1960

Evaluation of phenoxybenzamine therapy in shock

Richard H. Lynch
University of Nebraska Medical Center

EVALUATION OF PHENOXYBENZAMINE THERAPY IN SHOCK

Richard H. Lynch

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1960

Omaha, Nebraska

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I. Introduction:

Should hemorrhagic shock be treated with vasoconstrictors or vasorelaxants? Opinions differ as to the right answer to this question. Because of these differences of opinion, I have studied the effect of administering phenoxybenzamine (Dibenzyline) to dogs subjected to controlled hemorrhage. The phenoxybenzamine was administered at the time treatment was started with reinfusion of the withdrawn blood. The results suggest that phenoxybenzamine increased the survival of those dogs that received it.

The body responds to hemorrhagic shock by a complex physiologic reaction. Although shock has been studied for years many areas still require clarification. Hemorrhagic shock which fails to respond to blood volume replacement (irreversible shock) is one of these areas.

II. Physiologic Response to Shock:

CARDIOVASCULAR SYSTEM — After a significant hemorrhage the venous return to the heart is substantially reduced. This reduces the cardiac filling, the diastolic size of the heart, and the strength of myocardial contraction according to Starling's Law. In an attempt to compensate for the reduced blood volume the veins, which normally contain approximately 60 per cent of the blood volume, constrict. Also, the spleen contracts increasing the blood volume by 10 per cent (46). As long as the blood loss is below 10 to 15 per cent of the total blood volume signs of shock are lacking except perhaps minimal increase in the diastolic blood pressure. Blood losses from 16 to 25 per cent produce early signs of shock, a rise in the pulse pressure and a rise in diastolic pressure. Not until blood loss has reached 25 to 50 per cent do classic signs of shock appear. At this point compensation for blood loss fails and cardiac output is decreased. The carotid and aortic sinuses inhibit the cardiac control center, which exerts a depressor influence on the heart via the vagus, and cardiac acceleration occurs. An increase in heart rate from 40-60 beats per minute causes an almost proportional increase in cardiac output. An increase from 60 to 120 beats per minute increases the output but no longer proportionally. From 120 to 180 beats per minute no great change in output occurs, and with rates above 180 beats per minute the output of the heart actually decreases (125).

With progressive bleeding the size of the heart decreases until terminally when the diastolic and especially the systolic size of the heart increases (125). As the cardiac size increases myocardial contraction becomes stronger according to Starling's Law until the heart becomes overly depressed either by anoxia or "toxic products" liberated during shock. Acidosis and hyperkalemia present during shock both tend to weaken myocardial contraction and lower output. Smith, et al (100) found that sodium chloride solution which counteracts the hyperkalemia but does not change the blood pH increases cardiac output more then sodium bicarbonate which also corrects the pH. Terminally in dogs the left ventricle then the right ventricle fails after a prolonged period of hypotension. Clinically while electrocardiographic changes are rarely seen in shock in the young patient they are not uncommon in the older age group.

When the blood volume is restored before death the blood pressure rises and a reflex bradycardia occurs. Failure of the heart to slow subsequent to reinfusion of blood indicates poor prognosis (125). Blood reinfusion effects a definite rise in output although it usually does not reach control levels and the output soon deteriorates again with a progressive deceleration of the heart. Remington (80) found venous pressure increases following reinfusion and is associated with a decreased cardiac output and cardiac size. He postulated that cardiac filling may be

restricted by slow ventricular relaxation and short duration of diastole. One explanation for some of the cardiac failures may be fat infiltration and necrosis of myocardial muscles as found in soldiers and in dogs who survived prolonged periods of shock (59). According to Harris (39) electrocardiographic evidence shows that in hemorrhagic shock the heart fails via four patterns. Fifty per cent exhibit a failure of the pacemaker, 33 per cent show conduction failure while the remainder of dogs are equally divided between fibrillation and a combination of the first two failures (39).

The vascular bed plays a most important part in shock as already mentioned and will be considered in detail. The shunting of blood in the body from nonvital to vital areas is determined by central control and local tissue factors. The increased carbon dioxide content of the arterial blood brings about a centrally controlled vasoconstriction and a localized vasodilation. These effects shunt blood to those tissues in greatest need of oxygen (79). Shock states render the terminal vascular bed, particularly the terminal arterioles, metarterioles, and pre-capillary sphincters, hypersensitive to the effects of epinephrine and they show spontaneous vasomotion and constriction (9,40). It has been found that the metarterioles and pre-capillary sphincters have no autonomic control and are regulated by local metabolic factors and humoral agents of visceral origin, while

the peripheral arteries and arterioles are regulated predominantly by sympathetic nerves (43). Kramar (49) demonstrated that capillaries do not respond in shock in the same way that they do in normotensive states. They are especially sensitive to the adrenal steroids so that even when an animal is relatively steroid deficient the increased sensitivity of the end organs compensates for their deficiency.

Prolonged vasoconstriction of the blood supply to vital organs is deleterious and will accelerate the onset of irreversible shock (113). This has stimulated the work using vasodilators in the treatment of shock. Selkurt (94) found experimentally that the mesenteric resistance increases with blood loss but decreases with reinfusion. After reinfusion, as the arterial blood pressure rises, the resistance again increases but only to control levels. Resistance in the vascular beds is inversely proportional to the fourth power of the diameter of the vessel, (Resistance increases $\frac{\text{Mean Arterial Pressure}}{\text{Volume Flow}}$).

Mesenteric blood flow is decreased as the mesenteric resistance increases during the progressive bleeding in shock, and then falls to approximately 50 per cent of control levels following reinfusion (94). A secondary increase in resistance then occurs and is maintained until the final fall prior to death (86). Selkurt, et al (94) concluded that the initial rise in mesenteric resistance was secondary to arteriolar vasoconstriction that,

although preventing the pooling of blood in the gut, promotes anoxia of the tissue. The fall in resistance with reinfusion was attributed to dilated arterioles and atonic mesenteric vessels in addition to increased intraheptic resistance. The "damming" of blood by the liver effects stagnation of the mesenteric blood with resultant intestinal hypoxia. Increased vasomotion explains the secondary rise in resistance. The mesenteric blood flow decreases during hypotension and then increases with reinfusion. At a blood pressure of 40 mm of Hg the blood flow is around 23 per cent of the control level. When the secondary rise in mesenteric resistance occurs, the blood flow to the gut begins its progressive fall until death. It is interesting that the intestinal blood flow begins its fall before the terminal fall in systemic blood pressure. This indicates that, following reinfusion, the body is again able to compensate for blood loss and does so by shunting blood before the blood pressure falls (2,9).

Closely related to the mesenteric blood flow the resistance is the liver circulation, resistance, and hence portal pressure. Table 1 and 2 reflect the preferential shunting to the mesenteric hepatic system with maintenance of blood flow at relatively high rates. Although the absolute values are not comparable some comparison of flow is possible. Selkurt and Brecher (95) found the portal vein flow decreases by approximately 59 per cent at 60 mm/Hg pressure, and by 68 per cent at 40 mm/Hg pressure.

The hepatic artery flow which furnishes 70 per cent of the hepatic blood supply decreases by 33 per cent at 60 mm/Hg and by approximately 60 per cent at 40 mm/Hg pressure (95). The portal venous pressure drops from a control level of 8 mm/Hg to 4.5 mm/Hg after acute hemorrhage and then rises gradually to 6 mm/Hg, a reflection of mesenteric and/or hepatic vasoconstriction. After further hemorrhage this vasoconstriction is inadequate to maintain pressure and the portal pressure falls to 5 mm/Hg (95). Following reinfusion Wiggers, et al (115) found the mean portal pressure rises as high as two times the normal level.

Other abdominal organs are also affected by blood loss. The spleen immediately contracts liberating red blood cells and plasma up to 10 per cent of the circulating volume into the blood stream (125). The adrenal circulation is impaired, but evidence does not support this as a cause for any degree of adrenal insufficiency. The renal circulation is impaired more than that of any other abdominal organ. With this diminished blood supply the kidney maintains its glomerular filtration of relatively greater constriction of the afferent arterioles than the efferent arterioles thus maintaining filtration by increasing the filtration fraction. The renal ischemia apparently stimulates the release of erythropoietic stimulating hormone (E.S.H.).

Extra abdominal circulation is as much affected by blood loss as is the intra abdominal. The skin and muscle blood flows

are reduced more than the flow to any other organ, however, these organs are especially tolerant of ischemia. Wiggers (125) has shown that vasomotor activity in the legs is increased with hemorrhage and persists into shock. This presents blood pooling in the lower extremity and adding to the insult of blood loss.

SERUM — The blood and the blood plasma reflect the metabolic changes occurring during shock and in the post shock period in addition to the fluid and electrolyte changes. In an attempt to maintain vascular fluid volume the body shifts large amounts of fluid from the extravascular space into the intravascular space. This volume is in addition to the contraction of the spleen which may add up to 10 per cent to the blood volume. The hematocrit decreases with this fluid shift.(114). Wilson, et al (116) showed that following acute hemorrhage of less than ten minutes duration maximum plasma dilution occurs within 30 minutes after which time the dilution decreases. This reflects the rapidity with which the body fluids may shift.

As blood is reinfused the hematocrit tends to rise to normal or slightly above normal level. The spleen dilates but not to its prehemorrhage size in an attempt to remove blood from the circulation since immediately after reinfusion the blood volume is slightly above normal (125). During the period of impending

irreversible shock circulating blood volume progressively decreases. Overbey, et al (69), using Evans blue technique, demonstrated that two hours post reinfusion the blood volume was reduced 17± 1.14 ml/Kg. There is no hemoconcentration as would be found if the intravascular fluid were lost through dilated capillaries with increased permeability. Fine and Seligman (27) using radioactive plasma protein substantiated that fluid is not lost through the capillary bed. However, as the final decline in pressure takes place the hematocrit increases above its previous subnormal level, and the plasma hemoglobin increases apparently due to reabsorption of hemolyzed blood from the congested necrotic bowel (44,55).

In addition to the above fluid changes in shock the plasma has many other changes. The coagulation time shortens with the acute loss of blood then returns approximately to the control values of 10 to 15 minutes during the bleeding period then again becomes as short as 15 to 30 seconds immediately after reinfusion. This extreme shortening of the coagulation time is very transient and may be missed unless specially checked for (16). Crowell (14) states hypocoagulability with a coagulation time up to several hours follows the brief hypercoagulability. He postulates that even though the central nervous system can tolerate anoxia for a short period without damage patients are unable to withstand circulatory arrest because of minute thrombi formed in the intestinal vessels which lodge in the liver and brain. He was

able to prevent irreversible shock after circulatory arrest in dogs using heparin (10 mg/Kg). The exact agents which antagonize heparin and shorten the coagulation time have not been specifically identified. Of interest is the decrease coagulation time seen when the blood pressure in the femoral artery falls. The reason for this relationship is not known.

Shocked animals exhibit increased susceptibility to infections partly due to the decreased number of granulocytes and partly due to morphologically abnormal granulocytes which possess the ability to ingest only 60 per cent of the bacteria ingested by normal granulocytes (21,87). The serum properdin, a serum globulin which acts in association with complement and magnesium ions as a natural bacteriocidal system, shows a progressive fall during hemorrhagic shock (28).

Nelson and Noyes (66) report 22.4 per cent positive blood cultures in unshocked control and in test dogs subjected to hemorrhagic shock. Clostridium perfringens was the predominant organism cultures. Although bacteremia does not increase in shock endotoxins play an important part in the granulocytopenia seen during shock. Smiddy and Fine (97) showed that in rabbits endotoxins cause a granulocytopenia which reaches a maximum after 60 to 100 minutes and lasts for around 3 hours.

Decreased circulation to tissues retards excretion of the acid metabolic by-products. Lowered pH of venous blood

results (21,29). Part of the reason for the metabolic acidosis of the venous blood is the shift of hydrogen ions and potassium ions from the anoxic cells. This results in an elevated serum potassium and lowered serum sodium in the plasma (4,29,125). Although potassium in high levels is detrimental to cardiac function many workers have reported no improved survival when the serum potassium is lowered by electrolyte correction. Stirman (102) however reported 60 per cent canine survival when saline solution plus shed blood was reinfused as compared to 20 per cent survival reinfusing blood alone.

Blood glucose levels, high early in shock, become subnormal late after the hepatic and muscle glycogen are depleted. The serum lactic and pyruvic acid levels increase with the severity of the shock as the result of increased peripheral production and decreased liver metabolism. The lactic to pyruvic acid ratio decreases late in shock along with the blood pH (20,125). See Figure 3. The amino acid nitrogen concentration, the blood ammonia level, and the albumen-globulin ratio rise as shock progresses while the albumen-globulin level falls secondary to decreased liver function (13,29,125). Animals pretreated with neomycin exhibit a higher ammonia level than control animals and an increased urea synthesis (111). The explanation of this is unknown.

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LIVER -- Selkurt, et al (95) demonstrated that the hepatic utilization of oxygen is reduced by over 53 per cent in severe hypotension. Since during hypovolemic states the oxygen supplied to the tissues is reduced to a greater extent than is the tissue demand for the oxygen the venous oxygen tension is reduced to below normal levels. The liver being in its unique position of receiving a large proportion of its blood supply from the portal system, which furnishes oxygen to the gastrointestinal tract before supplying it to the liver, would appear to be at a disadvantage during shock states. As hemorrhagic shock develops hepatic blood flow is progressively decreased. However, according to Shoemaker, et al (96) the liver's blood flow is maintained preferentially during shock. These workers showed that during chronic hemorrhage hepatic blood flow remained stable early but then exhibited a brief erratic increase followed by a decline (96). Seligman and Fine (27) found a direct relationship between impairment of liver blood flow, function, and the onset of irreversible shock. This finding would agree with the findings of Keland and Zweifach (48) who found animals with an intact hepatic artery had increased resistance to shock compared with animals with a ligated hepatic artery. Other workers have increased survival and prevented irreversible shock in dogs by perfusing the liver (31). In contrast to this Wise, et al (118), studying shock in angora

goats, demonstrated no correlation between liver function or blood flow and survival.

Bacterial endotoxins given to produce a picture closely resembling irreversible shock have been shown to cause vasospasm of the liver vessles which in turn traps large volumes of blood in the liver causing a fall in blood pressure (55). Intrahepatic vasoconstriction persists after the replacement of lost blood (29). The possible relationship of these two facts will be discussed later in this paper.

Liver high energy phosphate bonds have been shown to be decreased in shock (83,111). Reduced blood flow and supply of nutrients and oxygen to the liver reduces the formation of high energy phosphate bonds. During the shock the liver must detoxify the toxins and metabolic products formed. Since it is these high energy bonds that furnish the energy for the liver tissue it is not surprising that they are depleted in shock. Frank, et al (31) found shock seriously affected the phosphorylation of co-enzymes essential to carbohydrate metabolism. This too is related to the decreased concentration of high energy phosphate bonds.

Wiggers, et al (112) demonstrated that the excretion of bromsulphalein is also reduced following shock. This may result from several factors all or any of which may play a part: First, liver damage resulting from the hypoxic state; second, liver congestion due to portal hypertension which occur following

reinfusion of bled blood; and third, diminished liver blood flow. Drucker (20) however presents evidence that the hepatic removal of lactic and pyruvic acid is not impaired late in shock after retransfusion. This indicates that at least part of the liver function depressed during the hypotensive period is reversible if the shock state has not persisted too long. Wiggers (125) showed that after six hours of shock the serum level of globulin decreased and that this caused an increase in the albumen-globulin ratio. Late in shock the blood ammonia level also rises along with the amino acid nitrogen both reflecting depressed liver function.

Chambers and Zweifach (9) furnished evidence that the liver and the kidney release vasoactive substances, V.D.M. (ferritin) and V.E.M. (angiotonin) respectively. According to them, impaired liver flow leads to an increase in the V.D.M. which renders metarterioles hyporeactive or unresponsive to sympathogenic vaso-constrictive agents. V.D.M. is generally believed to be produced in the liver and the skeletal muscles and according to Chambers and Zweifach (9) appears in the circulation only after prolonged periods of severely reduced peripheral circulation. Ferritin (V.D.M.) has been shown to have a free sulfhydryl group in its structure and enough dibenzyline to react with 0.1 per cent of the body's sulfhydryl groups is protective in shock. The combination of the ferritin with the iron binding protein also abolishes its vasodepressor action (42,124).

Smith, et al (99) found that during trauma the soluable liver iron is increased and the liver function of storing iron is impaired. Hampton, et al (37), studying rats, found that increasing the serum ferritin (V.D.M.) by giving intraperitoneal iron as hemoglobin and then producing drum trauma had no effect of increasing susceptibility to shock. The reduction of the ferritin level also produced no increased resistance to shock. These workers concluded that the increased ferritin level was due to tissue anoxia and malfunction of the liver and was not of prime importance in irreversible shock.

The liver plays an important part in the metabolic response of the body to shock. Early, as epinephrine is released into the blood stream there is a release of liver glucose via glycogenolysis and the blood glucose level rises. Late, after the liver supply of glycogen is depleted the blood glucose level falls and remains low during the remainder of the shock state. The liver and the rest of the reticuloendothelial system most likely plays a major portion in the detoxification and metabolism of toxins liberated by gram negative bacteria and degenerating tissues. This will be discussed further.

KIDNEY — In hypovolemic states the renal blood flow is reduced more than the cardiac output. Even with mild degrees of

hemorrhage almost immediate selective vasoconstriction of the renal arteries occurs. Wiggers (125) pointed out that, following massive hemorrhage, the renal blood flow may decrease as much as 41.5 per cent solely as a result of lowered blood pressure and decreased circulating blood volume. The importance of selective vasoconstriction was shown by Phillips, et al (73) when they demonstrated that, following 30 to 40 ml/Kg. hemorrhage in dogs, renal function decreased even when the blood pressure was maintained at 110 mm/Hg.

This study of renal circulation at hypotensive levels is complicated by the fact that, at blood pressures below 30 to 60 mm/Hg. creatinine and inulin extraction methods of measuring glomerular filtration are reduced more than the renal blood flow, and PAH and diodrast clearance no longer reflect plasma flow. Selkurt (93) found that urine formation almost ceases at this blood pressure. He measured renal blood flow when the blood pressure was 40 mm/Hg. and found it approximately 11 per cent of normal. With a hemorrhage of 40 to 45 ml/Kg. of B.W. he also showed that, despite a blood pressure of 80 to 100 mm/Hg. glomerular filtration fell almost to zero.

Following hypotensive periods, renal vasoconstriction usually persists for sometime even after reinfusion of blood and return of the blood pressure to normotensive levels (29). PAH clearance also remains at zero following reinfusion (93). This shows that

the tubular damage which occurred during the anoxic state decreases the clearance even when renal flow normalizes. Eder (21) suggested that tubular damage leads to the escape of fluid into the interstitial tissues which causes an increase in the intrarenal pressure that lessens the blood flow and increases tissue ischemia. It is conceivable that such a mechanism could result in continued tissue damage following restoration of renal circulation.

The kidney plays an important part in the body's compensations for blood loss. Vasoexcitatory material (angiotonin) elaborated by the kidneys after a blood loss of as little as one per cent of the body weight appears to sensitize the metarterioles and possibly other vessels rendering them hyperresponsive to vasoconstrictive influences of both humoral and neurogenic origin (112). Chambers and Zweifach (9) claimed that the persistance of V.E.M. or a vasoexcitatory reaction of blood samples taken during shock in dogs invariably indicates eventual survival. All their surviving animals had V.E.M. and no V.D.M. Because of the wide spread use of levophed in shock states, it is of interest to note that in spite of its effect of increasing blood pressure it decreases the renal clearance which potentiates renal damage but probably increases the elaboration of V.E.M.

GASTROINTESTINAL -- During oligemic shock an ischemic condition developes in the gastrointestinal tract in dogs with resultant edema, necrosis and ulceration along the bowel most marked in the small bowel (29,46,125). The intestinal tract in humans does not show the marked pathologic changes seen in dogs due to differences in metabolic demand of the intestinal cells and blood supply.

The pathology in the intestinal tract plays an important part in shock since experimental perfusion of the superior mesenteric artery increases resistance to shock (54). Lillehei (53), Sanford and Noyes (88) achieved up to 90 per cent prevention of irreversible shock in dogs by perfusing the superior mesenteric artery. Lillehei (53) found dogs shocked with superior mesenteric artery perfusion did not show congestion and necrosis of bowel but did show the liver congestion seen in control animals. This indicates that necrosis of the intestines is related to the development of irreversible shock. Three factors may be responsible; first, bacteremia resulting from bacteria entering the blood stream as the bowel becomes necrotic; second, endotoxemia resulting from breakdown of bacterial content of the intestines; and third, toxemia resulting from breakdown of intestinal cells secondary to ischemic hypoxia.

Zweifach, et al (12) found rats subjected to irreversible shock had a transient bacteremia following the bleeding period. However, work done by experimentors on dogs in hemorrhagic shock

showed no increased bacteremia (54,66). Other workers have shown a 22 per cent incidence of positive cultures in both control and shocked dogs (66). Therefore, one must conclude that bacteremia is not a cause of irreversible shock.

Sanford and Noyes (88) found that in the normal dog the bacteria in the small intestines average around 100 per square inch of which two-thirds are gram positive until the terminal six inches of the ileum. In contrast the intestines of dogs subjected to irreversible shock contain 45 million aerobic bacteria per inch with gram negative bacteria, especially Escherichia coli, predominating (88). These bacteria could liberate much endotoxin or contribute to the destruction of intestinal mucosa. This is further discussed with endotoxins.

Intestinal factors are important in shock. Preferential cooling of the intestinal tract prolongs survival but does not prevent irreversible shock (72,75). McRae, et al (58) and others resected intestines and showed an increased survival time in irreversible shock. These findings show that the intestinal factors are important but by no means the sole factors in irreversible shock. Jacob Fine and others have advocated that endotoxins from gram negative intestinal bacteria especially E. coli are responsible for irreversible hemorrhagic shock. In support of this they showed an increased resistance to shock in animals

pretreated with nonabsorbable oral antibiotics, although others have not found them beneficial (51).

Schweinburg, et al (92) and Fine (25) found a toxin present in the blood of shocked animals during the first two hours of hypotension. Ravin (78) showed this toxin causes irreversible shock in otherwise reversibly shocked animals, causes Shwartzman reactions in prepared animals, is pyrogenic, and when given in small doses induces tolerance. Wendel, et al (111) using rats found Permutil T, which absorbs intestinal toxic products and bacterial hysates, protects them from shock. Landy and Shear (50) isolated nonbacterial endotoxin-like products from normal plant and animal tissues, including red blood cells. They further showed that these lipopolysaccharide toxins could give cross-resistance with endotoxins from gram negative bacteria and that many produced the same picture in respect to fever, tolerance to pyrogenic action, leukopenia, Shwartzman reaction, damage to Sarcoma 37, dermal hemorrhage, necrosis by epinephrine, enhancement of antibody production and lethality (24,50).

Fine, et al (25) showed the reticuloendothelial system protects against the toxin present in shock. He used Thorotrast, a 25 per cent colloidal suspension of thorium dioxide in dextran, given in the dosage of 3 mg/Kg., to destroy the reticuloendothelial tissue and produced significant increase in susceptibility to shock. Animals pretreated with Thorotrast and transfused with

blood containing endotoxin developed irreversible shock and died (25). Related to this is the finding of Rosenbaum, et al (83) that there is a decrease in the reduction of high energy phosphate bonds in the liver in hemorrhage shock if the intestinal tract is pretreated with chlortetracycline. These authors feel this reflects that the liver requires energy stored in high energy phosphate bonds to metabolize toxins.

At the present time there is still disagreement as to the source of the lipopolysaccharide toxin present in shocked plasma. Fine, et al (78) believe the toxin is bacterial in origin and not from intestinal cells for two reasons. The toxin appears too early in shock, they say, to be from tissue damage, and the toxin is not found after six hours of shock if the animal is pretreated with nonabsorbable antibiotics (78). Zweifach, et al (120), however, demonstrated that the same picture of irreversible shock can be produced in germ free rats as in normal rats. This would mitigate against bacterial toxins as the etiology of irreversible shock. Fine (92) explains this by showing that these rats are sensitive to from 10^{-5} to 10^{-6} the MLD/100 of endotoxin needed to kill normal rats. Sanford and Noyes (88), using radioactive Cr^{51} tagged Boivin type *E. coli* endotoxin, could not demonstrate absorption of endotoxins along the intestinal tract from the stomach to the colon in shock. The tagging of the endotoxins may have prevented its transport across the intestinal barrier.

Russel and Noyes demonstrated an increase in Claustridia toxin in peripheral blood following the gastric administration of Clostridium botulinim toxin in the stomach (86,96).

Thomas (106) has shown that endotoxins found in shock have many actions similar to epinephrine. These include peripheral vasoconstriction, hyperglycemia followed later by hypoglycemia, decrease in the liver glycogen, increase in the blood lactate, and increase in the blood pyruvate. The finding that epinephrine in endotoxin treated animals could lessen the venous outflow from capillary beds at doses that had no appreciable effect on arterial caliber in nontreated animals may be explained by a synergistic action between endotoxins and epinephrine (122). Endotoxins may contribute to the bowel lesions by their actions on the hepatic resistance. Lillihei and MacLean (55) showed that endotoxins cause a vasospasm of liver blood vessels trapping large volumes of blood in the liver. In endotoxin treated animals this trapping supposedly causes the initial fall in blood pressure. The effects of endotoxins are enhanced as the dosage and duration of shock increases (87). Schweinburg and Fine (92) demonstrated that the increased sensitivity to endotoxins in shock persists approximately 48 hours after the shock state is corrected. Typical lesions have been described resulting from endotoxins. These are intestinal edema and necrosis, renal and hepatic congestion and in some cases left ventricular subendothelial hemorrhages (55).

CENTRAL NERVOUS SYSTEM — The cerebral circulation is preferentially maintained during hypotensive and shock states. Proof of this is that the damage and degeneration usually seen after a few minutes of asphyxia or cardiac arrest is infrequently seen even after hours of severe shock (29). Stone, et al (103) showed that in man the cerebral circulation is impaired immediately after hemorrhage. The hypovolemia induces a reflex hyperventilation which effects a lowered carbon dioxide content in the blood. This in accord with Hassalbachs formula ($pH = pK + \log \frac{HCO3}{CO2}$) raises the blood pH. Allen (1) found alkali solutions detrimental in hemorrhagic shock in agreement with the finding of Stone, et al (103) that alkalosis may decrease cerebral circulation by as much as 33 per cent (1). Smith, et al (100) demonstrated that sodium chloride solution is more beneficial to the shocked animal than is a buffered sodium chloride solution which raises the blood pH.

Later in shock as respirations are depressed the resultant elevated alveolar carbon dioxide and lowered blood pH effect cerebral vascular dilation and increase cerebral blood flow. The shocked patient may clinically improve at this time only to later deteriorate as the cerebral blood flow fails secondary to inadequate blood volume.

External stimuli to the brain in the form of psychic trauma, excitement, or pain are known to decrease survival from hemorrhagic

shock. The mechanism by which these stimuli are detrimental is not specifically defined but must be cortical or reflex since spinal anesthesia or local anesthesia will increase survival (81). Clinically, patients with tissue damage and pain will have significantly greater mortality than patients with equivalent blood loss without pain. Remington demonstrated this increase susceptibility to shock was not due to nerve trauma per se (81).

Because of the decreased circulation rate in shock and the stagnant flow in many vessels the tendency for thrombosis is increased. This explains the increased incidence of cerebral thrombosis during shock.

LUNGS -- Gerst, et al (32), studying hemorrhagic shock, found that pulmonary blood pressure falls initially and then stabilizes unlike the systemic blood pressure which progressively falls as bleeding continues. These workers also demonstrated that after reinfusion of blood the blood pressure in the lesser circulation rises above normal levels before returning to normotensive levels. They concluded that a decrease in the pulmonary blood flow with hemorrhage may cause partial closure of the pulmonary vascular bed which is reflected in the transient pulmonary hypertension during reinfusion.

Changes in the systemic blood pressure reflexly have a marked effect on respiration. With increasing degrees of hemorrhage, there is a proportional increase in the respiratory minute volume (125). As expected in stress situations and shock where epinephrine is released, the bronchi musculature relaxes which facilitates gaseous exchange. Although an increase in respiratory exchange is necessary to maintain oxygen tension in shock states, this may have a detrimental effect. Frank (29) pointed out that as the pulmonary ventilation increases, there is a decrease in the carbon dioxide level, venous return, and cerebral blood flow. The latter relationship is discussed with the central nervous system. In 1959, Gerst, et al (32) found that the alveolar dead space is increased in hemorrhagic shock as reflected by the large carbon dioxide gradient between the end tidal gas and the arterial blood carbon dioxide.

Crowell (15) postulated that small clots lodging in the brain and the lungs cause irreversible shock in animals. He proposed that these minute emboli form in the vessels of the gastrointestinal tract during the hypovolemic period and are flushed into the general circulation about 30 minutes after reinfusion. In support of this theory, he shocked animals and washed fibrin from their lungs, then prevented irreversible shock entirely by heparinizing them with 10 mg/Kg. of heparin. Crowell (15) used a different method of producing shock than is generally employed;

however, but it is still possible that emboli may form in the gastrointestinal vessels during the period when blood flow is sluggish there and stagnation occurs.

ADRENALS — There is no doubt that the adrenal gland is important in the response to shock and/or that adrenalectomy makes an animal hypersensitive to shock (124). In this discussion the adrenal medulla and cortex with emphasis on the glucocorticoids will be considered separately.

Greever and Watts (35), in studying irreversible shock in dogs, found that epinephrine level rises from nondetectable control levels of below 1 mcg/L. to a mean level of 29 mcg/L. in early shock, then decreases to a mean of 7.5 mcg/L. when 10 per cent uptake occurs. During the compensated period after reinfusion, just prior to the final drop in blood pressure, the epinephrine level sinks again to nondetectable levels. When blood pressure finally drops, the epinephrine level rises slightly in a last attempt to maintain blood pressure (35). These same workers studied the epinephrine level in the adrenal gland of shocked dogs and found that the concentration was only 42 per cent that found in control animals. In shock, canines also exhibit a 700 per cent increase in blood epinephrine, but only 50 per cent increase in blood norepinephrine level (35).

Remington, et al (79) demonstrated that epinephrine infusion during shock causes an increase in initial blood pressure and in total peripheral resistance and a decrease in blood flow, followed within 10 minutes by a fall in blood pressure and an increase in blood flow while the pressure remains above and the flow below normal levels. This rise in blood pressure would seem only to be a false indication of well being and may well be detrimental to the animal.

Epinephrine affects metabolism as well as blood pressure. It increases glycogenolysis and causes an immediate hyperglycemia. This action helps furnish nutrients to body tissues during the shock situation and increases their ability to withstand stress. Thomas (106) found that epinephrine increases the susceptibility of endotoxins. Fine, et al (25) found the converse that in traumatic shock endotoxins may increase the local effects of epinephrine and norepinephrine. The endotoxin-epinephrine relationship is discussed further under the heading of endotoxins.

Therapeutically epinephrine is not generally used in shock states; L-norepinephrine is the drug of choice despite the fact that its blood level never rises in shock as does the epinephrine level (35). In man norepinephrine is not only vasopressor, but also causes a slight decline in the hepatic blood flow and also a rise in the splanchnic resistance. In contrast to epinephrine, norepinephrine exerts only minimal direct cardiac stimulation.

Usually a reflex bradycardia, mediated via the carotid and aortic sinuses, overcomes this stimulation preventing tachycardia. Experimental work with norepinephrine has shown it to be both beneficial and detrimental in shock. It appears that the resulting effect depends on both amount of norepinephrine and the stage of shock in which it is used (109). Late in severe hemorrhagic shock it probably is detrimental and even in early hemorrhagic shock if the blood volume is replaced there may be little or no benefit derived from the additional use of norepinephrine. Close, et al (10) showed that norepinephrine given during hemorrhagic shock raised the mortality rate 64 per cent above that of control animals. This harmful effect is most likely due to the shunting of blood away from vital organs. Roy and Husni (86) found that in oligemic hypotension, norepinephrine causes either a decrease renal oxygen tension, temperature, and urine flow or a very slight increase in oxygen tension.

The adrenal medulla does not function independently of the adrenal cortex, since adrenalectomized dogs have a failing response to norepinephrine with continued use which is renewed by the addition of adrenal cortical extract (77). Hayes (40) suggests that a lack of blood flow to the kidney and the adrenal during hemorrhagic shock causes a relative adrenal insufficiency but this hypothesis has not been supported by other workers (12).

The adrenal cortex has a diminution of its cholesterol, ascorbic acid and lipid content during shock states which is a reflection of the metabolic processess occurring during stress. These changes are shown only if the shock states persists for some time and is not produced by acute shock states (29). These chemical changes are accompanied by anatomical lesions in the zona reticularis and the zona fasciculata which alledgedly produce androgens and glucocorticoids respectively (125).

Goldstein, et al (33) feel that a failure of adrenal oxysteroid production interferes with autonomic control and that a relative lack of these steroids accompanied by sympathetic stimulation has a detrimental affect on shocked animals. In agreement with this Lillihei and MacLean (55) showed that hydrocortisone, given to dogs treated with endotoxins to produce irreversible shock, protected them against the lethal effect of high concentrations of epinephrine by preventing excessive vasoconstriction. Zweifach, Fritz and Levine felt cortisone restores the body's response to norepinephrine. Cortisone and other glucocorticoids have been used to treat shock with variable results. Knapp and Howard reported failure with hydrocortisone while Howard and DeBakey (44) reported no significant effect on 50 to 200 mg of cortisone intramuscularly given before, during hemorrhage, and after reinfusion of bled blood.

Bruns and Connolly (6), in a paper presented to the American College of Surgeons, demonstrated a blood pressure elevation with doses of hydrocortisone, corticosterone and prednisolone. They concluded that this action was independent of water and electrolyte shifts and was probably a glucocorticoid action in restoring or potentiating vascular tone. However, this beneficial effect is achieved only if the steroids are administered within 45 minutes after the blood pressure is reduced to 50 mm/Hg (12). Hayes (40) demonstrated a clinical use of adrenocorticoids. He found that some patients, who are not adrenal insufficient by tests pre-operatively, were insufficient when placed under the stress situation of surgery or shock. In these cases corticosteroid therapy led to dramatic recovery from shock. Elevated eosinophil counts, excessive urine output, and low blood pressure may all indicate relative adrenal cortical insufficiency.

III. Phenoxybenzamine in Shock:

Zweifach, et al (119,121), studying mesenteric capillary bed, showed (dibenamine) decreased the vasoconstriction response to shock while having no effect on the hyperactivity or increased vasomotion of the terminal vessels. The capillary flow is increased in the gut even at pressures as low as 25 mm/Hg and even terminally the venular backflow is minimal. Hersey, et al (43) showed phenoxybenzamine (dibenzyline) dilated arteries, arterioles, and metarterioles but slowed vasomotion in mice. Remington, et al (78) found dogs in hemorrhagic shock pretreated with dibenzyline have a more elevated venous pressure than untreated animals which may reflect its effect on the arterial side of the circulatory bed. Dibenzyline's action of dilating vessels explains the lower initial blood pressure, slower bleeding rate, and greater fall in blood pressure with a given blood loss (98). Treated dogs show ten or more units decrease in hematocrit reflecting opening of previously closed vascular channels trapping cells (112,113). Assuming that a toxin or toxic substance is liberated into the circulation in shock, the protective effect of pretreatment with dibenzyline can be explained in several ways. First, decreased production of the toxic substance, through improved circulation; second, increased destruction of the toxic material; third, increased tolerance to the toxin present.

Zweifach, et al (119) demonstrated by direct visualization that dibenamine when given prior to hemorrhage will lessen the vasoconstriction and effect adequate circulation through the omental capillary bed. Reflecting this increased circulation Lillehei and MacLean (55) found no intestinal necrosis in dogs subjected to bacterial endotoxin shock. Remington, et al (84) reports that dogs pretreated with dibenamine recover from cerebral depression better than controls indicating possible better cerebral blood flow.

Renal blood flow is increased at hypotensive levels of 50 mm/Hg by 3 to 6 mg/Kg. of dibenamine, according to Brandfonbrener and Geller although they were unable to demonstrate increased survival.

In addition to their affects on the blood flow, dibenamine and dibenzyline have been shown to affect the ferritin system of the liver. While the release of V.E.M. from the shock kidney is unaffected by dibenzyline, the blood ferritin level increases, the plasma iron level raises, and the plasma iron-binding capacity decreases in shock (119). Baez, et al (2) and Zwiefach (119) found dogs not treated with dibenzyline transfer ferrous iron from the liver to the blood while dogs treated with dibenzyline do not and were still able to inactivate vasoactive ferritin (V.D.M.).

Baez, et al (2) found that in vitro slices of liver taken from animals treated with dibenzyline retain the ability to inactivate ferritin and also do not release ferritin into the media. In contrast liver slices from nontreated animals were unable to inactivate ferritin and did release it into the media (2). Incubation of ferritin with dibenzyline produced no alteration in the strength of the V.D.M. thus demonstrating that dibenzyline's effect on the ferritin system depends upon the existance of intact liver cells. The finding that enough dibenzyline to react with 0.1 per cent of the total body sulfhydryl groups will protect an animal against shock may be related to the changes occurring in the ferritin system (124). Pointing to the importance of the liver effects of dibenzyline in protecting against shock, is the work of Kelan (48) that showed dibenzyline protected against shock only if the liver is present. The bowel may be absent. This is in contrast to chlorpromazine which protects when both the liver and the bowel are removed (48). Noyes, et al (68) studying bacterial shock in mice found that dibenzyline and chlorpromazine protected against bacterial toxins. This being another possible protective action of dibenzyline.

Other explanations for the protective action of dibenzyline have been that it controls the release of serotonin, blocks histamine, and excites the central nervous system (61,98). The latter two actions are unlikely since antihistamines do not

protect against shock and chlorpromazine which is C.N.S. depressive has been shown to protect against hemorrhagic shock. (See Table 4.)

IV. Irreversible Shock:

For years clinicans have puzzled over the problem of why some cases of shock do not respond to the replacement of lost blood or serum. Most commonly this syndrome is seen after massive burns, severe septic states, or prolonged hemorrhage, although occasionally it occurs early in shock. The multiplicity of theories explaining irreversible shock reflects the uncertainty as to its etiology. Dale and Richards developed the theory that histamine or a related agent liberated from the tissues was responsible for irreversible shock. The work of Cannon and Bayliss lent more support to this theory. Blalock attributed irreversible shock to the loss of intravascular fluid into the tissues of the body and discredited the histamine shock theory.

Later, Zweifach and Shorr (119) demonstrated that the kidneys liberate vasoexcitatory material (V.E.M.) early in shock. The liver, spleen and skeletal muscle liberate vasodilatory material (V.D.M.) which has been identified as ferritin. Normally, the liver inactivates ferritin; however, late in shock the liver fails to do so. Zweifach and Shorr (119) have attributed irreversible shock to the vasodilation produced by ferritin. However, the recent work of Hampton, et al (37) suggests that the accumulation of ferritin results from depressed liver function in shock but does not cause irreversible shock. They showed raising the ferritin level in a shocked animal does not decrease survival (37).

Erlanger and Gasser were among the first to show that prolonged administration of epinephrine can induce shock. This immediately brought up the possibility that excessive vasoconstriction produces irreversible shock by contributing to the ischemic degeneration of tissue and the resultant release of "toxic" substances into the blood stream.

In recent years Fine's bacterial toxin theory has been favored in explaining irreversible shock. Fine (26) has found antibiotics effective in protecting against, shock and has isolated a lipopolysaccharide toxin from shocked animals serum. Culbertson, et al (18), however, have demonstrated gross bacterial contamination using Fine's method and numerous workers have found antibiotics ineffective in protecting against shock. Also, Zweifach, et al (120) have shown that germ-free rats show the same shock picture as control animals. Lany and Shear's (50) finding that toxins from plants, animal tissues, and bacteria are similar would also favor a tissue toxin theory. Adrenal insufficiency and electrolyte imbalance have been considered and may explain some cases of irreversible shock.

Assuming that prolonged vasoconstriction produces ischemic tissue necrosis and subsequent release of tissue toxins especially from the gastrointestinal tract, it seems logical that an adrenolytic agent would be beneficial if given with blood replacement thus reducing vasoconstriction and increasing blood flow.

Harold C. Wiggers, et al (125), Spoerel, et al (101), Rosenbaum, et al (83), and Lotz, et al (56), reported increased survival in dogs treated with 2-4 mg/Kg. of dibenamine or dibenzyline 15 to 30 minutes after the start of bleeding in hemorrhagic shock. Dibenzyline along with other adrenolytic agents has also been shown to protect against hemorrhage when given prior to the bleeding but the protection has been largely or entirely attributed to reduction in the bleeding volume (3,46,81,82,124). In fact, Spoerel (101) stated adrenolytic agents cause increased mortality when given after irreversible shock is present. Fine (30) was unable to show the increased survival in hemorrhagic shock with dibenamine as Wiggers had reported, although Fine used a slightly larger dosage. Recently, however, some doubt has been cast on Fine's concept of the bacterial factor in irreversible shock by the report of Culbertson, et al (17) who found that with Fine's method gross bacterial contamination occurred. Baez (2) showed that liver slices taken from dibenzyline treated animals maintain the ability to metabolize ferritin. This suggests either improved liver blood flow or a direct protection of liver cells.

Richard C. Lillehei and Lloyd D. MacLean (55) found 0.5 mg/Kg. of dibenzyline administered parenterally protective in shock produced with endotoxins from Escherichia coli suggesting either direct action against the toxin or an action of increasing the body's resistance to the toxin.

The French have reported beneficial results using chlorpromazine, which also is adrenolytic, and hypothermia in treating patients with hemorrhagic shock in Indo China. Inglis, et al (46) recently reported that chlorpromazine is beneficial after irreversible shock. This stimulated my interest in the possibility that dibenzyline might likewise be effective when administered after irreversible shock has developed.

V. Experimental Study:

INTRODUCTION -- The purpose of these experiments was to determine if the adrenolytic agent dibenzyline had protective action in irreversible shock. This author knows of no work administering dibenzyline after the blood uptake in irreversible shock. In these experiments dibenzyline was administered after 25 per cent uptake of the hemorrhaged blood to insure that irreversible shock had developed. A modified Fine shock technique was employed in the final experiments after Wigger's technique was found to produce too variable a shock state. Much of the work with dibenzyline has used morphine sulfate and/or a barbituate for sedation or anesthesia. Both these agents depress vasomotor reflexes and alter the physiologic response to shock. (See Table 5) This experiment was designed to be as physiologic as possible with minimal vasomotor depression and with heparinization of the dogs only after the hypotensive period was completed, when blood replacement occurred.

The results of these experiments suggest that dibenzyline in a dose of 3 mg/Kg is beneficial in irreversible shock in dogs when given after 25 per cent uptake of bled blood has occurred if the blood volume is replaced by retransfusion. However, because of the limited number of dogs in both the test and control groups, additional work must be done before definite conclusions can be drawn.

PART I.

METHOD -- Preliminary experiments were carried out using Wigger's technique for experimental shock. Thirteen grossly healthy mongrel dogs weighing 13.6 Kg. to 28.2 Kg. were used. They were fed daily meals of Purina dog food and observed for three days to insure their health. The dogs were allowed no solid food for the 24 hours preceding the experiment but were allowed water ad libitum. Each dog was weighed, clipped and shaved before being anaesthetized. Electrocardiograph electrodes were placed to record standard lead II with the ground lead placed lateral to the thoracic spine. Redux electrode jelly was used to insure adequate electrode contact. The electrocardiograph electrodes were later attached to the leads from an electronic recorder (Electronics for Medicine) and a control electrocardiogram taken.

The dogs were rapidly anaesthetized with 2.5 per cent intravenous thiopental in normal saline via a front leg vein after sterile preparation of the leg using a 1/500 Virac solution. Nitrous oxide and oxygen by mask were started at flow rates of four liters and one liter per minute respectively with a soda lime absorber in the system. Occasionally dogs required a short period of assisted respiration when they were overly depressed from the administration of thiopental.

The dogs were then secured on their backs with ropes on all four extremities. The right groin and inner thigh were prepared with a Dial soap scrub followed by a Vivac scrub. All personnel wore caps and masks; the operator also wore sterile gloves. The field was draped and an incision was made exposing the femoral artery, vein, and nerve.

Blood for culture and lipid determination was taken from the femoral vein using a two needle technique. The femoral artery was cannulated and the recording system filled with heparinized saline (2 mg/20 ml). Care was taken to remove all air bubbles from the system to prevent a cushion effect upon the transducer head.

The electronic recorder was adjusted linear to the transducer and calibrated. The bull dog clamp was then removed from the femoral artery and a control blood pressure recording taken.

The dogs were then placed on their right side and secured to the operating table. Bleeding was begun at a moderately rapid rate into a sterile reservoir placed 64.5 cm (50 mm/Hg pressure) above the dog's spine and the gas anaesthetic discontinued. Heparin sulfate (10 mg/ml) was added slowly to the blood as it entered the cannula at the rate of approximately 1 mg/25 ml. Bleeding was continued until a systolic pressure of 50 mm/Hg was reached. This was doubly checked not only by the height of the reservoir but also on the recorder oscilloscope. Respiratory

rate, blood pressure, electrocardiogram, and bled blood volume records were recorded at approximately 15 minute intervals.

The blood pressure was maintained at 50 mm/Hg for 90 minutes then lowered to 30 mm/Hg by lowering the reservoir to 38.8 cm. The blood pressure was maintained at 30 mm/Hg for 45 minutes or until the dogs had taken up 25 per cent of the bled blood in maintaining the blood pressure at 30 mm/Hg. Dogs #4,6,10,11,12, 13) required blood replacement before the 30 mm/Hg premier period ended because of respiratory arrest.

After the 45 minute period all the blood was reinfused at a rate that would not raise the mean blood pressure above 120 mm/Hg. Test dogs received 3 mg/Kg. dibenzyline (50 mg/ml) with the reinfused blood. Observations were continued until the dogs died or until they had survived 24 hours. Dogs alive at the end of 24 hours were given 500 mg. crystalline tetracycline hydrochloride to combate hypostatic pneumonia.

Immediately upon the death of the dogs, the thoracic cavity was opened and a sample of blood for culture, lipid studies, and in some dogs for erythropoietic hormone essay was obtained from the left ventricle. An autopsy was then preformed on the dogs and tissue specimens taken for histologic study.

The method of producing shock was that of Wiggers as already described. However, after running 13 dogs with only 5 of those living beyond the 30 mm/Hg pressure period and the degree of shock

varying in those so greatly that no definite conclusions could be drawn, it was decided advisable to change methods and to use one which depended more upon physiologic response then upon time. During the preliminary experiments several dogs showed definite evidence that they simply could not tolerate blood pressures as low as 30 mm/Hg without respiratory arrest and immediate death. Room temperature was concluded to be more critical than originally realized after studying the premature deaths of dogs 10 through 13 and finding only a 2-4°C. increase in temperature to explain the early deaths.

Premedication with morphine sulfate and a barbituate has been used for many experiments. In many respects the vasomotor effects of the two agents counteract each other as shown in Table 5. However, morphine sulfate was avoided in these experiments since liver blood flow is reduced by as much as 25 per cent by 2-6 mg of morphine (124). Such a curtailment of liver blood flow would have detrimental effects on the shocked animal.

The anaesthetic agents used in these experiments were selected for their relatively short durations of action and their minimal effects upon vasomotor reflexes. Nitrous oxide, since it has no known effect on body physiology except depression of cerebral function, is an ideal anaesthetic agent. Because it lacks potency, an additional anaesthetic had to be given. Canine metabolic rate is too high for induction with nitrous oxide alone.

Thiopental was selected for induction of anaesthesia since its duration of action is quite short due to its rapid storage in body fat when given rapidly in one dose. Theoretically the maximum effect of thiopental would pass by the time the bleeding was begun. Even if some neuromuscular depression persisted during the early bleeding period, the vasomotor reflexes would be essentially normal during the critical hypotensive period. This was found true. The dogs in these experiments were lightly anaesthesized, had control of their extraocular muscles, and looked around before the shock state deepened and they became unresponsive to their environment. Vasomotor reflexes were considered to be minimally depressed, hence the dogs were capable of meeting the hypovolemic state physiologically.

The physiologic responses were essentially the same in all dogs. No attempt to give the same dose of thiopental was made although the rate of administration and depth of depression were kept approximately the same for all dogs.

To evaluate the actions of dibenzyline in addition to its adrenolytic action and to determine if its protective action is dependent upon only altered bleeding volumes, dibenzyline was added only after the hypotensive period was terminated. This insured that each animal would be placed under the same hypotensive strain and would show whether dibenzyline protects against shock through some other action than merely altering the volume

of blood bled. The dosage of 3 mg/Kg. selected was thought sufficient to inhibit the sympathetic system and yet not high enough to block the sympathetic reversal that occurs at higher dosages.

In these experiments it was considered preferable to heparinize the bled blood as it entered the bleeding system instead of heparinizing the entire canine circulating volume since Crowell, et al (14,15) have implicated in vivo coagulation as a possible cause for irreversible shock. If this hypothesis is correct many hemorrhagic shock experiments using heparinization of the animal prior to bleeding have changed the physiology of shock. Heparinizing the blood after it is outside the dog does not alter the physiologic changes occurring during shock. The reinfusion of heparinized blood of course may have a great effect on <u>in vivo</u> coagulation if the coagulation time drops to 15 seconds immediately after reinfusion as suggested by Crowell (15). Any therapeutic replacement of lost blood however, would have the same effect and hence is unavoidable.

During the bleeding period roughly 1 mg of heparin was added for each 20 ml. bled, being added slowly at frequent intervals to prevent not only coagulation in the reservoir but also coagulation at the tip of the cannula. After the bleeding rate slowed, heparin was then added at approximately .2 mg. every five minutes. Despite this clots occasionally formed in the cannula tip and required removal.

Connolly, et al (12) reported 82 per cent mortality with reinfusion at six hours, and 92 per cent mortality at 12 hours, while Wiggers (125) reported 82 per cent mortality 24 hours after reinfusion, using the same method used in the preliminary experiments. Other workers, however, have found that this method is more severe than the dogs can tolerate as was found in these experiments.

Wiggers stated that after a rapid initial hemorrhage the body shifts extracellular fluid into the vascular space; this shift of fluid has been found to be practically complete in 30 minutes thus maximal fluid shifts should have occurred in all dogs tested (125). Before the 50 mm/Hg. pressure period is over maximum fluid shifts have occurred. Then with the 30 mm/Hg. period the dogs are shocked severely and irreversible shock is produced. In the preliminary experiments it was found necessary to sedate some of the dogs several hours after blood reinfusion since they aroused and became excited struggling to free themselves from the table. Since excitement and external stimuli decrease resistance of an animal to shock pentobarbital sedation probably causes less variation in the shock state than allowing the dog to struggle for freedom. The final group of dogs required no sedation after initial thiopental since they were all sufficiently depressed by shock and restlessness did not follow the reinfusion of blood although several opened their eyes and looked around.

To control external stimuli the noise and commotion in the room were kept as uniform as possible with any loud noises avoided. The operating table was padded with pillows to minimize the discomfort of laying in one position for prolonged periods.

MATERIALS -- The cannula and recording equipment for these experiments were designed to allow heparinization of the bled blood only after it left the dog, to prevent clot formation in the bleeding system, to obtain an accurate recording of the blood pressure and to prevent bacterial contamination of the blood during the storage period in the reservoir. To fulfill these requirements the bleeding system was designed as shown in Figure 6.

The polyethylene arterial cannula and the 2/16 inch bleeding tubing were siliconized to further decrease the co-efficient of friction and wetting property. The glass T-tube attaching the tubing to the transducer was designed to minimize Venturi effect and facilitate as precise recording as possible. The use of large tubing also lessened the tendency toward clot formation.

The cannula itself was fashioned from a Scripto ball point cartridge. The side tube for adding heparin was constructed using a twenty-two gauge needle shaft, a number PE 50 polyethylene tubing and a twenty-two gauge needle hub. The needle was placed

into the cannula so as not to protrude into the lumen of the cannula and produce turbulence. The side tube to the transducer was number PE 200 polyethylene tubing with a corresponding size needle. The transducer was a 0-75 cm/Hg P23AA, 12V max. Statham Instrument, Inc. transducer produced in Hato Rev, Puerto Rico.

For the reservoir, standard precalibrated one-liter intravenous bottles were used. They were changed when the bled volume exceeded their capacity. Reservoir bottles and the instruments were autoclaved. The polyethylene bleeding cannula and tubing which were sterilized by storage in a 1/2000 solution of Virac for a minimum of 12 hours.

RESULTS OF THE PRELIMINARY STUDY -- The shock produced by the preliminary method was found to be too variable for comparative studies in shock. Three dogs used in these experiments had previously undergone anaesthetics and operative techniques. The first two of these dogs showed such resistance to shock that they failed to develop irreversible shock. The third dog was therefore shocked at 30 mm/Hg. pressure for 108 minutes before blood uptake began. When these dogs are compared to dogs 10,11, 12, and 13 which had respiratory arrest soon after the blood pressure was lowered to 30 mm/Hg. and to dog number 6 who failed to withstand even the 50 mm/Hg hypotensive period it appears

that previous stress experiences greatly enhance an animal's resistance to subsequent stress. In both the control and treated animals the female of the species was found to be stronger and more resistant to stress than the male. Two dogs (Numbers 8 and 9) lived beyond the 24-hour period and are included in the survivals. However, number 8 which is an untreated female died some time between 24 and 36 hours while number 9 which was treated survived permanently. The survival time when considered alone is not very significant, but when the clinical course of the two animals is compared the results have more meaning. Dog 8 exhibited a mild shock period and as soon as the blood was reinfused the dog became quite alert and commenced struggling to get up from the table. This dog required repeated doses of pentabarbital to quiet her. In contrast dog 9 exhibited a very severe shock pattern, showed no sign of arousing after blood reinfusion, and remained unresponsive throughout the 24-hour period. Dog 8 did take up 2.7 ml/Kg. before the end of the 30 mm/Hg. period while dog 9 showed no uptake. Uptake, however, was not correlated with length of survival in dogs 10,11,12, or 13 which all died without exhibiting any uptake. The difference in these two dogs suggests that dibenzyline may well have contributed to the permanent survival of dog 9 which clinically was shocked much more than dog 8 and yet became a permanent survival. This

conclusion is very unconclusive considering the difference in uptake of blood in the two dogs even though the state of consciousness varied considerably.

Bioessay for erythropoietic hormone on the terminal blood of dog 4 showed a substantial level. This finding is in agreement with the finding of other workers who find elevated erythropoietic hormone levels in shock states. (See Table 8.)

Blood culture and autopsy results are discussed for all dogs under the results of the terminal experiment.

DISCUSSION OF PRELIMINARY RESULTS -- Overton, et al (70) using radioactive chromium tagged red blood cells found an average blood volume of 78.3 ml/Kg, a red blood cell volume of 39.1 ml/Kg. and a plasma volume of 39.2 ml/Kg. Wiggers (125) states that 40-45 ml/Kg. hemorrhage or losing about 50 per cent of an animal's blood volume will produce irreversible shock. In these experiments it was found that the mean bled volume at the end of the 50 mm/Hg. pressure period was 50.8 ml/Kg. and that the mean maximal bled volume occurring during the 30 mm/Hg. pressure period was 56.2 ml/Kg. (See Table 9.) Dog number 6 died after only 15 minutes at blood pressure of 50 mm/Hg. so no data as to the bled volume at the end of the 50 mm/Hg. pressure is available nor is data on the maximum bled volume. That is why these figures are absent from the tabulations.

Assuming that Overton's determinations of blood volume are valid for the group of dogs used by us the mean bleeding volume for the end of the 50 mm/Hg. pressure period was 65 per cent of the blood volume while the maximum bleeding volume was 71.8 per cent of the total blood volume. These values are appreciably higher than the 40-45 ml/Kg. hemorrhage that Wiggers claims will produce irreversible shock (125). Using the value obtained by Overton these figures become 51 to 57.4 per cent of the blood volume. Since the method of producing shock was the same the reason for this difference in values is not apparent although it may be related in part to the high incidence of premature fatality in this series.

No relationship between survival time, room temperature, bleeding volume, heart rate changes, respiration, blood pressure changes or thiopental dosage was found in these preliminary experiments.

Although some conclusions could be drawn from the 13 dogs subjected to the Wiggers technique of hemorrhage the shock produced was found to be too variable for comparison of survival times. For that reason it was decided to substitute Fine's technique for that of Wiggers since the former depends more upon a physiologic response of the animals than upon predetermined length of time.

PART II.

METHOD -- A modified Fine method was used to produce shock in the second group of dogs. Lipid studies and erythropoietic hormone assay were omitted. The first dog was maintained at 40 mm/Hg. pressure until 40 per cent of the maximum bled volume was taken up in maintaining the pressure. However, this technique was found to produce too severe shock so the method was further modified. In subsequent dogs the blood reservoir was placed 51.6 cm above the spine corresponding to 40 mm/Hg. pressure and regulated to maintain the blood at this level throughout the period of hemorrhage. This enabled us to draw conclusions about fluid shifts in the body by watching bled volume and blood pressure. Forty mm/Hg. pressure was maintained until the animals had taken up 25 per cent of the maximum bled volume at which point reinfusion was effected as before. This method proved to give clinically uniform shock. Only one dog out of nine failed to live until all blood was reinfused, thus failing to meet the requirements of the experiment.

The equipment used was the same as used in Part I.

RESULTS OF FINAL EXPERIMENTS -- The final series, using a modified Fine technique, produced a uniform predictable irreversible shock. The dogs treated with 3 mg/Kg. dibenzyline survived

an average of 174.5 minutes longer than the nontreated controls when survival time is calculated from the start of bleeding to the time of death. When considered from the common physiologic point of 25 per cent uptake, treated animals survived an average of 228.0 minutes longer than control animals. Neither of these mean survival values are statistically significant when the Standard Deviation of the Means is computed.

When number of dogs surviving is considered according to Chi square calculations, the results become significant at approximately the 3 per cent level. In other words, only 3 groups in a hundred would show as great a difference in survival as the groups considered.

Dibenzyline treatment in irreversible shock therefore increases survival very significantly while its effects on mean survival time are not statistically significant even though the mean survival is increased approximately 3.8 hours when considered from 25 per cent uptake to death.

Dogs treated with dibenzyline showed a definitely lower mean blood pressure 30 and 60 minutes after reinfusion than nontreated dogs. The best index to the vasodilation produced by dibenzyline is the ratio of initial blood pressure over the blood pressure at 30 and 60 minutes past reinfusion. (See Table 10.)

The treated dogs demonstrated no consistent effect on heart rate, or respiration. Length of survival could not be correlated

with room temperature, maximum bleeding volume, heart rate, initial blood pressure, respiratory rate, pentathal dosage, heparin dosage, rate of hemorrhage (ml/Kg.) or rate of uptake. (Figures 11 through 17)

Electrocardiograph changes were not found to be of value in foretelling the onset of demise. One indication of deterioration was a slowly falling blood pressure usually but not always associated with a bloody diarrhea. Before death the dogs all exhibited a slowing of respiratory rate. Most often the fall in respiratory rate was slowly progressive but occasionally a dog would have a sudden respiratory arrest from a respiratory rate of around 40 per minute. The heart showed a progressive fall in the pulse pressure as the mean blood pressure fell. Thus indicating either a decreased contractile power or a decrease in the cardiac filling.

The respiratory center failed in all cases prior to the cardiac center although the difference in time varied from a few seconds to many minutes. In dog 6 the respiratory arrest occurred while the heart function was still very strong. The serial electrocardiograms taken during the anoxic failure of the heart are included at the end of this paper.

During the shocked state many dogs had heart rates well over 200 beats per minute. Rates this high undoubtedly caused poor cardiac output and were probably detrimental.

Dogs 4,5,7,12,13,14, all showed a decrease in the serum total lipids. Results are shown in Table 8. No correlation with survival is shown.

Blood culture studies (Table 18) shows that all blood samples taken at the time of the femoral cut down were sterile except that of dog 23 which grew out a gram positive bacillus. This was probably laboratory contamination since the terminal culture was sterile.

The nonhemolytic diphtheroids, cultured after 10-day incubation in two dogs, are not considered pathogenic or toxin producers. The nonhemolytic Staphylococcus cultured at 10 days in two dogs may have been contaminants; however, these organisms could easily have entered the blood stream from the intestinal tract during the prolonged hypotensive period. Since the culture grew very slowly it is hard to consider these organisms influential at the time of death.

Dog number 18 showing beta hemolytic enterococci at 48 hours did survive 942 minutes from the time bleeding started and again probably developed the bacteremia from contamination from the gastrointestinal tract.

Dog 20 with a hemolytic Staphlococcus aureus culture at 48 hours lived 24 hours and then died. The final culture in this case was obtained from the fore leg being transcutaneously and this may account for the growth. The dog died after 24 hours

and since no post mortum culture was obtained, bacteremia cannot be excluded. Figure 20 shows the procedure for culturing.

Pathologic finding (Table 19) show no correlation between survival, and pathology although treated dogs seemed to have less liver degeneration than nontreated dogs.

The kidney, adrenal, and intestinal tract had varying degrees of degeneration. The kidneys showed tubular degeneration with only two dogs also having glomerular degeneration.

The adrenal glands showed a more or less uniform degree of degeneration throughout the gland with the exception of the zona glomerularis which in all except two dogs was not degenerated.

The intestinal tract slides were hard to evaluate since several sections did not show ulceration even when clinically gross intestinal hemorrhage was present. The basement membrane and muscularis mucosa were intact on all slides despite mucosal degeneration.

Various degrees of congestion and atelectasis occurred in the lungs of the dogs. Liver degeneration was in all cases most marked centrally in the lobules with the peripheral areas spared except in the most severely degenerated cases. The central vein showed some congestion in many sections. Frozen sections using Sudan IV stain were done on all lungs, and scattered kidneys and livers. Dogs 2,16, and 22 showed fat embolisms of varying degree in proportion to the length of survival (57). Evidently a dog

predisposed to develop fat embolism will develop it in increasing severity with the length of survival after a hemorrhagic shock state.

Every kidney examined revealed fatty degeneration of tubules but the livers showed only a rare fat globule in the tissue.

DISCUSSION OF FINAL RESULTS -- The fact that in these experiments the survival rate was significantly increased indicates that dibenzyline is beneficial when administered in the dosage of 3 mg/Kg. after irreversible shock has developed. Two actions of dibenzyline are most likely responsible for the increased resistance to shock. The adrenolytic action may be effective in increasing the blood supply to vital organs via lessening the degree of vasoconstriction produced during the shock state. The other explanation for its benefit may be a direct effect upon the liver cells unabling them to maintain their function of metabolizing toxins during the period of impending collapse prior to death. This theory would agree with the work of Baez, et al (2) that liver slices from dibenzyline treated shocked animals maintained the ability to inactivate ferritin in vitro. Although no precise explanation for dibenzyline's liver protecting action is known at the present time improved liver blood flow might explain it.

The finding that all except one of the initial blood cultures were sterile and that one probably a contaminant appears significant when compared to the reported approximate 22 per cent positive in control dogs by Nelson and Noyes (67). By obtaining the blood for culture through the cut down the chance of contamination from the skin was eliminated. From the findings here it appears that the normal dog does not have a bacteremia. Nelson and Noyes (67) reported a similar 22 per cent incidence of positive cultures in hemorrhaged animals and concluded that shock per se did not increase the incidence of bacteremia. They cultured Clostridium perfringes in the majority of cultures. In these experiments, however, while the incidence of terminal cultures which were positive approximated 25 per cent, not a single culture of Clostridium perfringes was found. Shock does appear to increase the incidence of bacteremia most likely via contamination from the ischemic gastrointestinal tract.

The decrease in the serum total lipid concentration may be a reflection of body metabolism or of the lipid clearing effect of heparin or both. However, it appears significant that all of the dogs tested showed the same decrease in lipid concentration.

The pathologic findings reveal several interesting things. First, livers in dibenzyline treated dogs showed less necrosis than nontreated dogs. This indicates that dibenzyline protects the liver via some mechanism. When considered in view of the

findings of Kelan (48) that dibenzyline protects against hemorrhagic shock only when the liver is present, this strongly suggests that maintenance of liver function improves resistance to hemorrhage. Going one step further this indicates that when the liver is able to metabolize toxins, either tissue or bacterial, liberated during shock the animal can better tolerate shock.

VI. Summary:

The preliminary studies in this series of experiments used Wiggers method of hemorrhagic shock which was abandoned in the final experiments because of the great variation in the shock state it produced. A modified Fine method of shock was used in the final experiments and proved to be a predictable method of producing uniform irreversible shock. The hemorrhage period was maintained as nearly physiologic as possible by using minimum sedation and adding heparin to the blood after it was bled from the dog. Dibenzyline was added in the dosage of 3 mg/Kg. along with the hemorrhaged blood after 25 per cent uptake had occurred, thus irreversible shock was definitely established prior to treatment.

The survival rate of treated animals was increased significantly over controls although the mean survival time was not significantly prolonged despite a 228 minutes longer mean survival. The results found here definitely show that dibenzyline exerts a protective effect when administered in this dosage to dogs in irreversible shock.and brings up the question as to its possible benefit in human cases of irreversible shock.

Blood cultures taken showed no bacteremia prior to shock and approximately a 25 per cent incidence of bacteremia at the time of death. Suggesting that much of the previous work reporting high incidence of initial bacteremia may well reflect error in method.

Pathologic findings of less liver degeneration in dibenzyline treated animals gives fair evidence to the fact that dibenzyline may well protect via either a direct liver effect or a secondary liver effect.

The results obtained in this experiment definitely indicate a need for further investigative work with this agent and a re-evaluation of the techniques and results obtained in the past.

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TABLE 1

Effect of Hypotension on Blood Flows (95)

	Hepatic Artery Flow	Portal Vein Flow
Control	175 ml/min.	309 ml/min.
60 mm. Hg.	100-130 ml/min.	127 ml/min.
40 mm. Hg.	71 ml/min.	100 ml/min.
Post-reinfusion	Approx. normal	470 ml/min.

TABLE 2

Blood Flows Following Acute Hemmorhage (74)

Portal vein flow decreased	7-77%	Mean 40%
Hepatic artery flow decreased	35-96%	Mean 52%
Ascending aorta flow decreased (output minus coronary flow)	27-50%	Mean 38%
Femoral artery flow decreased	20-70%	Mean 50%

TABLE 3

Blood Changes in Hemorrhagic Shock (20)

	Control	50 mm Hg.	30 mm Hg.	Terminal
Glucose	92.8	309.1	380.3	87.2
Pyruvic Acid	1.10	2.98	3.82	2.22
Lactic Acid	14.3	99.5	139.0	49.8
Inorganic phosphorus	3.8	6.5	6.5	5.4
Lactic Pyruvic	12.9	34.2	37.1	29.1
Blood pH	7.28	6.96	6.87	7.09

TABLE 4

Drugs and Their Modes of Action (43)

Action Drug	Drug Actions			
	Ganglionic Blocking	Adrenolytic	Anti-cholinergic	Anti-histaminic
SC-2159	+++	0	0	0
Dibenzyline	++	+++	+	+
Atropine	+++	0	+++	0
Hexamethonium	+++	0	+	0
Banthine	++	0	++	0
Probanthine	++	0	+++	0
Benadryl	0	++	+	+++

TABLE 4

Drugs and Their Modes of Action (43)

Action Drug	Drug Actions: Ganglionic Blocking	Adrenolytic	Anti-cholinergic	Anti-histaminic
SC-2159	+++	0	0	0
Dibenzyline	++	+++	+	+
Atropine	+++	0	+++	0
Hexamethonium	+++	0	+	0
Banthine	++	0	++	0
Probanthine	++	0	+++	0
Benadryl	0	++	+	+++

TABLE 5

Difference in Barbituate and Morphine Effect

	Barbituates	Morphine
Body temperature	Decreased	Decreased
B. M. R.	Decreased	Decreased
Blood sugar	Decreased	Increased
G. I. motility	Decreased	Decreased
Blood volume	Decreased	No effect
Heart output	Increased	Increased
Chemoreceptor reflexes	Depressed	Decreased
Pressor receptor responses	Depressed	Increased
C O_2 tension	Increased	Increased
Vagal tone	Decreased	Increased
Respiratory rate and depth	Decreased	Decreased
Spinal reflexes	Depressed	Stimulated
Peripheral Vascular dilation	Increased	***
Intestinal blood vessels	Dilated	***
Coronary vessels	Dilated	***
Myocardial contraction	Depressed	***
Nerve transmission	Depressed	***
Urine formation	Decreased	***
Filtration fraction	Increased	***
Liver function	No effect	***
Muscle tremors	***	Decreased

Figure 6.

BLEEDING CANNULA

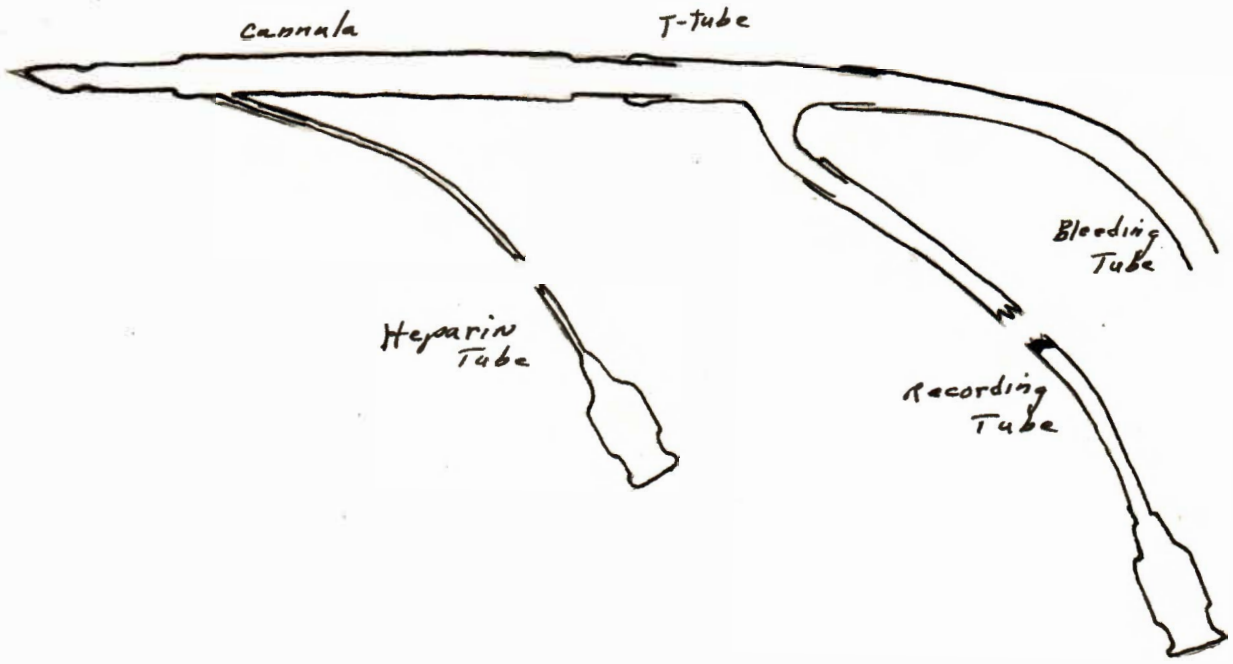


TABLE 7

Preliminary Experiments
Survival

Survival in minutes from start of hemorrhage to death	Survival in minutes from start of reinfusion to death
CONTROLS	CONTROLS
832 female #4	611 female #4
1440 female #8	1290 female #8
TEST GROUP	TEST GROUP
262 male #5	116 male #5
895 male #7	750 male #7
1440 female #9	1278 female #9

TABLE 8

Lipid Determinations

Dog No.	Sample	Serum Lipids	Survival after Start of Hemorrhage
# 4	Initial sample	Sample lost	832 Minutes survival
	Terminal sample	0.35%	
# 5	Initial sample	0.55%	262 Minutes survival
	Terminal sample	0.54%	
# 7	Initial sample	0.43%	895 Minutes survival
	Terminal sample	0.37%	
#12	Initial sample	0.38%	122 Minutes survival
	Terminal sample	0.28%	
#13	Initial sample	0.65%	147 Minutes survival
	Terminal sample	0.53%	
#14	Initial sample	0.52%	175 Minutes survival
	Terminal sample	0.45%	

TABLE 9

Preliminary Experiments
Bled Volume

Dog. No.	Bled Volume End 50 mm/Hg Period	Max. Bled Volume During 30 mm/Hg Period	Room Temperature
# 1	38.4	41.75	26.5
# 2	53.8	60.5	25.0
# 3	58.8	80.2	23.0
# 4	48	50.8	27.5
# 5	39.7	42.7	28.5
# 6	-	-	28
# 7	57.1	63.2	29
# 8	49.75	53.7	28
# 9	52.2	62.2	30
#10	44.3	47.8	30
#11	61.2	65.25	30
#12	55.6	57.5	31
#13	50.25	53.8	28
Mean	50.8	Mean 56.2	

TABLE 10

Vital Measurements of Experimental Dogs

Treated Dogs	Initial	Start of Reinfusion	30 Min.	60 Min.	End Mean Initial Mean	30 Min. Mean Initial Mean	60 Min. Mean Initial Mean
#17 MBP	137	122	90	78	.89	.66	.57
HR	136	187	187	192			
BP	183/111	158/107	113/73	93/65			
PP	72	51	40	28			
#19 MBP	134	93	90	103	.69	.67	.77
HR	125	146	145	160			
BP	177/115	131/77	133/87	130/41			
PP	62	54	46	39			
#20 MBP	144	71	68	73	.49	.47	.51
HR	160	230	230	214			
BP	168/118	87/58	92/53	87/57			
PP	40	29	39	30			
#23 MBP	128	81	53	47	.63	.41	.37
HR	136	187	214	200			
BP	143/110	110/62	66/47	58/43			
PP	33	48	19	15			
Non-treated Dogs							
#15 MBP	133	115	100	107	.86	.75	.80
HR	150	158	113 Irreg.	104 Irreg.			
BP	169/123	157/99	205/87	124/83			
PP	46	58	118	41			
#18 MBP	166	104	101	93	.63	.61	.56
HR	199	134	136	136			
BP	196/142	135/94	130/88	124/85			
PP	54	41	42	39			
#21 MBP	128	118	125	122	.92	.98	.95
HR	144	176	174	175			
BP	175/112	167/107	172/113	175/108			
PP	63	60	59	67			
#22 MBP	158	106	120	94	.67	.76	.59
HR	143	160	167	175			
BP	190/138	140/90	160/104	134/88			
PP	52	46	56	46			

Figure 11.

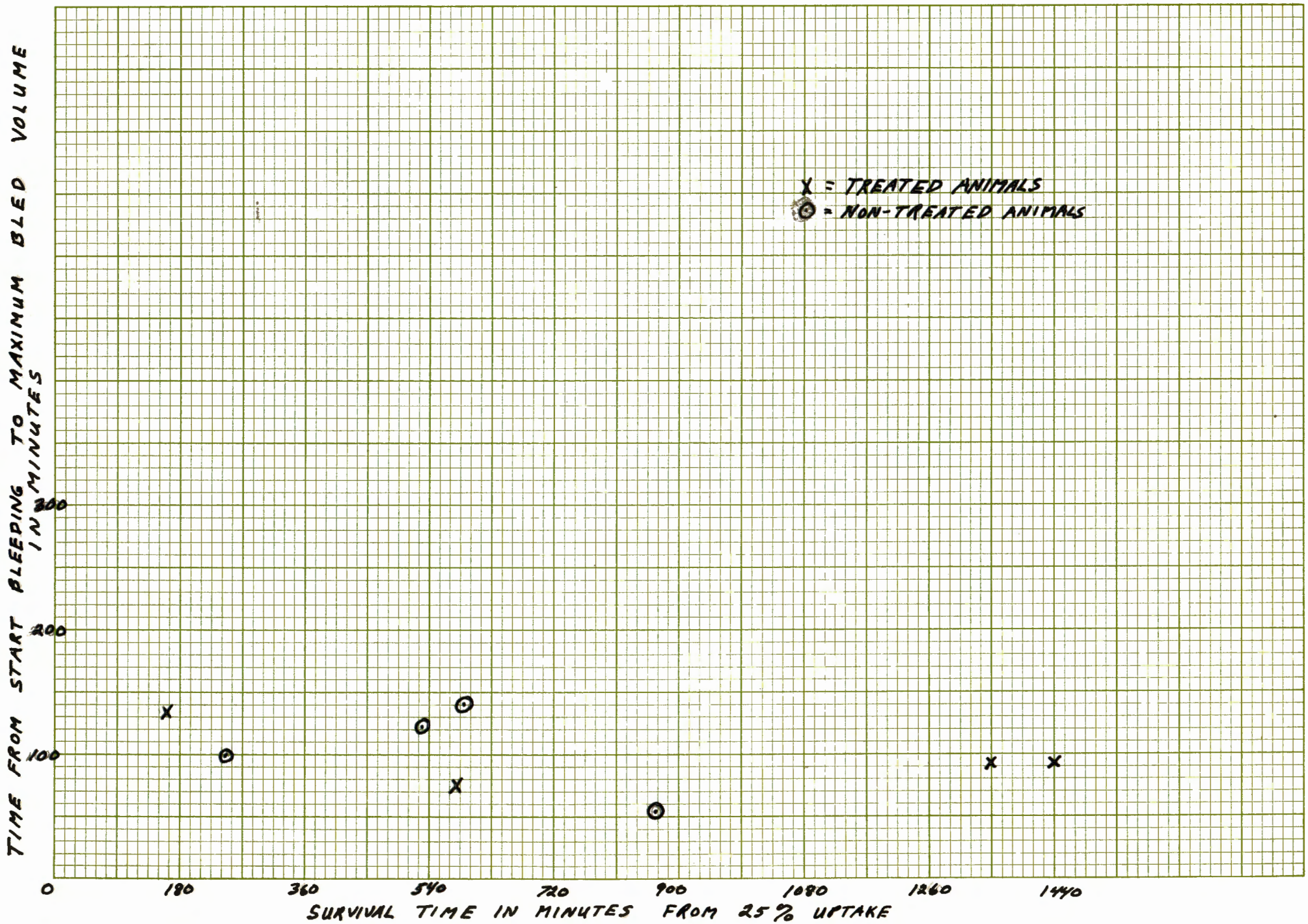


Figure 12

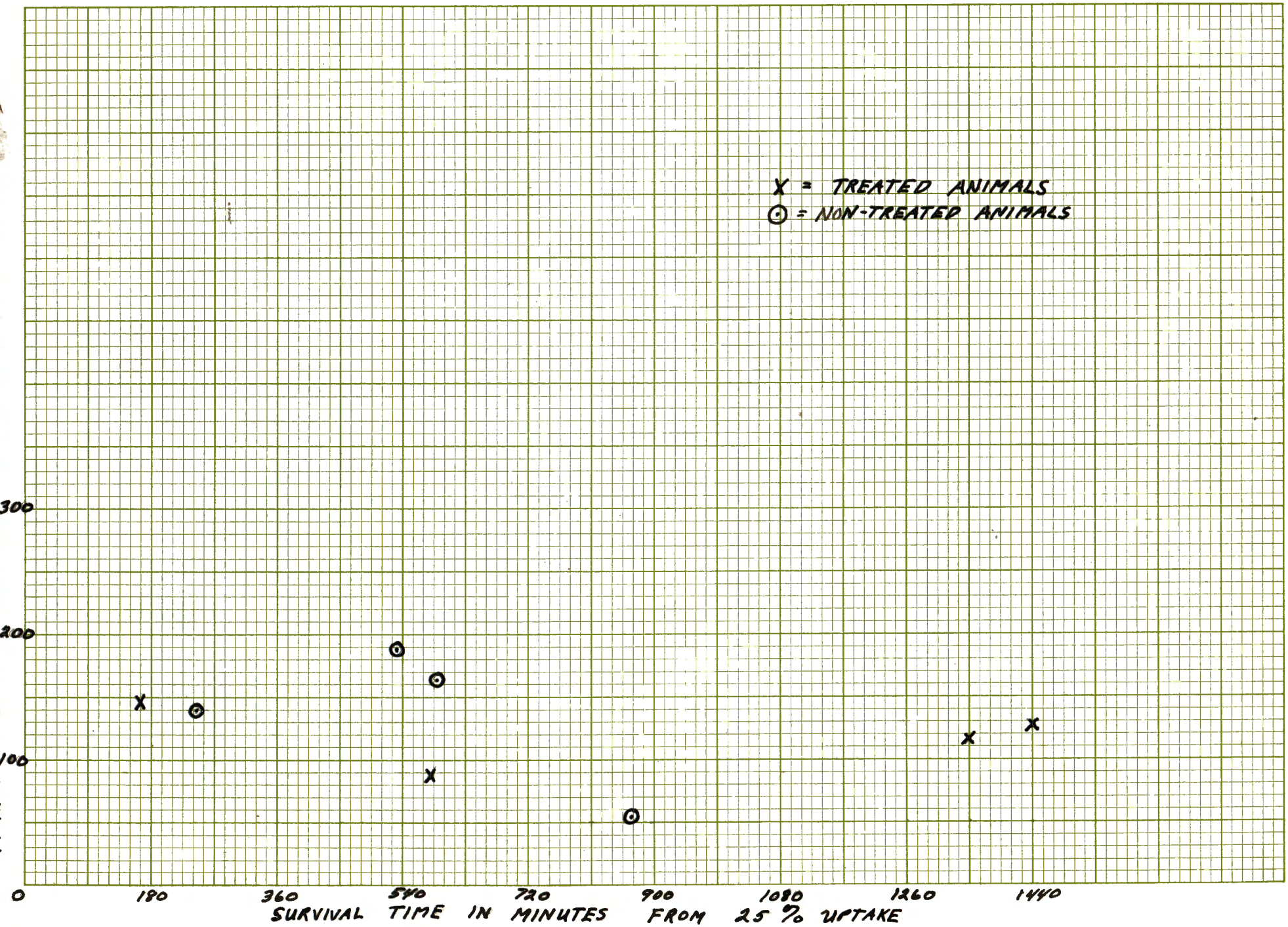


Figure 13

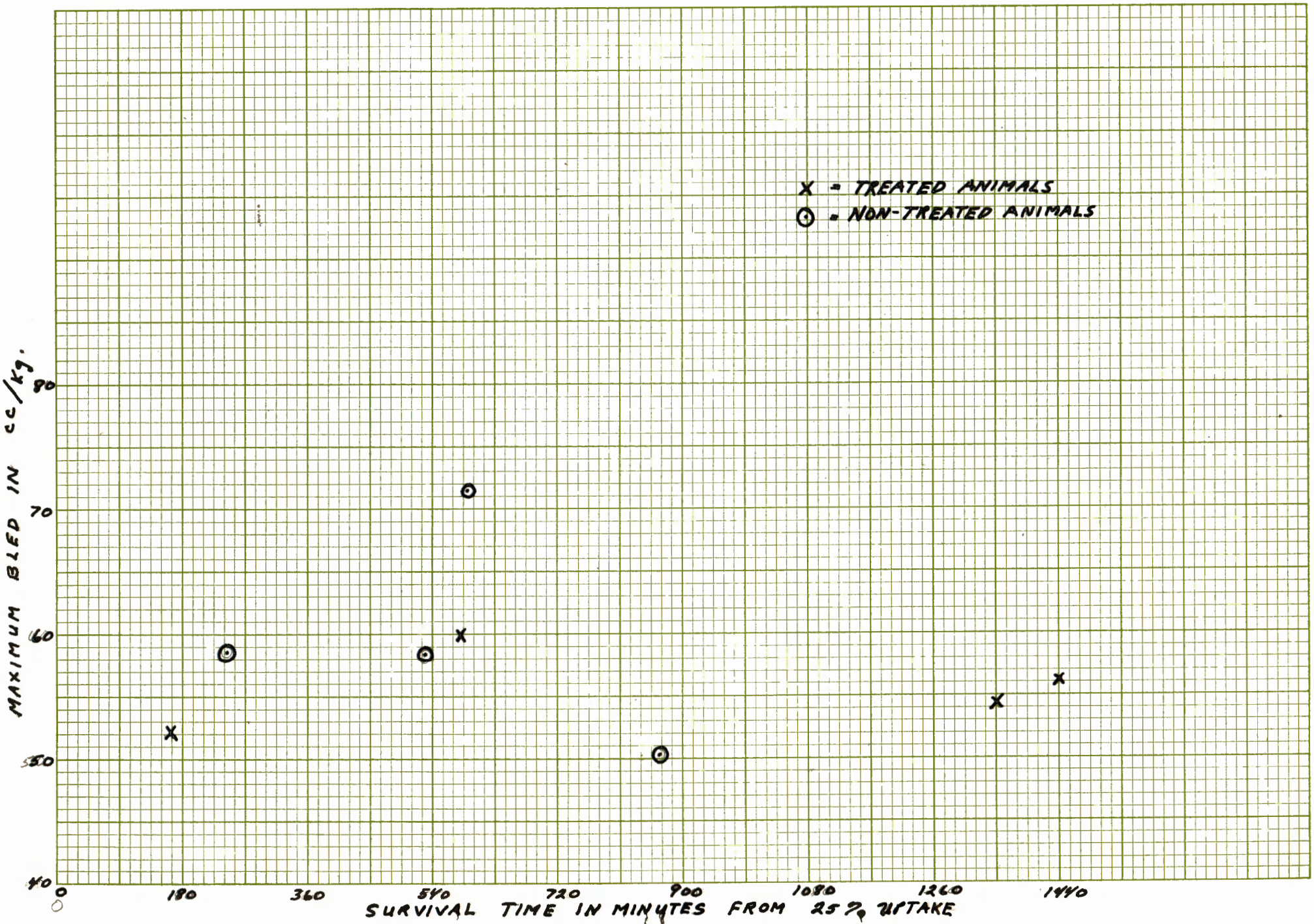
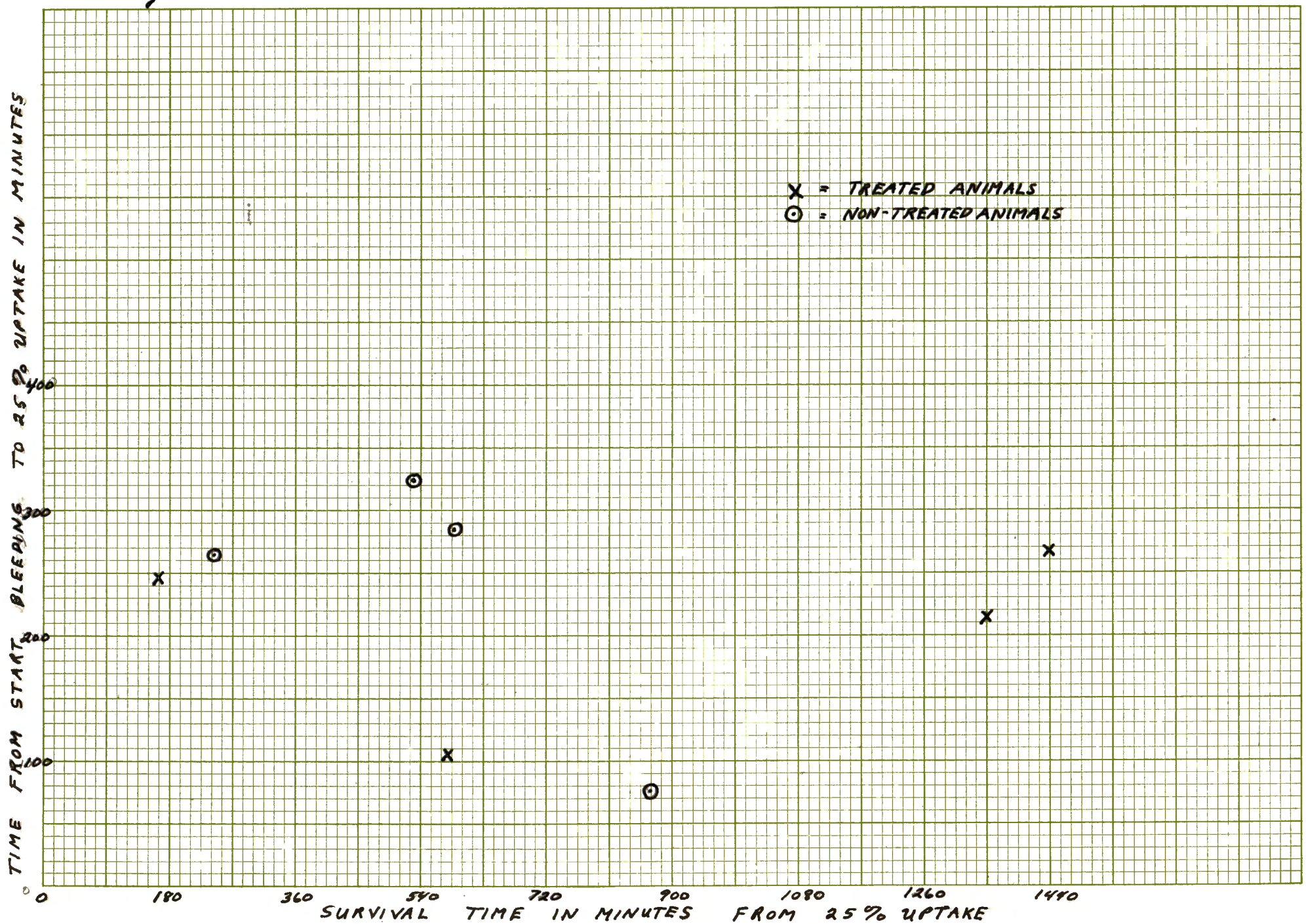
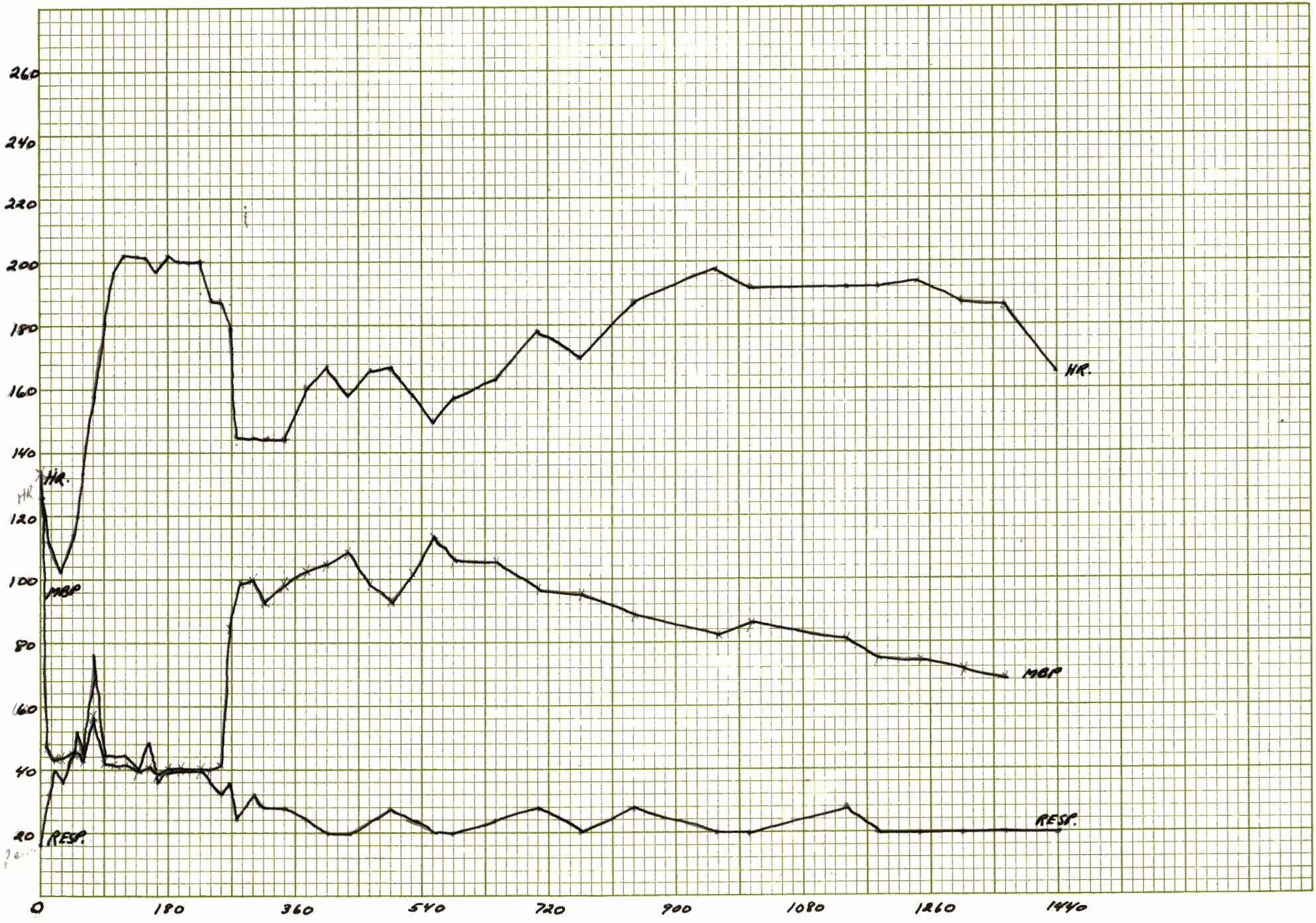


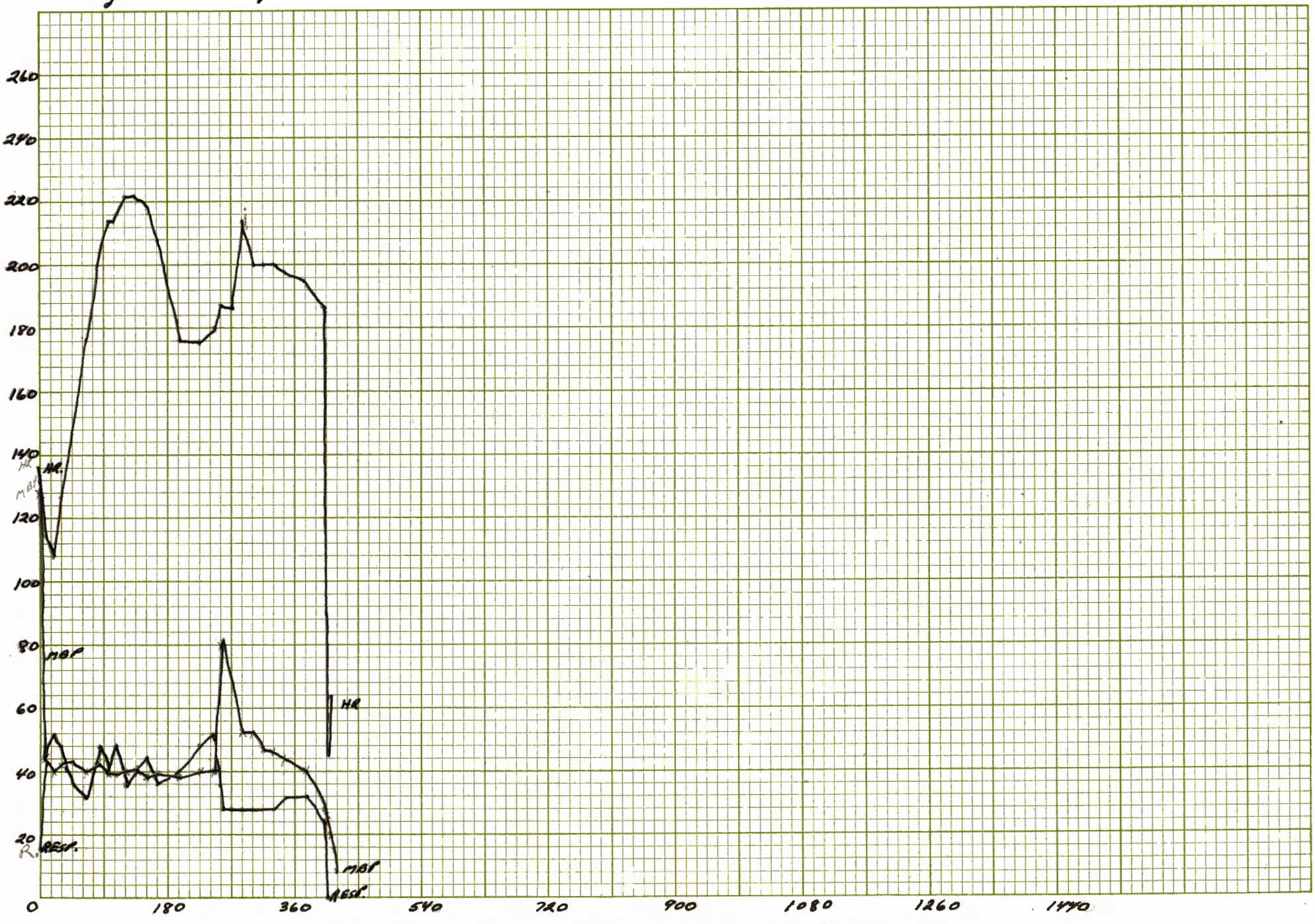
Figure 14



Dog #19 Figure 15



Dog #23 Figure 16



Dog #21 Figure 17

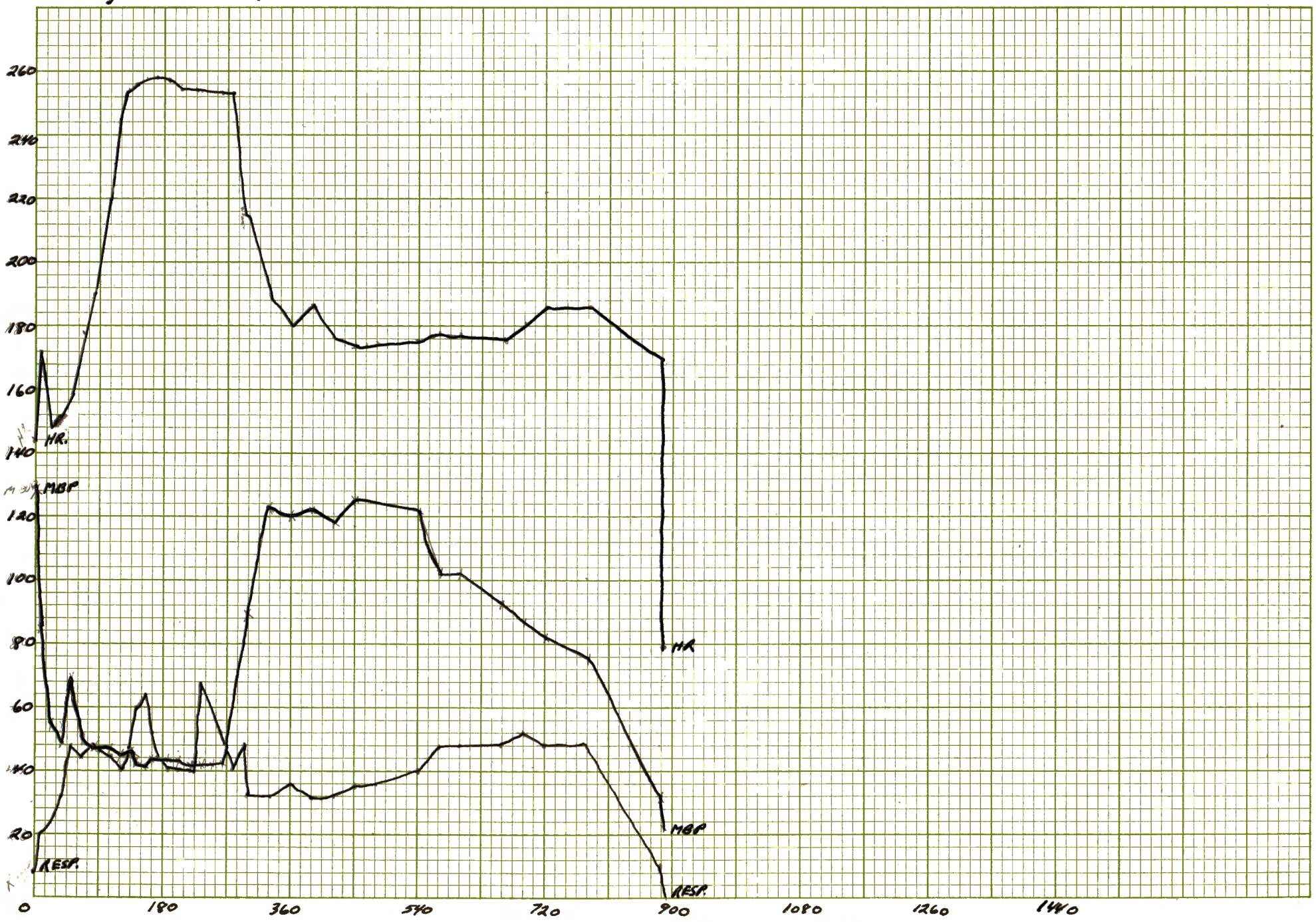


TABLE 18

Blood Cultures

Dog No.	Growth at 48 hrs.	Growth at 10 days
4 Pre	None	None
Term	None	None
5 Pre	None	None
Term	None	None
6	No cultures taken	
7 Pre	None	None
Term	None	Non-hemolytic Staph. albus
8 Pre	None	None
Term	None	None
9 Pre	None	None
Term	Anaerobic diphtheroid	
10 Pre	None	None
Term	None	Anaerobic diphtheroid
11 Pre	None	None
Term	None	Non-hemolytic Staph. albus
12 Pre	None	None
Term	None	None
13 Pre	None	None
Term	None	None
14 Pre	None	None
Term	None	None
15 Pre	None	None
Term	None	None
16 Pre	None	None
Term	None	None
17 Pre	None	None
Term	None	None
18 Pre	None	None
Term	Beta Hemolytic Streptococcus (enterococci)	
19 Pre	None	None
Term	None	None
20 Pre	None	None
Term	Hemolytic Staph. aureous	
21 Pre	None	None
Term	None	None
22 Pre	None	None
Term	None	None
23 Pre	Gram Pos. bacillus (contaminant)	
Term	None	None

Pre---Prehemorrhage blood sample
Term--Terminal blood sample

TABLE 19

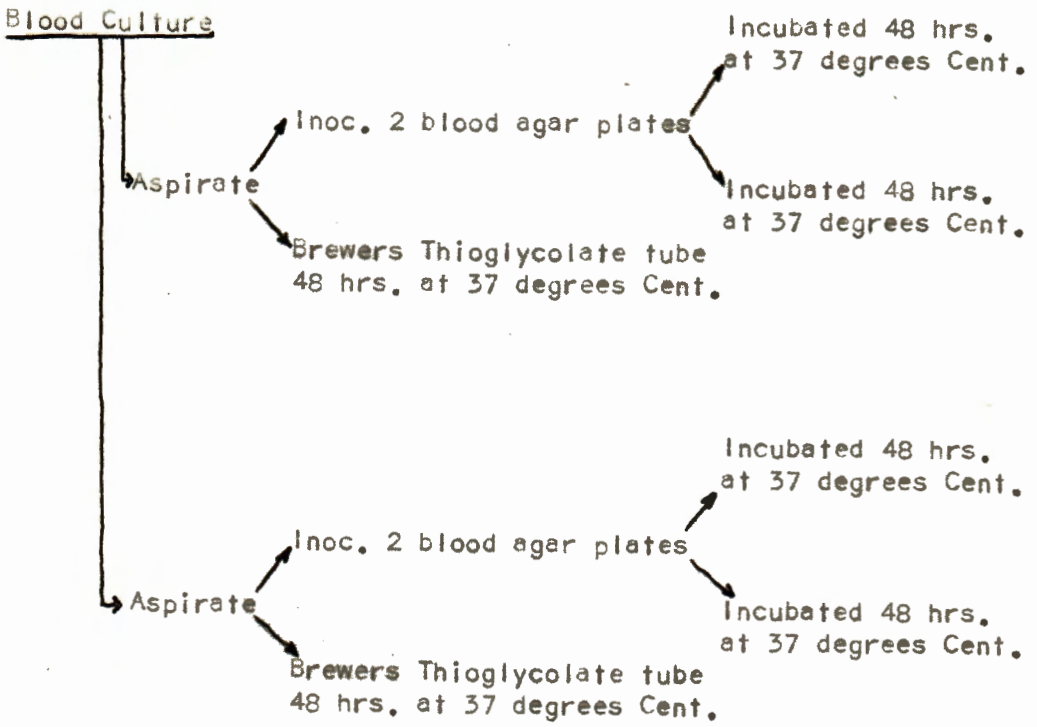
Pathologic Finding

Dog No.	Survival Time	Lung Congestion	Liver Degen.	Spleen Blood	Adrenal Degen.	Kidney Degen.	Colon Degen.	Small Bowel Degen.
# 1		None	Mod.	Little	-	Marked	-	-
# 2		Mod. Cong.	Mod.	Mod.	-	-	-	-
# 3		Mod. Cong.	Mod.	Very little	Slight	Marked	Sl. Degen.	-
# 4	832	Mild	Marked	Mod.	Mild	Mod.	-	-
# 5	*262	Mild	Mod.	Marked	Slight	Slight	-	None
# 7	*895	Mild	Mild	Mod.	-	Mild	-	-
#10		Mild	Very Slight	Little	None	Mild	None	Slight
#11		None (Parisite)	None	Little	Slight	Marked	-	None
#12		Mod.	None	Mod.	Very Slight	Marked	Mild	Mild
#13		Mod.	Mild	Mod.	Mild	Mild	Slight	Mild
#14		Marked	Slight	Marked	None	Marked	-	Slight
#15	510	Very Sl.	Slight	-	Mild	Mod.	Slight	Slight
#16		Slight	-	Little	Mild	Mod.	Slight	None
#17	*684	Slight	Slight	Mod.	Slight	Mod.	Slight	Mod.
#18	942	Mild	Marked	Mod.	None	Marked	Mod.	None
#20	*1440	-	Slight	Little	Mod.	Mild	None	None
#21	873	Slight	Mild	-	-	Mod.	-	-
#22	852	None	Mod.	Mod.	Very Slight	-	Marked	Slight
#23	*311	Slight	Very Slight	Mod.	-	Mild	Slight	Mod.

* = Treated animals

FIGURE 20

Culture Method



Isolated colonies were culturally and morphologically identified.