of formalin for mammals given intravenously is .08 to .09 g of formalin per kg

of body weight. On this basis the fatal dose of formalin for the average 1000 or 1100 pound horse would be 85.5 cc to 112.5 cc.

In equine practice formalin solutions have been used for treating purpura. Udall (78) stated that Imrie used eight to 12 cc of formalin in a two to three percent solution successfully for over 20 years in treating purpura. Various practitioners vary this dose from 4 cc of formalin in 40 cc of distilled water to 16 cc in 120 cc of distilled water and repeat the treatment if indicated. There has been no scientific explanation for the beneficial results obtained in purpura hemorrhagica by the formalin treatment. Possibly the results of the experiments undertaken will partially explain this action. According to Milks (51) McClelland advises 4 cc of formalin in a quart of water for treating septicemia conditions. Also formalin solutions have been used by certain practitioners in treating flatulent colic in doses of 8 cc to 10 cc in 40 cc of water.

Twenty-two intravenous injections of four percent to 12 percent formalin solutions were given to 19 horses. The amount of formalin injected varied from 4 cc to 50 cc in solution with 40 cc to 500 cc of distilled water. These injections were given at room temperature at rates varying from 40 cc to 125 cc per minute with the average rate being 90 cc per minute. The reaction of the horses' bodies to formalin solution varied with the amount of formalin injected, the rate of injection, and the concentration of the formalin solution. The smaller amounts of formalin, 4 cc to 8 cc, caused relatively slight

reactions including restlessness, lacrimation, elevation of tail, slight salivation, and occasional defecation. The larger and more concentrated formalin solutions produced definite to marked reactions including lacrimation, salivation, nasal discharge, increased peristalsis with defecation, sweating, slight quivering to spasms of muscles, and severe abdominal pain and distress with tenesmus. One horse in poor condition given 50 cc of formalin in 500 cc of distilled water died 20 minutes after the injection with symptoms of suffocation; possibly the formalin solution was given too rapidly. These symptoms correspond very closely with those described by Andberg, Boyd, and Cole (4) of histamine and foreign protein shock produced in horses. In fact the similarity of symptoms was marked even to the deep abdominal type of respiratory dyspnea and the duration of the reaction. One difference, however, between the reactions produced by formalin and those produced in foreign protein shock is that the coagulation time is markedly lowered after formalin injections, whereas the coagulation time is prolonged in foreign protein or histamine shock due to the excessive mobilization of heparin from the liver, Howell (32).

The pulse was generally accelerated after all of the injections, but most markedly after the injections of the larger amounts of formalin; the average increase in the pulse was 19.5 beats per minute. The respiration rate showed only a slight average increase of 3.5 respirations per minute, but after the

larger injections of formalin the respirations were deeper and of the abdominal type. The body temperature showed a slight to definite rise especially 30 to 45 minutes after the injection and was most marked in the horses showing the greater physical reactions. The red blood cell count in eight of the horses showed a general rise immediately after the injection, which rise in 24 to 72 hours became very definite in five subjects. No hemolysis was noted. The white blood cell counts, hemoglobin, specific gravity, and total protein determinations underwent no significant changes.

There was a very definite drop in the coagulation time noted after each injection. The average percent decline in coagulation time in all of the injections based on the coagulation time before and the greatest drop in coagulation time after the injection was 75.18. This greatest decline occurred approximately 66.5 minutes after the injection. It was noted that the amount of formalin in the solution and not the concentration of the solution had the greater effect on the coagulation time. The larger amounts of formalin, over 16 cc, caused an 86.29 percent drop, the 8 cc to 16 cc amounts a 67.3 percent drop in the coagulation time. On this basis the larger amounts of formalin would be used to produce a lowering of the coagulation time, but since these solutions also produced the greatest reaction in the horse, the smaller amounts would be more advisable in practice. It was noted that the lowered coagulation time of the blood lasted for nearly 24 hours before

beginning to rise. In several horses the coagulation time had risen to above normal in 48 to 72 hours after the injections, (Plate III).

During these experiments 10 cc of formalin in 100 cc of water was used to control hemorrhage in two clinical cases. One purebred seven-year-old saddle mare affected with a chronic catarrh of the gutteral pouches developed a profuse nasal hemorrhage during the irrigation of the pouches. The other, an eight-year-old bay draft mare developed severe hemorrhage following the removal of an exuberant mass of granulation tissue too high on the forearm to bandage. In both cases the hemorrhage decreased and finally stopped five to ten minutes after the injection.

Summary

1. The clinical reaction on the horse produced by formalin closely resembles that of histamine or foreign protein shock.

2. The intravenous injection of 4 cc to 16 cc of formalin in solution produced a marked lowering of the coagulation time occurring immediately and lasting for nearly 24 hours.

3. The amount of formalin used and not the concentration of the solution determined the reduction in the coagulation time.

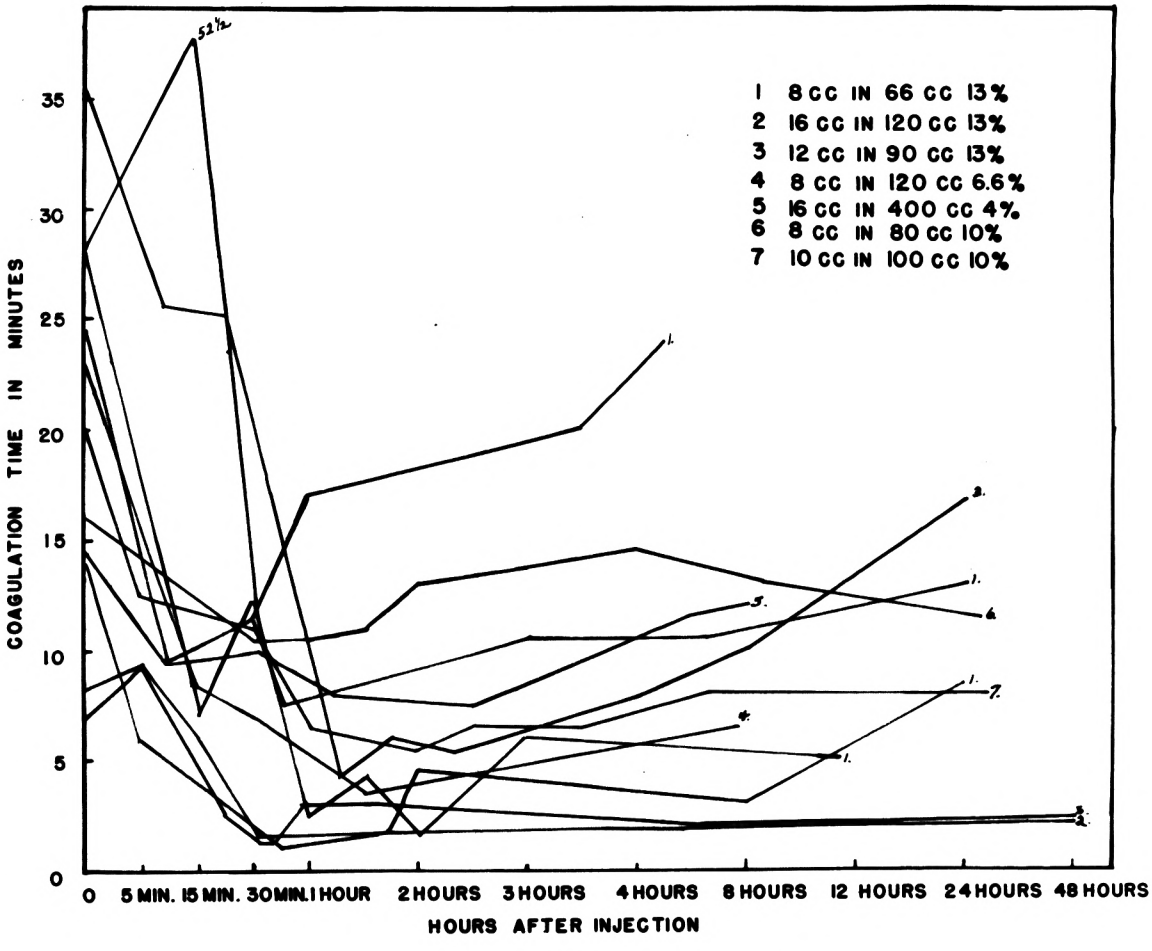
4. The slower the solution was injected, the less the physical reactions produced.

5. Following formalin injections the red blood cell count showed a general increase for 24 to 72 hours; however, this should be studied further.

EXPLANATION OF PLATE III

Graph of the course the coagulation time followed in eleven horses after the injection of 8 cc to 16 cc of formalin in 4 to 13 percent concentrations in distilled water.

PLATE III


1 8 CC IN 66 CC 13%
2 16 CC IN 120 CC 13%
3 12 CC IN 90 CC 13%
4 8 CC IN 120 CC 6.6%
5 16 CC IN 400 CC 4%
6 8 CC IN 80 CC 10%
7 10 CC IN 100 CC 10%
COAGULATION TIME IN MINUTES
0
5
10
15
20
25
30
35
0 5 MIN. 15 MIN. 30 MIN. 1 HOUR 2 HOURS 3 HOURS 4 HOURS 8 HOURS 12 HOURS 24 HOURS 48 HOURS
HOURS AFTER INJECTION

GELATIN

Gelatin is a common drug and a product that has been recommended intravenously in dilute solutions in combatting shock and in stronger solutions for reducing the clotting time of blood. Experiments were mainly run to check the latter effect in horses.

According to Milks (51), Dastre and Floresco in 1896 demonstrated the increased coagulability of blood after the intravenous injection of five percent solutions of gelatin. They demonstrated that it was an increased coagulability and not the solidification of the gelatin. Later it was shown that gelatin also had this stimulating power on the coagulability of blood after intramuscular injection; some practitioners have even reported this action after oral administration. Bastedo (5) reported that a one percent solution and Milks (51) that a two percent solution injected intravenously will cause decreased clotting time of the blood. The action of gelatin in producing this effect was not known; however, it was noted that the viscosity of the blood increased. Sollmann (71) stated that Zibell believed this coagulation reaction was due to the .6 percent calcium normally present in gelatin. Because of this stimulation of the coagulation properties of blood it has been used in hemorrhages, hemophilia, shock, and purpura hemorrhagica.

Gelatin has been used in shock, Milks (51), to replace lost blood volume and it proved superior to physiological saline

since its colloidal nature prevented rapid loss of the solution into the tissues. However, Sollmann (71) reported that a two percent gelatin solution may leave the blood as rapidly as saline solution, but under ordinary circumstances it does not. The gelatin is partly excreted in the urine. Recent work has shown that large intravenous injections of gelatin solution given intravenously may produce pulmonary distress by pulmonary distention and cardiac dilatation, Bastedo (5). Udall (78) reported excellent results from using gelatin subcutaneously in treating purpura hemorrhagica in the horse. Since gelatin is not a complete protein there is no danger of producing anaphylactic shock by repeated intravenous injections of gelatin solutions[1]. Bastedo (5) and Milks (51) warn against the general use of gelatin solutions subcutaneously without proper sterilization of the solution, as tetanus spores may sometimes be present. The chance for the production of tetanus by intravenous injection is small, but the possibility still exists, therefore the gelatin solutions should be sterilized in an autoclave at 15 pounds pressure for 20 minutes[2].

Recently many workers have reported experiments on feeding gelatin to humans and have reported that it caused a marked reduction in rate of muscular fatigue and a marked increase in the work output of persons regularly fed gelatin, Ray, Johnson, and Taylor (61) and Kaczmarek (39) (40). Therefore the intravenous use of gelatin might be of value in treating race horses

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1. Foltz, V.S. Kansas State College. Personal communication.
2. Bushnell, L.D. Kansas State College. Personal communication.

that have a tendency toward nasal hemorrhage both to increase the coagulability of the blood and possibly to reduce fatigue and increase work output.

In the experiments ten injections of gelatin solutions were given to seven horses. The solutions ranged from two percent to six percent in strength, and from 250 cc to 500 cc in volume. These were given intravenously at the average temperature of 105° F. The amounts of gelatin, Knox U.S.P., injected at any one injection ranged from seven grams to 30 grams. The rate of the injections averaged 93 cc per minute. No clinical reactions or symptoms were noted after the injection. No hemolysis occurred and the pulse rate, temperature, red blood cell and white blood cell counts, specific gravity and total protein values were not significantly changed. The respiration rate was slightly increased and the hemoglobin values slightly decreased. The coagulation time was definitely reduced, (Plate IV). The percent of decline based on the average time before the injection and the greatest decline after the injection was 76. The average time of the greatest decline was 32.4 minutes after the injection. This lowered coagulation time lasted about eight hours after which it rose gradually toward normal. In two horses given two and three injections respectively of unsterilized gelatin solutions three weeks to four months apart no signs of anaphylaxis or tetanus resulted.

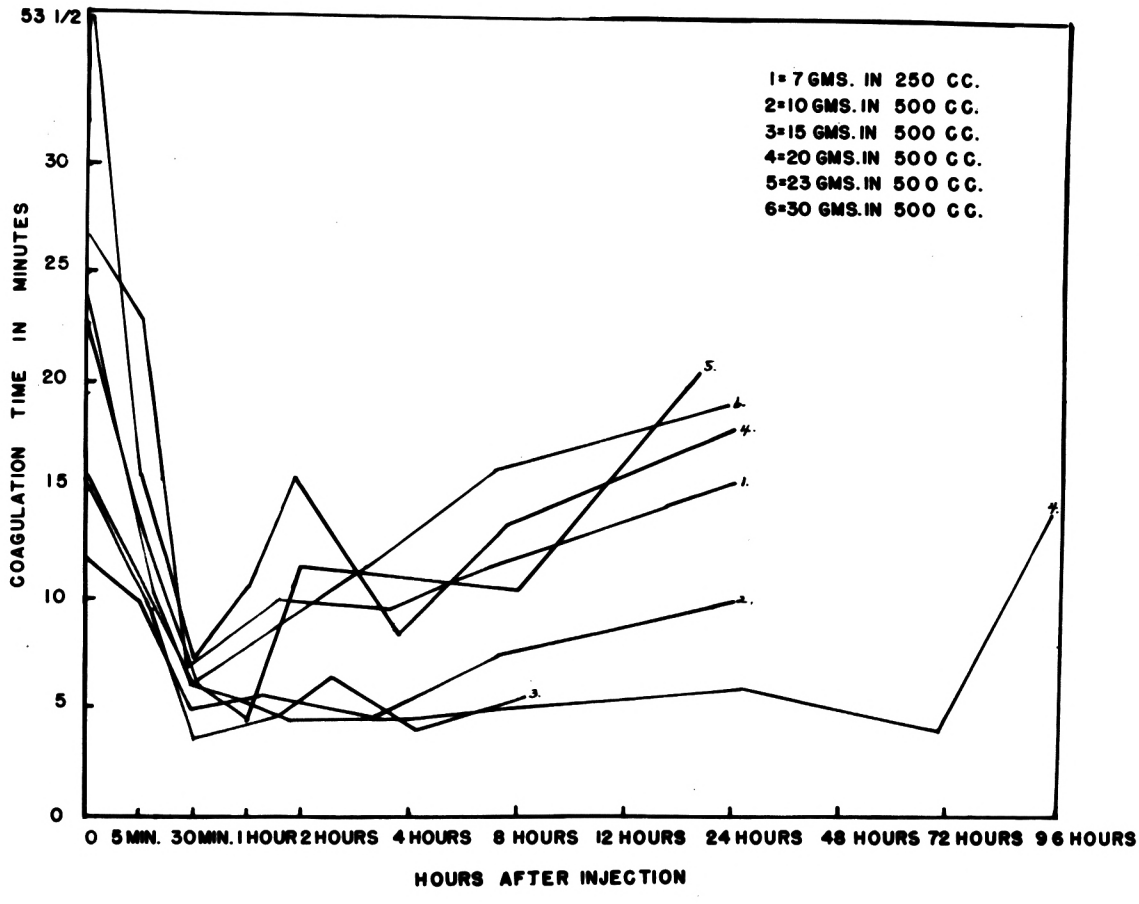
Summary

1. Gelatine solutions produced a marked drop in the

EXPLANATION OF PLATE IV

Graph of the course the coagulation time followed in seven horses after the injection of gelatin solution.

PLATE IV


53 1/2
30
25
20
15
10
5
0
COAGULATION TIME IN MINUTES
1= 7 GMS. IN 250 CC.
2=10 GMS. IN 500 CC.
3=15 GMS. IN 500 CC.
4=20 GMS. IN 500 CC.
5=23 GMS. IN 500 CC.
6=30 GMS. IN 500 CC.
0 5 MIN. 30 MIN. 1 HOUR 2 HOURS 4 HOURS 8 HOURS 12 HOURS 24 HOURS 48 HOURS 72 HOURS 96 HOURS
HOURS AFTER INJECTION

coagulation time occurring in 30 minutes and lasting for about eight hours.

2. No unusual immediate symptoms were noted after giving these solutions intravenously; neither anaphylactic symptoms nor tetanus occurred.

BLOOD TRANSFUSION

The Egyptians and Romans made crude attempts at transfusions, but it was not until 1492 that Doctor Gabets of Paris invented the first transfusion apparatus. Progress was rather slow in this field until the latter part of the nineteenth century and the first part of the twentieth century when the discovery of blood types, improved transfusion methods, and anticoagulants caused the marked rise in importance of blood transfusion in modern medical and veterinary therapy. Transfusion has been used successfully in many conditions including shock, hemorrhage, anemia, hemophilia, malnutrition, and severe infectious diseases such as purpura and infectious anemias.

There are two general methods of transfusing blood; first the direct method where the artery of the donor is attached to the vein of the recipient; since this is rather complicated and offers many technical difficulties the second or indirect method is largely used today. The indirect transfusion is performed by using either a syringe and cannula and rubber tubing or by two large needles and a connecting tube, Lyon (47), or by anticoagulants where blood is drawn and kept from clotting

by an anticoagulant such as hirudin, heparin, or sodium citrate and then at a later date is injected into the recipient. Sterile citrated blood may be stored ten days to two weeks and even up to 60 days with safety[1].

In transfusion therapy in humans it is very important to check the blood types of the donor and the recipient to be certain that the recipient's serum doesn't agglutinate the donor's blood cells. These well defined blood types are not found in domestic animals. Lyons (47) checked 100 horses and found essentially four blood groups based on their iso-agglutination properties, but stated that for all practical purposes these groups may be disregarded in transfusing blood. Amadon (2) in an excellent article stated that no shock or clinical symptoms were produced in transfusing blood in ordinary domestic animals but that occasionally symptoms of shock were produced when purebred dogs or horses were transfused. Koch (41) reported four cases of incompatible blood out of 21 transfusions in horses with symptoms as follows: trembling, sweating, lowered pulse rate and respiration rate, muscular weakness, and urination.

Following the injection of blood intravenously there was a rise in blood pressure depending on the amount of blood transfused and this rise was sustained since the blood colloids tended to prevent the excess volume from being rapidly eliminated, Dukes (18). If excessive amounts of blood were transfused

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1 Dr. Erwin, Oklahoma City. Personal communication.

a circulatory collapse might occur due to the failure of the right side of the heart. Koch (41) stated that in horses where no incompatability was observed following transfusion there was a slight increase in the pulse rate, and in the blood pressure lasting three to six hours with a one to two degree rise in body temperature.

Many workers advised injecting blood at approximately body temperature. However, Krill (42) and others (16) stated that there was less likelihood of producing shock in animals, especially sensitized animals, if chilled blood or serum was injected. Krill's advised rate of injection of blood or serum was 15 cc to 30 cc the first minute, then increased to 50 cc per minute thereafter. It still should be a practice to give blood or serums slowly and to watch the pulse, respiration and other clinical symptoms that might become apparent if the injection produced shock. This should hold true especially in giving serums and biologics intravenously to animals that are suffering from a disease or are sensitized to the product. Epinephrine should be kept handy for immediate use. Many serums on the market are pasteurized at 58 to 59° C. or 136.4 to 138.2° F. for 30 minutes. According to Reiche (62) pasteurization favors shock reactions. In all intravenous injections homologous serums are indicated.

Milks (51) and Bastedo (5) stated that in hemorrhage blood is frequently transfused to aid clotting by increasing the coagulability of the recipient's blood. Blood is superior

to saline in the restoration of blood volume because it restores the quality as well as the quantity of lost fluids. In hemorrhagic conditions such as sweet clover poisoning Amadon (2) noted a hastening of coagulation and a vasoconstrictor action after blood transfusion.

In the epxeriments five injections of 500 cc of citrated blood were given to five horses at rates of from 63 cc to 125 cc per minute at extremes of temperature from 32 to 150° F. The blood was injected 15 minutes to 24 hours after it had been collected from the donor. Since only 500 cc of blood was injected at a time, no cardiac embarrassment occurred in any of the horses. In our limited number of experiments with horses we noted no significant symptoms indicating shock during or following the transfusing of blood, even when a large draft horse's blood was administered intravenously to a pony at rates faster than generally advised by physiologists and clinicians.

There was a slight average increase of 4.66 beats per minute in the pulse rate; a definite increase in the respiration rate with an average increase in three injections of 18.33 respirations per minute. As with the saline injections, the chilled blood, 32° F., caused an average drop of .4° F. in body temperature, and heated blood, 150° F., in one experiment caused a rise of 1.6° F. Since serums or blood heated above pasteurization temperature are usually toxic when injected intravenously, interesting symptoms of shock were produced in one horse injected with overheated blood in which part of the

protein had coagulated. After the injection of about 200 cc to 250 cc of this blood the horse developed signs of shock including dyspnea, sweating, distress, defecation, falling down and rising after seven minutes; and returning to a normal attitude in 30 minutes. It was also noted in this horse that the blood cells settled out very slowly after the injection.

The coagulation time was checked before and after three injections of blood. The average decline in coagulation time based on the average decline before the injection and the greatest drop in coagulation time after the injection was 38.6 percent, which when compared with the controls was not significant.

Summary

1. A pint of blood may be transfused into horses with the temperature varying from 32 degrees to 138° F. with little or no effect on the animal except for a slight rise in pulse rate, a definite rise in respiration rate, and slight effects on body temperature.

2. The transfusion of 500 cc of blood caused no significant change in the coagulation time.

3. Injections of overheated blood, above 150° F., should be avoided as they produced symptoms of shock.

HYDROCHLORIC ACID SOLUTION

Hydrochloric acid in very dilute solution was advanced several years ago as an intravenous treatment for various

infections in human medicine. It has since been used for many infectious conditions in veterinary medicine such as mastitis, influenza, navel ill, metritis, nephritis, fistula, poll evil, canine distemper, osteomyelitis, open joints, periodic ophthalmia and other eye diseases, and puncture wounds. Hixon (29) highly recommended the hydrochloric acid therapy for puncture wounds.

The fact that very little if any controlled experimental work has been done on this type of intravenous therapy was brought out in a special article in the Journal of the American Medical Association, 1934 (36). This article stated that uncontrolled clinical work has been the basis of the advancement of this treatment for various infections. Sollmann (71) stated: "Since the action of this drug in the body cannot be accurately controlled, it seems to be an undesirable form of non specific therapy." However, many reputable veterinary clinicians of the author's acquaintance endorse the hydrochloric acid therapy for certain of the above mentioned conditions.

The therapy in horses consists of the intravenous injection of 200 cc to 500 cc of a 1:1000 to a 1:3000 solution of hydrochloric acid. Sollmann (71), Bastedo (5), and Ingmand (35) recorded that this therapy caused a flocculation of plasma proteins with colloidoclastic reactions including stimulation of leucocytosis and thus increasing the body resistance against infection. Bastedo (5) and Sollmann (71)

stated that this solution is strongly hemolytic due both to its hypotonicity and to the acid reaction, and the resulting hemolysis and alteration of blood colloids produced a foreign protein reaction. Fort Dodge Serum Company pamphlet (29) stated that this injection caused a shifting of the alkaline-acid balance of the blood with resultant increase in phagocytosis. Thus a bodily resistance to infection particularly subacute or chronic infections was markedly stimulated.

In the series of 23 experiments dilute hydrochloric acid solutions in concentrations of 1:100 to 1:2500 in amounts of 500 cc to 4000 cc were given intravenously to 11 horses. In making these dilutions concentrated hydrochloric acid, 33 to 35 percent, was used. For example, in making 500 cc of a 1:1500 cc concentration, 1 cc of concentrated hydrochloric acid was added to 500 cc of distilled water. These intravenous injections were given to the horses at room temperature at rates varying from 100 cc to 200 cc per minute. No clinical reactions to the injections were noted. No significant changes in pulse rate, respiration rate, body temperature, specific gravity and total protein values were noted after any of the injections. No hemolysis was observed. The hemoglobin values showed a slight average decline of .47 g per 100 cc of blood. This decline in hemoglobin was most noticeable after the injections of 1000 cc to 4000 cc of 1:2500 solution of hydrochloric acid. The coagulation time showed slight change with a 17.43 percent decline based on the average coagulation time before and the

average greatest decline after the injection. The average red blood cell count showed in general a slight to a moderate rise reaching its peak in 24 hours except in the horses given 1000 cc to 4000 cc of 1:2500 hydrochloric acid solution where no rise occurred.

It was noted in these series of intravenous injections in horses that no marked increase in leucocytosis occurred except in three horses affected respectively with cellulitis of the hind limbs, a periphlebitis due to the leakage of some hydrochloric acid solution around the vein on injection, and a fistula of the withers. In these horses there was a slight Schilling shift to the left. In fact, most of the injected horses showed a slight decrease in leucocytes after 24 hours. The injection of 500 cc of a one percent solution of hydrochloric acid produced no observable hemolysis or reaction. Since blood is rich in buffer salts it is difficult to envision how 1 cc or even 5 cc of concentrated hydrochloric acid could alter the acid-base balance as suggested by the Fort Dodge pamphlet (29). That hydrochloric acid therapy is beneficial in many cases of acute or subacute infection is unquestioned by many experienced clinicians.

Summary

1. Hydrochloric acid solutions did not cause a leucocytosis in normal horses.

2. A slight to moderate increase in the red cell count occurred after the injection and lasted for 24 hours.

3. No other significant changes occurred in the blood picture or body reactions following these intravenous injections.

4. These solutions injected subcutaneously or intramuscularly produced a marked tissue reaction.

MISCELLANEOUS OBSERVATIONS AND CONCLUSIONS

It was noted that the brief excitement incident to the confining of the horse in the stocks and inserting the needle into the jugular vein caused in many cases slight rises in pulse and respiration rates, so attempts were made to keep the horses quiet. During the injection of practically any material the horses often became slightly restless and would occasionally champ their jaws; these symptoms apparently had little significance. Repeated frequent or daily injection of nearly any drug or solution over a period of time tended to lower the hemoglobin value, red cell count, specific gravity and total protein values, and to increase the coagulation time. These results were especially noted in the horses given large and frequent intravenous medication of some of the more irritating, hypotonic and hypertonic solutions. If the injections were far enough apart, the above effects were not noted. A definite fact brought out in these experiments was that in giving large or near maximal doses of intravenous medicants to old, thin, or debilitated horses extreme care should be used. The injections should be given slowly and the patients' pulse, respiration, and physical reactions should be closely observed.

It was noted in many cases given near maximal doses of various intravenous medicants, especially those producing rather severe physical reactions, that there was a marked slowing of the sedimentation rate of the red blood cells. Since the red cells of horse blood normally settle rapidly, the sedimentation rate could easily be observed and a delayed sedimentation rate was noted after the following injections: 16 cc to 50 cc of formalin; overheated blood; large injections of a hypotonic solution; two ounces of chloral hydrate; two ounces of sodium citrate; and 200 cc of five percent oxalic acid solution. It was also noted in the horse suffering from urticaria. Of course, these observations were incidental to the experiments but in human medicine the sedimentation rate of red cells is an important diagnostic symptom. According to MacLeod (48) the rate of sedimentation depends primarily on the rate and degree of fouleaux formation of red cells and only secondarily on the red cell count, viscosity of plasma, and so forth. Thus the more rapidly the red cells form rouleaux the more rapidly do the red cells and serum separate. Apparently the plasma has the property of causing rapid or slow rouleaux formation but further work is based only on theory. Apparently in the above injections the substance in the plasma causing rouleaux formation was altered so that the sedimentation time was markedly reduced.

Following a surgical operation or the escape of some irritating substance outside the vein into the subcutaneous

or muscular tissue there was a marked rise in the white cell count with a shift to the left in 24 to 48 hours. Rosenvold and Miller (67) noted that during the summer months coagulation time in humans was shortened; it was further shown that temperature had a definite effect on the coagulation time. In the experiments it was noted that 31 horses' coagulation times checked during the rather warm months of September and October averaged 17.47 minutes while the average coagulation time of 25 horses during November and December was 23.67 minutes or a difference of 6.2 minutes between the warm and cold months. It is very possible that the colder room temperature caused a slight increase in the coagulation time. In the experiments it was noted that occasionally horses or mules had coagulation times in excess of 30 minutes, several over 50 minutes. These excessively long coagulation times may have been due to the fact that these horses were old and thin or suffering from some wasting disease and as a result the serum protein as well as the calcium titer of the blood was excessively low. In one mule the coagulation time was 78 minutes and the red cell count was 2,250,000 which is abnormally low. Riser (65) stated that in anoxemia due to a lowered erythrocyte count the coagulation time of blood often is prolonged. Foster (23) stated that in repeated veni or heart punctures an increased coagulability of blood is observed. This latter condition was not particularly noted in the experiments with horses.

The decrease in coagulation time produced by the injection of various intravenous medicants is very interesting and also

important, as horses normally have long coagulation times and it is often desirable to check or stop hemorrhage in these animals. Intravenous agents such as gelatin, calcium gluconate, sodium citrate, oxalic acid, and blood have been previously advanced as agents to hasten coagulation time of blood in horses. From the following plate it may be noted that other drugs are even better than those that have been previously used as intravenous coagulants in horses, (Plate V).

In the experiments of 63 horses and mules of all sizes, ages, and conditions the normal coagulation times, pulse rates, respiration rates, body temperatures, specific gravity and total protein values, red cell counts, and white cell counts and hemoglobin values were noted if possible and the results were compared with those of other authors, (Table 3). However, it should be kept in mind when observing the table that 91 percent of these horses and mules were over 12 years of age and most of them were fairly thin, and a few of them were suffering from chronic ailments.

Conclusions

These conclusions were based on over 200 intravenous injections with 21 separate materials into 69 horses.

1. There is much work yet to be done on the subject of intravenous injections and their effects on the horse.

2. Small amounts of air or oxygen injected into the venous circulation were harmless, but small amounts of air injected into the arterial circulation caused severe reactions.

EXPLANATION OF PLATE V

Graph comparing the relative effects of the various intravenous solutions on the coagulation time of horse's blood.

PLATE V

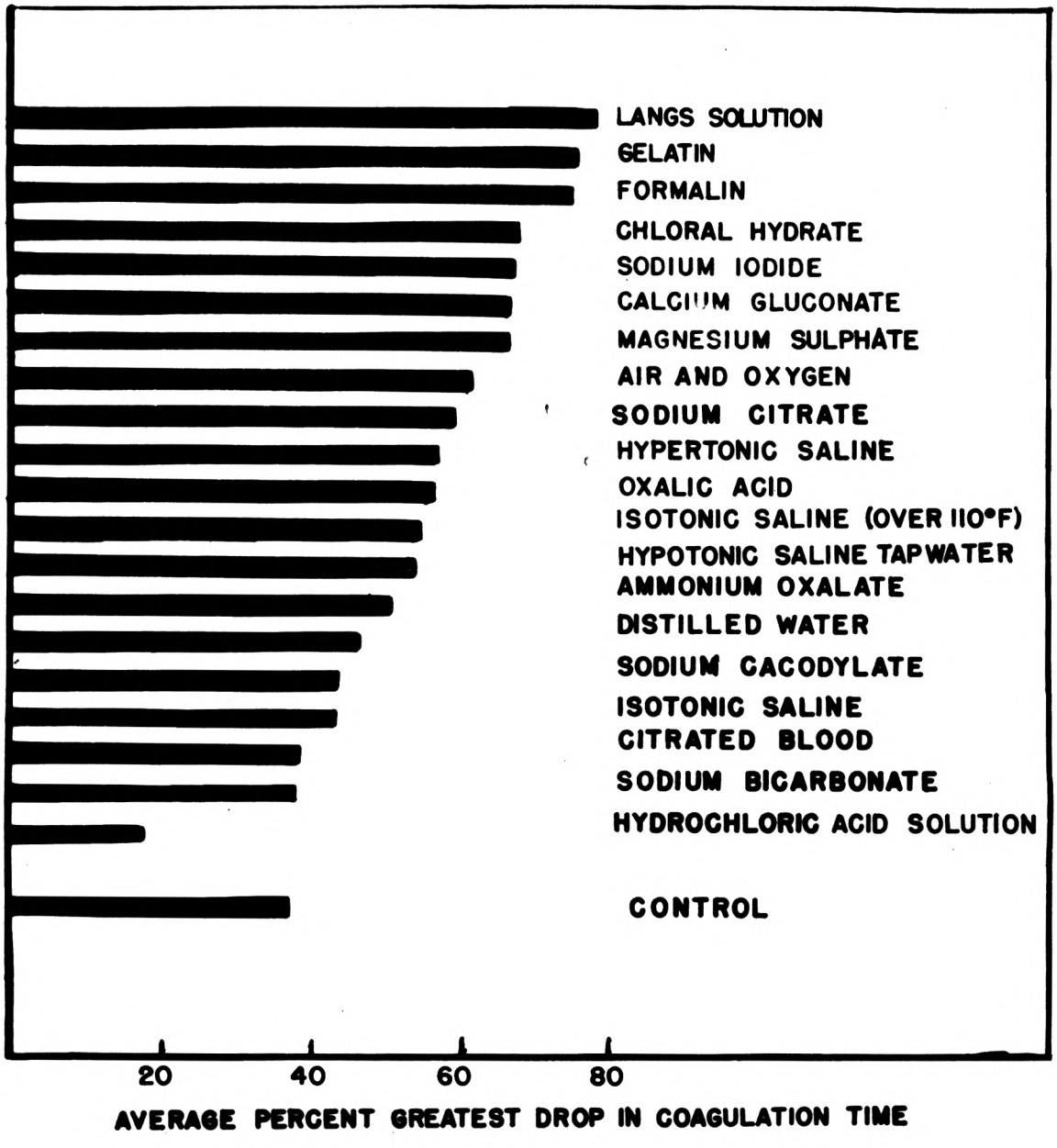
LANGS SOLUTION
GELATIN
FORMALIN
CHLORAL HYDRATE
SODIUM IODIDE
CALCIUM GLUCONATE
MAGNESIUM SULPHATE
AIR AND OXYGEN
SODIUM CITRATE
HYPERTONIC SALINE
OXALIC ACID
ISOTONIC SALINE (OVER 110°F)
HYPOTONIC SALINE TAPWATER
AMMONIUM OXALATE
DISTILLED WATER
SODIUM CACODYLATE
ISOTONIC SALINE
CITRATED BLOOD
SODIUM BICARBONATE
HYDROCHLORIC ACID SOLUTION
CONTROL
20
40
60
80
AVERAGE PERCENT GREATEST DROP IN COAGULATION TIME

Table 3. Comparison of normal tests before injection with results of other authors

Tests	Duke's results (18)	Malkmus' results (49)	Experimental results Range	Average	Number of horses
Coagulation time	11.5 min.		7 - 78 min.	22.35 min.	56
Pulse rate	32 - 44 per min.	28 - 40 per min.	25 - 72	42	54
Respiration rate	8 - 16 per min.	8 - 16 per min.	10 - 68	20.9	54
Temperature	99 - 100.8° F.	99.5 - 101.3° F.	98 - 101.9° F.	99.58° F.	51
Red blood cell count	6,940,000 cells per cc	7,500.000 cells per cc	2,125,000 - 9,250,000	5,627,768 cells per cc	28
White blood cell count	10,000 cells per cc	10,500 cells per cc	3,600 - 17,600 per cc	9,920 per cc	28
Specific gravity of serum			1.0250 - 1.0333	1.02786	48
Total protein of serum	7.23 g per 100 cc	6.1 (Craige, Gadd, (14))	6.00 - 8.37	6.99	48
Hemoglobin	12.4		7.5 - 14	9.75 g per cc	43

3. The symptoms produced by the intravenous injection of large amounts of air were primarily cardiac and respiratory embarrassment together with a drop in the aortic blood pressure.

4. Extremes in rates of injection and in temperatures and amounts of physiological saline solutions injected had slight clinical effects on the horse.

5. The normal horse could tolerate large quantities of hypotonic solutions intravenously, but amounts over 4000 cc regularly produced a temporary hemolysis of the blood and hemoglobinuria.

6. Following the hypertonic sodium chloride injections an increased peristalsis was noted with a definite decline in the coagulation time of the blood.

7. Sodium citrate solutions injected intravenously caused a definite decline in the coagulation time and large injections produced symptoms characteristic of acute calcium deprivation.

8. Sodium iodide injected intravenously produced a definite drop in coagulation time and in the red blood cell count. No clinical symptoms were produced.

9. Lang's solution caused a marked drop in the coagulation time with an increase in peristalsis, and when it was injected rapidly in large amounts it produced symptoms of characteristic calcium deprivation.

10. Injection of sodium bicarbonate intravenously produced no clinical symptoms.

11. Sodium cacodylate produced very slight clinical effects when injected into the horse.

12. Intravenous injections of oxalic acid lowered the coagulation time but produced dangerous toxic effects on the circulatory and excretory systems.

13. Magnesium sulphate solutions injected intravenously caused a definite decline in the coagulation time but were poor anesthetic solutions as the anesthetic dose was too near the fatal dose.

14. Chloral hydrate was occasionally toxic for certain old debilitated horses, especially if the animal struggled during the period of narcosis or anesthesia.

15. Chloral solutions produced a definite decline in the coagulation rate and in the body temperature.

16. Following calcium gluconate injections there was a definite decline in the coagulation time, and large amounts could be injected rapidly in horses without producing marked clinical symptoms.

17. Formalin in 8 to 16 cc amounts in various concentrations with distilled water was relatively non toxic and caused a marked rapid decline in the coagulation time and a slight temporary increase in the red blood cell count.

18. Moderate or large doses of formalin injected rapidly produced clinical symptoms similar to those of histamine or foreign protein shock in the horse.

19. Gelatin solutions produced a marked rapid drop in the coagulation time after the injection with no development of unusual symptoms.

20. Injections of dilute hydrochloric acid did not produce a leucocytosis and failed to produce other observable circulatory or clinical effects.

21. Blood transfusions may be given at wide ranges of temperature, from 32 to 138° F., without clinical effects, while the injection of overheated blood produced definite symptoms of foreign protein shock.

22. The average normal reading or tests on the 69 experimental horses showed an average slight to definite increase in the normal coagulation time, respiration rate, and pulse rate and a noticeable decline in the red blood cell count, and hemoglobin values when compared with the averages of other workers. These differences might possibly be due to the fact that the horses in general were thin and aged.

23. The circulatory system of the horse is capable of handling large volumes and strong concentrations of many drugs and materials without permanent injury to the system or to the body.

ACKNOWLEDGMENTS

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APPENDIX

Form 1. Original clinical form used for tabulation of results of intravenous experiments.

Animal -
Date -
Time -

Material -
Amount -
Rate -
Temperature -

Coagulation time ( )
Before -
After -

Hemoglobin
Before -
After -

Hemolysis
Before -
After -

Cell counts
Before
RBC -
WBC -
Dif.-
After
RBC -
WBC -
Dif.-

Special tests or chemical analyses
Before -
After -

Observations - Pulse
Before -
After -

Respiration
Before -
After -

Temperature
Before -
After -

Other observations -

Discussion -

Apparatus used -

Other notes -