HYDRALAZINE, L-NOREPINEPHRINE, AND HYDROCORTISONE IN THE TREATMENT OF HAEMORRHAGIC SHOCK

by

Robert W. Hakstian, M.D.

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfilment of the requirements for the degree of Master of Science.

Department of Experimental Surgery,
McGill University,
Montreal.

August 1960

PREFACE

As the zealot increases his effort when the solution to his problem eludes him so reasearch workers everywhere continue to investigate more eagerly than ever the remaining unsolved enigmas of irreversible haemorrhagic shock. Paralleling the work that attempts to find the basic truth about the process of irreversibility in shock is an endeavour to discover a treatment for this condition. In this laboratory in the past several years both courses of action have been followed. While an attempt has been made to explain certain observed phenomena relating to fluid and cell shifts and metabolic changes and account for them causally in the process of irreversibility the effects of certain pharmacological agents and intravenous infusions have been examined.

The investigator who tries to accomplish only the latter, that is to find a cure for the condition, might be accused of impatience for first not solving the complete puzzle of causes. However in respect to this condition it is reasonable to assume that although the etiology of it is not an established fact, enough important knowledge is now available so that a fairly logical approach to treatment can be made. The current work was undertaken chiefly with a view to finding reliable therapy but with the hope that a byproduct of the work would be an addition to the body of knowledge concerning the etiology of the process.

With a fresh approach to the problem we have sought to find a satisfactory pharmacological treatment for irreversible haemorrhagic

shock. A form of standardized shock procedure was developed which was sufficiently severe to produce regularly the desired irreversible process but which would not lead so far into the hopelessly irrevocable state that had been experienced before with the Fine[29] method. We have employed this variation in technique throughout the experimental work. With it our aim has been to take the knowledge previously gained and by applying Platonic reasoning arrive at a logical treatment regime for specific cases. Hereby we sought to evaluate in hypovolemic shock the agents hydralazine and l-norepinephrine.

A final purpose has been to adopt the reasoning method of Aristotle apropos treatment with hydrocortisone in our animal preparation and after careful observation and assessment of the results try to account for its actions. Our views on the value of this drug in the shock state were not settled at the outset. It was,then,with a modification of the technique of inducing hypovolemia that we sought to learn how beneficial these three agents are in the treatment of irreversible haemorrhagic shock.

The contents of this treatise will include an introduction to treatment in shock with references to the presently accepted views of the process per se. The historical review will be concerned with the different restorative agents that have been proposed and especially with pharmacological products. This account will parallel the ideas concerning etiology and mechanism of various researchers. The shock technique used and the results will be outlined and followed by a discussion and conclusions.

I am extremely grateful to Dr. D.R. Webster, director of the laboratory for providing me with the occasion to persue this work at the Donner Building. For the opportunity of working on the problem of shock I am indebted to Dr. F.N. Gurd, sponsor of the project. Both he and

Dr. L.G. Hampson have given generously of their time throughout the year to guide the work and offer suggestions of importance and interest.

I should like to thank Dr. H.R. Robertson and Dr. S.C. Skoryna for their interest in the project and also those who were present for the presentation of this work and whose criticism and ideas were subsequently used in the experimental work.

My good friend Dr. R.M. Baird has frequently made astute observations and suggestions in respect to the project. It has been a pleasure also to associate with my fellow research workers: Dr. H.H. Sigman, Dr. R.K. Greenlaw, Dr. G.K. Wlodek, Dr. G.M. Lucciolo, Dr. A. Becerra, Dr. J.C. Rodriguez, and Dr. E.D. Monaghan.

The accomplishment of satisfactory experiments would have been impossible without the efficient organization of the laboratory by Mr. Albert Nagy and his staff.

Miss Anne Watkins eagerly undertook the extra work of biochemical measurement of blood samples and to her and Miss U. Murer our secretary I owe my thanks.

The experimental work was assisted by a grant-in-aid from the Rotary Club of Montreal;(the Cripples' Aid Committee).

Hydrocortisone was donated by the Upjohn Company of Canada, Ltd.

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

PART III. RESULTS

PART IV. CONCLUSIONS

LIST OF TABLES

LIST OF TABLES - Continued

LIST OF ILLUSTRATIONS

INTRODUCTION

In 1947 and again in 1954 Jacob Fine and his associates emphasized that in severe haemorrhagic shock replacement of the blood lost was not enough to guarantee a survival of the experimental animal[29,36,89]. He pointed out that factors come into play which result from haemorrhage but cannot be corrected by transfusion. This concept was reiterated by Moyer[73] who made the point that death and morbidity in severe hypovolemic shock is undoubtedly due to a lack of perfusion of vital organs but that simple replacement of fluids is not enough to renew this flow. A reversal of the process which is active in inciting the exclusion of vital tissues from the nutrient flow of blood is needed, he argued.

This well recognized situation whereby replacement of the blood lost fails to lead to recovery is termed irreversible haemorrhagic shock. It is indeed a condition seen rarely in clinical practice because as astute clinicians and research workers have observed [40,45] adequate restoration of the patient's blood volume almost always corrects shock in the absence of overt sepsis. The fact that irreversible shock, or as Weil[105] prefers to term it, 'delayed shock', does occur clinically is enough to justify the effort being made in many separate laboratories to understand the mechanism of it. Certainly the state can be easily produced experimentally and so laboratory animals, dogs especially, are used to investigate this disease.

Simply because blood volume replacement fails to save the severely

shocked animal one can not presume that survival is precluded. To be sure patients who have developed delayed shock from severe blood loss during drastic surgery have been retrieved with adrenal corticoids for example.[17]

The challenge of the so called irreversible state has been met by a barrage of therapeutic agents. Their use has usually been carefully thought out; occasionally the advocate is encouraged by limited empirical results.

Corrective regimens fall into three main groups: Intravenous infusions of either blood, plasma expanders or electrolytes; hypothermia; and pharmacological agents. These may be employed separately or in combination in experimental work and as preshock or postshock treatment. The concern of the present work is with pharmacological agents used at some time after the shock process has begun. The fallacy of preshock treatment will be discussed.

It is necessary to outline the present theory of the irreversible shock process in order that a base line for treatment be known. As has been indicated there is not universal agreement concerning the mechanisms acting in shock and the picture from initial haemorrhage until death has not yet been painted in colours which are perfect in their harmony. Nonetheless enough is known and the discordance is sufficiently little that the image can be understood. An excellent review of the opinions and ideas that have gone to form the knowledge we now have on the subject of shock and a discussion of experiments is to be found in the dissertation of Inglis.[53] An historical review of theories on the production and evolution of shock and discussion of blood volume changes is given by Richards.[86] For a complete background picture of the strides made in

shock investigation the textbook of C.J. Wiggers is perhaps the classic work.[106]

The following is a description of the process as an animal continues to be bled out. The concepts of the mechanisms acting are interposed: The initial period of haemorrhagic hypotension is reflected in an increased pulse, reduction of both systolic and diastolic blood pressure, a decline in portal venous pressure, inferior vena cava flow, and ultimately a fall in cardiac output. Coronary artery flow is reduced and the spleen contracts. Vascular resistance increases first in the limb vessels, next in the gastrointestinal tract, then in the kidney vasculature. This contraction represents the normal vasopressor response and occurs in arterioles, metarterioles and precapillary sphincters.[13] Respiratory rate increases and there is good arterial oxygen saturation. Animo nitrogen begins to rise. If blood is replaced at this time the residual effects are minimal and include a persisting elevation of the non-protein-nitrogen. If bleeding is not stopped but persists the heart continues to accelerate; arterial and pulse pressures decline; coronary flow, venous pressure, cardiac output, and portal pressure drop. Inferior vena caval flow becomes especially low. Total peripheral resistance continues to augment as a rule but may decrease slightly. Resistances in specific areas show an increase. Now the nutrient flow begins to fall behind the requirements of the body at rest and anaerobic metabolism results. Blood lactate and pyruvate concentrations mount and acidosis occurs. Venous oxygen saturation is very low. The vasomotor centre of the brain nevertheless shows little evidence of exhaustion. Reduced blood flow is further aggravated by metarteriolar and precapillary sphincter spasm. This at one time was thought to be due to circulating V.E.M. (vaso excitor

material)[70,93] but now is thought to result from endotoxin potentiation of circulating adrenergic drugs,[30,66] Effective tissue flow is greatly curtailed. The kidney reacts to a reduced renal blood flow and oliguria evolves. Tubular injury and lower nephron nephrosis occurs later[90,91] It is in the mesenteric region that curtailment of capillary circulation is thought to be most dangerous.[66,67] Here vasoconstriction occurs early and the response to the vasoexclusion of tissues is ischaemia of the bowel with concomitant changes in the mucosa and other layers. Petechial haemorrhages begin to develop in the mucosa and wide scale edema of the mucosa and submucosa occurs. Even now it is possible for blood transfusion to save the animal because enough small channels are open to permit some oxygenation of tissues. If bleeding continues however the critical stage appears and is manifest by either cardiac slowing or acceleration; very low arterial pressures; small pulse pressure; further reduction in venous return, effective right atrial pressure, and hence cardiac output. Resistance in the mesenteric vessels, the arterioles, metarterioles, and capillaries, undergoes a secondary increase at this time and further aggravates the anoxemia of the tissues. It is thought that the initial bowel ischaemia which predisposes to necrosis of the mucosa leads to a release of endotoxin which is either bound to the tissues as a lipopolysaccharide or is elaborated by the E. coli normally present in the bowel.[30] Fine feels that, when absorbed, this toxin damages the reticulo-endothelial system and its effect becomes overwhelming when this system which normally disposes of it is hampered. Lillehei[66] believes that the necrotic bowel provides a field for rapid proliferation of E. coli and release of unusually high concentrations of endotoxin. Both men agree that the toxin acts by potentiating the circulating adrenergic drugs and aggravate the vasospastic state. It is

held that capillaries are affected by the endotoxin so that there is fracturing and hence leakage of large amounts of fluid.[30] Extensive bowel necrosis results from the ischaemia of the entire length of the bowel which represents the area of supply of the mesenteric vessels but primarily of the superior artery. Actual bleeding into the bowel lumen occurs because vessels are eroded in the ulcer bases. Plasma may escape by the same route or through fractured endothelium and is lost into the submucosal layers. Haemoglobin appears in the plasma and the haematocrit may rise. Because of this fluid loss there is a great reduction in the total blood volume and death occurs soon from cardiac and respiratory failure, unless transfusion is begun. However even if the entire amount of blood shed is returned to the animal there will be death, not immediately but within a few hours since the irreversible process is well under way. This is thought to mean that while not all capillaries are shut down, the vast majority of them are constricted at their sphincters and their infeeding metarterioles are critically narrowed thus forbidding blood flow by these routes.

It is interesting at this point to consider the manner of death in acute bowel obstruction. Markovitz[69] noted that often human beings die from intestinal obstruction while apparently in normal electrolyte balance, and therefore wondered if the outpouring of ion-rich fluids into the bowel was really accounting for death as had once been presumed. He felt that the effects of distention and necrosis of the bowel must play a part. This view was borne out by Harper and Blain.[48] In their dog experiments bowel obstruction was produced and death was noted to occur really before electrolyte imbalances could develop. At autopsy they noted the same changes of the bowel that are seen in haemorrhagic shock, viz.:

red, swollen mucosa with gross ulceration and the bowel lumen filled with red haemorrhagic material. Bacteria were present in large concentrations, especially gram negative types, and the conclusion they reached was that in the face of bowel distention and necrosis of the mucosa the products of these bacteria were absorbed and caused a toxemia. They did not elaborate on the possible mechanisms of action of the toxin but implied that blood volume was being depleted because fluid accumulating in the obstructed bowel was not being absorbed and additional losses from the intra vascular compartment were occurring due to ulceration of the bowel.

While reduced blood flow to the bowel is presently regarded as being of greatest significance in irreversibility the effect of diminished circulation to other organs has been considered too. Although it is known that the adrenals do not receive a normal circulation in shock it has not been established if this results in a deficiency of adrenal corticoids for tissue needs.[42] In late shock some investigators feel that brain ischaemia acts in a synergistic manner to speed the lethal effect of fluid loss.[59] Myocardial damage has been found and reported in shocked animals and no doubt this state adds to the animal's problem of maintaining an adequate circulation.[105]

The situation must be viewed clearly however and it is the prevalent idea now that when the capillary circulation of the bowel is virtually obliterated the process of irreversibility has begun. Survival does not relate to fluid replacement into the remaining open channels of larger calibre but to the reestablishment of capillary flow. The premise that the action of hydralazine might be beneficial and that of l-norepinephrine harmful in respect to renewing this flow has motivated the desire to evaluate these agents.

PART I

LITERATURE REVIEW

CHAPTER I

TREATMENT IN HAEMORRHAGIC SHOCK

Endorsement of a restorative agent or regimen generally reflects the investigator's thinking apropos the mechanisms involved in shock and perhaps also his ideas concerning etiology. In any case the history of treatment in haemorrhagic shock has closely followed the history of other developments in this field.

SECTION A. Intravenous Infusions.

Subsection 1. Blood. Perhaps the greatest amount of attention in respect to intravenous infusions has been given to blood perfusion of specific tissues by either cross vivperfusion of animals or direct mechanical infusion into isolated vessels. Selkurt[92] believed that increased hepatic resistance and hence elevated portal pressure led to a decrease of mesenteric vascular resistance and subsequent pooling of large volumes of blood in the visceral vessels. He supported this belief experimentally by using non-shocked dogs and producing an artificial portal obstruction. He hereby created the shock picture by greatly reducing the circulating blood volume. In an attempt to prove that liver function is important in the survival of a shocked animal Frank, et al.[37] crossed perfused the splenic vein, and hence portal, of shocked dogs from systemic arteries of normal animals. With the test animals the majority survived whereas with shocked dogs which were perfused into the

the jugular vein from the donor dog 15 out of 17 died. Cohn and Parsons[16] preferred to do without a donor animal and perfused their shocked dogs by means of a vessel grafted between the aorta and the portal vein of the experimental animal. There resulted an increase in portal vein pressure to beyond normal levels and concomitant survival of 7 out of 8 animals. Three out of 23 control animals survived and from this the authors drew the same conclusions as Frank, viz., that in shock a protective effect is provided by the liver and that this is due to an improved blood flow through the liver. No attempt was made to explain the mechanisms of such and effect. Again Hay and Webb[49] concluded that some protection is afforded to shocked animals by increasing the arterial blood flow to the liver. Their animals were autoperfused by a splenic artery - splenic vein anastomosis and showed less than 10% mortality versus more than 85% mortality in controls. Some controls were splenectomized and others not but this did not alter their results. Delorme[20] felt that oxygen concentration of portal blood was more important than the perfusion rate and he attempted to show this by perfusion experiments in animals held at 35 mm Hg. Control animals consisted of those either perfused from a systemic artery to a systemic vein (generally femorals) or from the inferior vena cava to the portal vein whereas test animals were either perfused from systemic artery (femoral) to portal vein (via splenic) or were perfused with oxygenated systemic venous blood. This latter group fared best but the prolongation of survival time over controls was not significant. He concluded that portal blood of oligaemic animals has an oxygen saturation approaching zero and the reason for prolonged survival in his test group was better oxygenation of the liver. This oxygneation, he hypothesized, either prevented the development of a vasodilatory agent such as Shorr's V.D.M.

(vaso dilator material) or favored the elaboration of a vasopressor substance (cf. V.E.M.) by improving liver cell function.

Even while the liver was being incriminated as the organ most responsible for irreversibility of the shock syndrome investigators could not help noticing the changes in bowel mucosa which appeared regularly at autopsy. Before 1950 this condition was blamed on the liver. It was reasoned[92] that an increase in vascular resistance in the liver led to a damming effect of the inflowing mesenteric blood and accounted for the increase in bowel weight and the ischaemic mucosal changes. It remained for Bradley[9] to show that there is actually a blood volume decrease in the splanchnic vessels. R.C. Lillehei[66] confirmed this finding that there is less than 25% of normal mesenteric vessel flow in haemorrhagic shock and by perfusion experiments went on to demonstrate that the liver does not play a crucial role in irreversible hypovolemic shock. His premise was that the ischaemia of the bowel with subsequent necrotic changes and extensive fluid loss was due to a reduction of arterial flow into, rather than a blockage of venous flow out of, the bowel. To substantiate this opinion with proof he cross-perfused the superior mesenteric artery of dogs being shocked to 35 mm Hg. maintaining a pressure in this vessel of 140 mm Hg. Donor dogs received blood from the shocked animals. Lillehei claimed 90% survival of these dogs whereas control dogs all became irreversible. Also lost were control animals receiving aortic blood (donor) into the femoral artery and vena cava blood (donor) into the femoral vein. All the usual signs of irreversibility appeared in the three control groups. A contribution was made concomitantly which when added to Jacob Fine's work of a few years previously weighed heavily against the liver as being the most significant organ responsible. Both these investigators

observed that in Eck fistula dogs (animals with an end-to-side porto-caval shunt) there was no increase in the number of survivals.[39,66] This forcefully inplied that increase in intrahepatic resistance to blood flow was not responsible for death and not likely the cause of the bowel changes since by means of the shunt all flow was diverted from the liver. At this juncture some argued that with a shunt there was no flow of portal blood to the liver and hence a greater opportunity existed for lethal metabolites to accumulate and encourage irreversibility. Further work by Frank using side-to-side anastomoses and thus allowing the liver a supply of portal blood showed no alteration in the survival picture however.

A by-product of the whole blood perfusion experiments has been pure oxygen infusion. Fine and Frank[35] in 1943 attempted to raise venous oxygen concentration by administration of up to 3 volumes of oxygen and found that there was no improvement whatsoever of the shock state. Although venous oxygen concentration was raised, apparently the tissues were unable to utilize it. The same finding was made by Wood.[112] When he gave 100% oxygen to animals (by inhalation) there was an increase of venous oxygen to the extent of two volumes percent but no improvement in survival rate. According to him the reason for the lack of benefit to the tissues by an increase in oxygen saturation was the reduction in shock of the cardiac output.

It may seem that there is an irreconcilable situation existing when the 1946 and 1951 work of Frank and Fine are regarded together.[37,39] Why did animals survive with an intact portal system in the earlier experiments when those with Eck fistulas died when subjected to the same type of shock four years later? The answer lies in the fact that although the damming effect of the liver due to increased vascular resistance with resulting

detention of large quantities of blood in the mesenteric bed was no longer deemed significant the increased flow of portal blood by perfusion did allow the liver to overcome a deleterious effect somewhere else. Perhaps, they suggested, the formation of harmful metabolites or toxins was retarded by a more nearly normal liver function, or perhaps the reticulo-endothelial system suffered less damage in the presence of some portal flow.

Some fascinating cross perfusion experiments have been done in Hungary.[59] Kovach isolated the heads of test dogs from their bodies except for nerve communications. He then shocked the body by Wiggers' technique and perfused the head via the carotid artery with arterial blood from normal donor dogs. He found that survival time increased in animals so treated and in some survival was permanent. All controls died. With these results he attempted to support his thesis that cerebral anoxia is an important factor in aggravating irreversible shock. A further conclusion can be drawn from his work, viz., that metabolites have been prevented from reaching the brain from the shocked bodies of these preparations and perhaps if these products are indeed toxic their harmful effect on the brain is forestalled.

Subsection 2. Plasma Expanders. The use of colloid expanders generally signifies a stopgap procedure when whole blood is not available or in limited supply[45] The qualities of nontoxicity or danger of producing haemolytic reactions and long storage life which these solutions possess make their use desirable however. It was because of the work of Aust[5] that the value of expanders has been reconsidered in recent years. He used radioactive iodine and chromium to reveal that plasma sequestration

occurs in the gut when dogs are shocked by a large dose of E. coli endotoxin. It was implied that there is an increase in capillary permeability and either a direct leakage of plasma or plasma skimming as a result. From his early radioactive protein studies Fine[27] maintained that plasma leakage did not occur except at the site of wounding in the case of traumatic or haemorrhagic shock but more lately[30] he has proposed that there is capillary fracturing with subsequent plasma leakage and it is this loss which ultimately lowers the blood volume to fatal levels.

Both of these workers indirectly inferred that plasma expanders might be more valuable than whole blood since with plasma volume loss there is already a relatively high haematocrit.

In Korean war field trials Frawley et al.[41] found that with gelatin of molecular weight 34,000 and dextran of molecular weight 42,000 less than 25% was retained in the intravascular space after 6 hours. They concluded that this loss was no greater in wounded patients than in normal persons. Experimental work on dogs done at about the same time by Slaney[95] demonstrated that dextran (relatively low molecular weight American type) was suitable for moderate degrees of shock only. He subjected his animals to major abdominal surgery after rendering them hypotensive. The controls were then reinfused with blood while the test animals were given a volume of dextran comparable to the amount of blood lost. There was a 20% mortality in this group as opposed to none in the blood-infused animals. This amount of trauma could be safely presumed to cause a moderate shock state but when Slaney carried the experiment to a severe point by further bleeding the animals and then reinfusing them with equivalent volumes of dextran the mortality rose sharply to 72%.

Such animals when infused with their own shed blood recovered in 96% of cases. A defect of haemostasis was considered to have been produced by the plasma substitute.

In a review of 3 injured patients treated with 6% Swedish dextran, Haynes and DeBakey[50] decided that the amount of whole blood loss rather than the degree of shock clinically observed is a better determinant for the advisability of expander use. They felt that when there is a great loss of red cell mass dextran alone is not sufficient but when the loss is up to 35% of blood volume the substitues were definitely advantageous both by permitting immediate surgery because of an amelioration of the patient's condition and by relegating the need for whole blood transfusion to a later date.

Perhaps the best attempt to compare, feature for feature, expanders with blood was made by Gropper.[44] He noted that the characteristics of a good expander included its ability to maintain a high colloid pressure, to be metabolized and excreted, and its faculty of non-pyrogenicity and non-antigenicity. He noted that if the molecular weight is too low the substance leaves the circulation too rapidly. If the weight is too high and the molecules therefore large they may be permanently stored. He devised a bleeding volume index which represented the amount of intravascular fluid that could be withdrawn to reduce the experimental animal to the same degree of hypotension as produced originally by bleeding. An expander had been given to match volume for volume the blood removed originally. With blood rated therefore as 100, the indices were as follows: dextran, 87; P.V.P., 84; gelatin 'P-20', 83; oxypolygelatin, 81; gelatin 'P-180', 65; and saline, 54. In a separate study the same investigator found that

oxypolygelatin compared very favourably with dextran and actually was better for prolonged hypotensive periods while the dextran was more effective initially. He found that with certain types of gelatin there was virtually no loss from the intravascular space. With most expanders he noted an increased sedimentation rate and with dextran there was a displacement of plasma proteins out of the vascular system. Similar conclusions were reached by Knutson et al.[60] who used rabbits for experimental purposes. They found that dextran and gelatin were the best expanders for restoring blood volume after acute haemorrhage. Although the total blood volume was restored to almost normal with the substitutes this was at the expense of the red cell mass naturally enough. Any expander would increase the plasma volume only.

During the search of the literature on this subject no proof was found that expanders are better than blood in the treatment of hypovolemic shock. These solutions have some advantages which distinguish them such as their ability to maintain the vascular space without producing any undesirable reactions in a way whole blood sometimes does but apparently they possess no power to reverse severe shock that blood does not have and certainly they lack many of the qualities of blood, oxygen carrying capacity probably being the most important.

Subsection 3. Crystalloid Solutions. Most workers agree that electrolyte solutions are of even less value than colloid solutions in the treatment of shock.[1,22,25,65,98] Others believe that they are really harmful because then reduce colloid osmotic pressure and therefore cause fluid to leave rather than enter the blood stream.[2,47] Fine[27] noted a transitory improvement to massive infusion of saline solutions and others

have agreed that some value is to be realized from the intravascular space filling effect which such infusions provide regardless of how brief this may be. The importance in severe or late shock is generally doubted. Dworkin[21] found for example that while Ringer's solution provided survival in dogs bled to 50 mm. Hg. for 30 minutes it did not guarantee success when the time was extended to 45 minutes. One positive approach to the use of electrolytes comes from the South Western Medical School in Texas.[109] This group noticed that generally the haematocrit is elevated in irreversible shock and that because blood is being lost from the vascular compartment through the bowel wall there is no point in giving more whole blood. Instead, they reasoned, why not fill the vascular compartment with interstitial-like fluid and thereby keep a balance with the 3rd space and help to lower the haematocrit. Their 48 hour survival in animals given saline solutions before reinfusion of blood was improved over that of control animals which were given their blood only. By way of explanation for better survival rate allusion was made to peripheral haematocrit values and reference to sludging in shock states. There is considerable disagreement however of these values even in normal health[25,26]. It is to be noted here that the saline was mixed with dextran and therefore some osmotic pressure was maintained intravascularly.

Some have argued that there are times when saline infusions may actually be superior to blood or plasma and the shock of severe burns with associated sodium depletion is an example often used.[32,33,88] However in hypovolemic shock the value of electrolyte solutions is not yet settled. The importance of the development of metabolic acidosis which occurs when tissues are hypoxic and the need for its correction by electrolyte solutions has been argued for many years. In 1919 Cannon[11] summarized

British thinking when he stated, "No evidence has been found to support the suggestion that acidosis indirectly favours shock by facilitating or intensifying the shock producing agencies with the possible exception of anaesthetics." However in more recent years there have been reports of beneficial effects of alkali therapy in shock both in laboratory animals and human beings.[18,32] Ingraham and Wiggers[54] disagreed with this at first but later decided that a continuous sodium bicarbonate (not sodium lactate) drip administered during the shock period lowered the acidosis and delayed but did not prevent irreversibility.[108]

It is generally conceded that although potassium concentrations in the blood increase during haemorrhagic shock they never become high enough to represent a threat to cardiac function.[111]

Although much work has been done on the importance of saline infusions in burn shock the value of sodium and chloride administration in hypovolemia certainly is not convincing. It is probably safe to say that while such phenomena as fluid and electrolyte shifts, haemoconcentration, and metabolic disorders such as acidosis accompany haemorrhagic shock they do not represent variables which have a key determining effect on the pathological processes involved nor on the outcome of the shock condition.[28]

SECTION B. Hypothermia.

Before the second world war the notion developed that hypothermia, by lessening the body's need for oxygen might be a useful procedure in the treatment of haemorrhage. Allen[1] was one of the first disciples and the idea quickly gathered supporters. Laborit[61] provided accounts of great success in 26 casualties of the Indochina war treated for shock by total body hypothermia. The casualties included victims suffering from multiple injuries caused by land mines, mortar blasts,and gun shot wounds and all presumably were suffering from marked blood loss.

Using dogs in laboratory controlled experiments, Postel et al.[78] shocked 15 control animals for 3 hours at 40 mm Hg. This resulted in a 24% survival rate. In 15 test animals, using ice baths to produce hypothermia to 27° C. dogs were cooled one hour after the start of the hypotansive period. With 93% survival the authors concluded that irreversibility had been thwarted by the cooling. While this technique might be questioned for its severity the results coincide with those of Overton and DeBakey.[75] These latter workers found that total body cooling, begun before haemorrhage produced a statistically significant improvement in survival time of animals subjected to the Fine method of haemorrhage. With this method there was almost 100% fatalities in the control animals and although survival times were better the absolute survival of cooled animals was not improved. Although with a similar experiment Cleghorn[15] found optimal survival at 22°C. Overton and DeBakey cooled their dogs to 31° C. only. At this temperature they felt that metabolism was reduced sufficiently to, "lower tissue oxygen requirements and prevent irreparable damage to vital centres responsible for maintenance of compensation mechanisms." They also postulated that cooling caused a better distribution of blood to the viscera by

a selective vasoconstriction in one part and dilation in another.

It remained for Swan[26] and his associates[110] to dispute the value of hypothermia especially as pretreatment. They noted that with the above experiments the cooled animals actually lost less blood in arriving at the predetermined hypotensive level. This meant that different degrees of hypovolemia were being experienced by normothermic and hypothermic animals. There they felt that a more reliable measure of the value of cooling would be arrived at by removing a fixed percentage of the animals blood volume in order to produce shock. Incidentally they have supported this technique for inducing shock in experiments other than those of hypothermia. This group found that by withdrawing 35% of the blood volume virtually no mortality results in normal animals. The surprising outcome of their experiments was proof that when an animal is cooled prior to haemorrhage mortality is greatly increased. Eighty two % of Swan's animals so treated died whereas all animals lived that were either simply bled 35% or bled 35% <u>then</u> cooled within 5 minutes to 25° C. What Swan did confirm was the impression of others that hypothermia improves tolerance to haemorrhagic <u>hypotension</u>. He quite appropriately made the point that this is not the same as improving tolerance to <u>haemorrhage</u>. Blalock[8] found the same fact to be true, viz., that cooled animals were able to withstand lower pressures for longer than normothermic animals but that ultimate survival was not improved. The latter's work was with tourniquet shock rather than with haemorrhage.

The dangerous complication of ventricular fibrillation at low temperatures accounted for a high percentage of deaths in Swan's series. He felt that probably the hypovolemia was responsible but added that cooling must be regarded as a predisposing factor certainly. One must note

his animals underwent total body cooling also.

Parkins[76] and his associates, who felt that the risk of cardiac arrest and fibrillation greatly increases when the temperature of the animal (rectal) is below 25° C. sought to explore the advantages of selective organ cooling. They chose to produce hypotensive shock by temporarily occluding the thoracic aorta because they had noted previously that this would result in a reduced blood flow and anoxia of viscera similar to that seen in hypovolemic shock. Surmising that specific organs vary as to their susceptibility to oxygen lack, and that the bowels are among the most vulnerable, he planned to cool the viscera by circulating cooled saline in the abdominal cavity. The results were most interesting. Whereas normothermic animals, and those cooled to a rectal temperature of 30° C. by either external hypothermia or generalized blood refrigeration (via a carotid-jugular shunt) died at the same rate, viz., 40% 24 hour survival after one hour of aortic occlusion, dogs which had their viscera rapidly cooled to 21°C. just before aortic occlusion all survived. He found that it was possible to save over 80% of dogs after 2 hours of aortic occlusion when the duodenal temperature was kept between 10 and 20° C. by means of visceral cooling. When cooling was delayed until 15 minutes after the onset of 2 hour aortic occlusion all dogs survived. Duodenal temperature here was 15°C. The bloody diarrhea and bowel changes which appeared in control animals were not seen in those dogs cooled selectively.

SECTION C. Antibiotics.

In some very carefully controlled bowel obstruction experiments in 1945 Harper[48] demonstrated the value of antibiotics. By obstructing an isolated 12 cm. segment of jejunum and restoring the continuity of the remaining bowel he foreclosed the possibility of fluid and electrolyte

complications in his experiments. The one difference between control and test dogs was the administration either of 50,000 units of penicillin into the isolated loop before it was closed or of larger doses of penicillin subcutaneously. While control animals died within several days and exhibited at postmortem a discoloured, distended loop of bowel filled with haemorrhagic material and showing gross mucosal ulceration all penicillin treated animals survived 9 days and 60% survived for more than one month. Their bowel loops became distended slightly up to the fourth day and thereafter diminished in size. There was no indication of mucosal ulceration. In the control animals large concentrations of gram negative bacteria were found in the loops while in the penicillin treated dogs there was a much lesser amount. The explanation given for these remarkable results was that with free proliferation of bacteria and distention mucosal ulceration and absorption of bacterial toxins took place. This toxemia then aggravated the general condition of the animal. Although there was some bowel distention in the treated dogs the fact that the bacterial proliferation was essentially stopped spoke against the likelihood of extreme distention and ulceration of the mucosa.

The similarity between the bowel lesion here and in hypovolemic shock greatly encouraged the thinking that irreversibility in haemorrhage is due to bacteria themselves or at least to their toxins and therefore if the proliferation of resident organisms in the bowel could be controlled the fatal ulceration, haemorrhage,and fluid loss could be prevented. Of course the entire bowel, not just a segment,is involved in shock due to haemorrhage and death occurs that much more rapidly than in the isolated loop animals.

Again Jacob Fine[28] took up the subject and in 1952 published work

on prevention of irreversibility when penicillin or aureomycin were given both orally and into systemic veins or into the portal vein. Whereas control animal mortality was over 90% with animals protected by these antibiotics it was only 60%. Fine concluded that the safest interpretation for this outcome was that antibiotics lead to a reduction of either bacterial toxins or the bacteria themselves and that this sort of protection must be provided before the shock is begun. In a later paper which has been regarded by many to provide some final answers for the question of pathogenesis in shock Fine elaborated on his previous views. He supported the role of antibiotics, pointing out that they reduced the toxins or the toxin producing bacteria to a below normal level. Since, as he proposed, the ischaemia of haemorrhage disables the reticulo-endothelial system which normally handles the gastro-intestinal tract's production of toxin only a subnormal amount of toxin can be dealt with. Should even the amount normally produced be absorbed it will have a deleterious effect. Hence the value of pretreatment with antibiotics was justified he felt.

Edwards[23] took similar evidence and altered the interpretation slightly. He experimented with dogs and antibiotics and aortic occlusion at different levels. He found that if control dogs were shocked by occluding the aorta at a given level, hence rendering the viscera ischaemic, death would occur in a certain number of hours. By preliminary sterilization of the bowel with either oral achromycin or intramuscular penicillin the mortality was significantly lowered for similar periods of occlusion. However this pretreatment did not prevent death if the ischaemia was prolonged indefinitely. Edwards interpreted this as meaning that although absorption of toxins from the gut hastens irreversibility really the extent

and duration of the ischaemia are the primary causes of death. With the other part of his experiment he attempted to prove this. When he occluded the aorta above the superior mesenteric artery thus allowing liver circulation the death rate was 80% in 2 hours. When the liver circulation was occluded but the superior mesenteric artery left open there were only 10% deaths in 2 hours. He used these figures to demonstrate that a more extensive ischaemia was fatal sooner than a less widespread shutdown; the bowel supply being greater in volume than the liver supply. He did not consider the end organs themselves but only their blood supply form the point of view of capacity.

Fine found in his studies of 1948 that bacteria are capable of migrating through ischaemic bowel and although he did not state definitely that bacteria move from the bowel to the portal circulation in shock he has frequently considered this as a distinct possibility.[28] Other workers including Culbertson et al.[19] have attempted to refute the implication that bacteria are directly responsible for irreversibility by culturing portal blood. By duplicating Fine's technique of shock production and using completely sterile technique this latter group tried to grow bacteria from portal blood samples. The dogs used belonged to two groups. They were either given 5 grams/day of Aureomycin for 4 days prior to, and another 5 grams of the same drug 2 hours before shock or were not treated at all. Portal veins were catheterized in both groups one day before and up to ten samples were taken during the shock procedure. These were cultured under anaerobic and aerobic conditions. All were negative. Although the conclusion was safely drawn that no bacteria were present in the portal blood in these shocked dogs the survival figures indicate that the antibiotic did protect the animals. In the control

group 27% survived while 65% of the aureomycin treated group survived 24 hours. Either the antibiotic reduced the number of bacteria producing a toxic substance in the gut or it acted as an antitoxin itself.

Richard Lillehei,[67] in a very clever experiment, sought to evaluate antibiotics. He noted that the shock produced by haemorrhage very closely if not exactly resembles shock caused by administration of an endotoxin itself. Mindful of this he sterilized dog bowels with neomycin and sulfasuccidine prior to giving the endotoxin. His results showed no difference from controls in survival time and he concluded that the antibiotics did not offer any protection at all in this type of shock which he equated with hypovolemic shock.

CHAPTER II

PHARMACOLOGICAL AGENTS

The history of the use of drugs in the treatment of shock is short but very full. Since it is a relatively easy matter to shock an animal, and then on speculation try several drugs just to see how they act, many different agents have been so used. They often have been dismissed or endorsed after inadequate trial or because the experimental situation was artificial and gave inaccurate results. Many clinicians and research workers however feel that the solution to the problem of irreversibility does rest with the use of drugs, whether alone or in conjunction with blood transfusion.[45] The reasons for this view are well founded. For example, Ravdin noted that in war casualties transfusion only of volumes of blood far exceeding the estimated blood loss saved wounded soldiers. He suggested that perhaps the vascular system must be primed with some agent before it can get on with the job of moving the blood along.

To be of any use in the treatment of shock an agent must meet several criteria. Primarily it must function with therapeutic effect because an agent that is effective only before shock is induced naturally can not be applied to a clinical situation. Secondly, an agent must be free from harmful aftermaths. If it is effective in maintaining blood pressure for example but at the expense of a deleterious action elsewhere

in the body it cannot be endorsed. Ease of administration, effectiveness in the presence of confusing or complicating factors,and safety are further general requirements.

Frank et al.[36] conducted a valid series of experiments in 1945 in an attempt to evaluate drugs for which claims had been made. His group was concerned with the use of these adjuvants in experimentally produced haemorrhage in dogs, at a stage when irreversibility to reinfusion of blood was a certainty. It was by careful standardization of their technique and with adequate control throughout that they were able to know when an animal had become irreversible. Treatment was begun at this time. The results showed that none of the agents they tried in any way altered the survival rate of the dogs. Some transitory improvement was noted with massive infusions of saline and of isotonic bovine albumin but the latter produced a marked bleeding tendency. The two together, they found, were harmful because they produced tissue oedema, serous effusion, venous distention, and small vessel haemorrhage. Believing that succinic acid increases oxygen consumption of tissues at low oxygen tensions, sodium succinate promised substantial improvement in the shock state. This was not borne out by the experiments however. Attempts to increase cardiac output with coramine and tuamine were unsuccessful. Postulating that an improved blood flow would result from constriction of lax arteries and veins in the periphery or from an increased skeletal muscle tone around these vessels, paredrine and pitressin(with and without ergotamine) were tried. Again no favourable outcome was recorded. The correction of acidosis by the administration of sodium bicarbonate did not alter the condition of the animals. Frank concluded that there must be biochemical changes involving one vital organ or several organs which develop from prolonged capillary

flow deficiency and which are not correctible by these agents he tried in spite of the careful reasoning behind the use of each one.

Some of Frank's ideas nonetheless were heeded by others and soon thinking became quite concentrated on the capillary beds and the circulation. Chambers and Zweifach[13] studied in detail the anatomy of the mesenteric capillary circulation. They pointed out that the main channel between arterioles and venules, in the dog at least, is the metarteriole which has a diameter up to 20 microns and possesses vasomotor power. The capillaries with their precapillary sphincters branch from either the metarterioles or the arterioles and in this latter case were found to connect directly to venule rather than return to the metarteriole. These were called arterio-venous capillaries. Usually capillaries returned to the metarterioles which in turn emptied into venule after draining the capillary network. After viewing the anatomical picture these same workers sought to study physiology. From their work many points were made which now are generally accepted as being fact. They noted that few capillaries are open at any instant in the tissue at rest but great numbers of capillaries open up when the tissue becomes active. The extent of this depends somewhat on the pressure in the arterioles and metarterioles feeding into the capillaries but also there is direct humoral and chemical control both on the precapillary sphincters and on the other vessels themselves. For example vasodilation will be produced by local anoxia, and acidity. Acetylcholine and histamine in dilute amounts dilate precapillary sphincters. Epinephrine and concentrated histamine solutions cause constriction of precapillary sphincters and metarterioles.

Of course nervous control of vessels was well known, that is that

parasympathetic impulses, probably with acetylcholine as the final link in the communication, produce vasodilation whereas the sympathetic system causes constriction of the capillaries and metarterioles. It is generally conceded that a greater force is needed, for example a stronger solution of epinephrine, or greater sympathetic discharge, to contract the metarterioles than the precapillary sphincters. This fact suggests that while capillaries may be shut down as a result of adrenergic action other channels may remain open and convey the blood by direct shunt from arterioles to venules. Because of the lack of musculature in capillaries it can be appreciated that if all the precapillary sphincters are paralyzed as might result from a substance such as Shorr's V.D.M., an extensive flooding of the enormous capillary bed would occur and result in a marked depletion of the circulating blood volume. Inertia, which might occur in shock with poor cardiac output associated, added to this trapping effect could conceivably account for a significant and fatal tissue ischaemia. Through this sort of thinking has developed the stout column of supporters for the use of vasopressor agents in shock treatment. In general their battle cry has been that shock becomes irreversible when, due to portal resistance with secondary damming back of blood in the viscera or to circulating humoral vasodilatory substances or both together there is widespread capillary pooling, sludging of blood, or sequestration of large amounts of red cells and plasma. Therefore a vasopressor is needed to mobilize this blood, it is stated.

There are many vasoconstrictor drugs available but probably the most important belong to the pressor amine or sympathomimetic amine group. Of these only a few have been used extensively in treatment either in clinical practice or in experimental work. The others show promise in that their

features vary and they become better known their value will be more obvious. An excellent review of pressor amines was made by Aviado[4] and he pointed up the fact that not all these substances act similarly at different sites nor does any one always act in the same way in a dilute solution as in a more concentrated one. For example epinephrine constricts vessels of the pulmonary and renal beds but dilates cerebral, coronary, and skeletal muscle arteries. Again epinephrine acts to increase cardiac output whereas l-norepinephrine decreases it. Of the group which includes epinephrine, l-norepinephrine, aramine, isuprel, vasoxyl, ephedrine, neosynephrine, methedrine, and others, l-norepinephrine has received the most attention in haemorrhagic shock therapy. This is mainly because it has its primary effect on the vessels with only a slight chronotropic effect on the heart. Moreover it does not produce the undesirable cardiac dysrhythmias that epinephrine does. The use of l-norepinephrine or 'Levophed' (trade name) has received much support.

Moyer et al.[73] undertook a careful trial of l-norepinephrine, compared it with epinephrine, and analyzed its effect on normal and shocked subjects. They decided that its characteristics, including the ability to increase systolic, diastolic, and mean blood pressures and its lack of undesirable effects on respiration, vital capacity, circulation time, haematocrit or blood glucose concentration made it a suitable agent in shock treatment. They went on however to endorse its early use in normovolemic shock. Included here were cases of myocardial infarction and toxemia. Moyer advocated early use because he feared the damage that prolonged vasoconstriction might have on brain, kidney, liver, and other vital organs.[74] Interestingly enough, Moyer [72] and Foster[31] both noted that while Levophed decreases renal blood flow and glomerular filtration

rate in normovolemic animals it improves, almost to normal values, the renal blood flow in animals which have been haemorrhaged and who have a reduced renal plasma flow from this cause. Moyer's explanation for this favourable response to Levophed in those animals which have lost blood was that it has an antagonistic effect to the vasopressor response in the kidney. This vasopressor action comes into play in hypotension reducing renal plasma flow, glomerular filtration rate, and hence urine volume, sodium,and potassium. As systemic pressure is raised, he reasoned, this vasoconstriction is no longer necessary and subsides or is antagonized by the Levophed. Foster however added that there is a 200% increase in renal blood flow when blood transfusion is the therapy rather than Levophed. He noted too that the passage of time alone does not improve renal blood flow whereas the administration of Levophed does help somewhat coincidentally with the rise in systemic blood pressure. Such observations as these encouraged subsequent workers who felt that splanchnic flow in general would be improved by this agent. The claims for it have become less conservative in recent years.

Fozzard and Gilmore[34] shocked dogs irreversibly and then treated a test group with sufficient Levophed in drip form to maintain the blood pressure at 100 mm Hg. After the pressure held itself at this point the drip was discontinued. Although there were no permanent survivals there was a significant prolongation in survival time, viz., 15.5 hours versus 5.7 hours in those dogs used as controls and given a placebo drip. These workers thought that the effect might have been due to a preservation of the cardiac output.

Thinking that the beneficial effect accorded to pressor amines might be as a result of splenic contraction with a subsequent internal transfusion,

Ebert and Stead[22] in 1941 sought to demonstrate this effect in man. They were obliged to conclude that there is no appreciable contraction of the spleen in man either to a pressor amine (epinephrine) or to haemorrhage.

Catchpole[12] and his group studied the effect on survival and on coronary and peripheral arterial circulation with severely shocked dogs. He noted that whereas coronary flow was increased and resistance decreased with Levophed, peripheral vascular resistance was increased and flow decreased. There was no increase in the rate of survival in their treated dogs which were kept at pressures between 80 and 90 mm Hg. with the Levophed drip.

Griffin and Webb,[43] using a brief but severe technique of inducing shock; 20 mm Hg. for 20 minutes; treated dogs with enough Levophed in drip form to bring the arterial pressure to between 80 and 90 mm Hg. At this rate their mortality was reduced from 50% to 18%. The severity of this technique could be questioned however. They noted that if pressures were kept over 90 mm Hg. with Levophed all dogs died and they recognized from this the potential hazard of the drug. They did not offer a hypothesis for its action in each situation. This same group a year later again endorsed Levophed, claiming that 17 out of 21 dogs shocked by the technique of Nickerson and Zingg[113] ; 45 mm Hg. for 40 minutes then 70 mm Hg. for 30 minutes, had survived. Pressures had been maintained at around 90 mm Hg. with the Levophed following the two hypotensive intervals.

Perhaps many research workers are encouraged to use Levophed by such claims of the manufacturer as, "because of the selective peripheral vasoconstrictive action of Levophed, pooled or stagnant blood in the dilated capillaries is driven into the central circulation, thus maintaining vital functions (eg. brain, heart, kidneys, etc.)." It is recommended for the restoration and maintenance of blood pressure in all acute hypotensive states.

Grouped together with such valid conditions as myocardial infarction, spinal anaesthesia, and septicemia, is haemorrhage. The fallacy of making this association will be mentioned later in the discussion.

More important than drug house claims however have been the thoughts concerning the shock process apropos the use of adrenergic agents. Their use as treatment has simply reflected the envisioned need for such an agent in hypovolemia. Such a need was extolled by Shorr and Zweifach[93] in 1951 in a classic paper. Shorr propounded two vasotropic substances, V.E.M. (vaso excitor material) and V.D.M. (vaso dilator material). The latter was later identified as the protein fraction ferritin.[70,71] Both these agents are elaborated by the body in the face of anaerobic metabolism apparently. V.E.M. is produced by the renal cortical cells and appears on the scene first, producing the increased total peripheral resistance which is always observed following haemorrhage. V.D.M. is elaborated more slowly and after severe hypotension, by kidney, liver, and skeletal muscle. It causes a secondary vasodilation of metarterioles and precapillary sphincters and thus allows stagnant pooling which he thought accounted for the phenomenon of taking up of blood from the reservoir after a certain duration of hypotension. Transfusion at this point increases arterial pressure but does little to move the blood along in the visceral capillaries. It was reasoned by Shorr that V.D.M. has an antiadrenergic action and therefore the correct treatment would be to overcome this with an externally administered vasopressor agent thus increasing capillary tone and encouraging the stagnant blood to get on its way. Pooling of blood in the liver, although not clearly understood, probably resulted from the same V.D.M. action on the liver vessel sphincters he felt. The anoxic, engorged liver of course was unable to perform its usual function of inactivating the V.D.M.

Such was the thinking one decade ago and even today V.E.M. and V.D.M. are still referred to although the emphasis has been taken from them in recent years. This same group of workers, in 1952, experimented with an adrenolytic and sympatholytic agent related to dibenamine in haemorrhagic shock. By direct visualization of the terminal vascular bed in the omentum they noticed that while this agent did not completely block the response of terminal vessels to adrenergic agents these latter drugs did not cause the customary marked vasoconstriction, but rather a very adequate blood flow persisted even while the animals were being severely shocked. While the control animals became irreversibly shocked those given the dibenamine-like compound did not decompensate. Zweifach and Shorr[114] found that V.E.M. elaboration by the kidney had not been affected but V.D.M. failed to appear and the liver had retained its ability to inactivate this substance. Unfortunately they did not offer a theory of action here nor was the time of administration of the drug carefully heeded. Nonetheless these observations were significant and important and a new school of thought on the problem of vascular changes in shock began to develop and attract many supporters. The inference was made that perhaps the harmful effects in shock resulted from vasopression on the arterial side rather than vasodilation on the venous side. This was a bold theory but subsequent careful experimentation has tended to support it. It was reasoned that all the changes of irreversibility could derive from ischaemia produced by arteriolar and capillary vasospasm.[66] Also pooling of blood in the liver and mesenteric bed (there was now some doubt about the latter) could be secondary to impoverished arterial flow and/or vasoconstriction of outflow tracts from the liver. Men began to wonder if the liver played such a crucial role in irreversible haemorrhagic shock as had formerly been thought.

To test these new hypotheses work was done with drugs which would cause vasodilation and supposedly improve arterial and secondarily venous flow. It is easy to see how difficult it must have been to gain support for such an idea. After all this meant a further reduction in blood pressure when vasodilation was produced. Didn't the body have a difficult enough time conserving what little blood it had left without opening up the capillaries further? A core of scientists insisted that this was the proper treatment pointing out that with capillaries closed, regardless of how high the systemic blood pressure, tissues were not being serviced adequately. The assumption was implicit that a condition can exist where precapillary sphincters will be closed with such force that they cannot be opened by high pressures proximally. Such force was being attributed to an endotoxin.

Remington[82,83,84] pointed to increased survivals when 5 mg/kg. dibenamine was administered to dogs before shock was induced. It was true that his animals experienced a rapid fall of blood pressure and an alteration of pulse as a result of the adrenolytic effect of the drug but somehow they seemed to withstand this. He argued that animals not given dibenamine suffer from vasoconstriction of their precapillary sphincters and metarterioles and that these animals are then more sensitive to blood loss and therefore a small haemorrhage becomes lethal. Such was his arguement.

Kovach[58] noted that renal sodium excretion and diuresis were improved over controls when animals were protected with dibenamine before tourniquet shock. He observed an adrenalinemia with subsequent increase in vasoconstrictor tone in shocked animals and reasoned that this sympathetic effect probably resulted from central nervous system hypoxia. At any rate the sympatholytic agent dibenamine gave an effect which led to favourable results.

Other sympatholytic agents have been used. In this laboratory Inglis[53] demonstrated a significant improvement in survival time with chlorpromazine administered to test animals part way through the shock process. Although there were no survivals, the severity of the shock technique was such that permanent survival was unexpected and the prolongation of life with the use of chlorpromazine to more than twice control values was quite remarkable. More support was given to the arguement that ischaemia induced by the arterial rather than venous side of the circulation was responsible for irreversibility by Lillehei's endotoxin experiments.[67] His best results were obtained in animals pretreated with dibenzyline, another sympatholytic agent, 0.5 - 2.5 mg/kg. Good protection was also given to dogs pretreated with from 25 to 50 mg/kg. of chlorpromazine. In this same series Levophed and aramine were given at the time of administration of the endotoxin. Results here were no better than in control animals. From this work Lillehei concluded that the endotoxin of haemorrhagic shock, like that he administered, acted to cause vasospasm of the small vessels either directly or by potentiating the circulating adrenergics or those attached to vascular endothelium. The ischaemia so produced accounted for the punctate haemorrhages in the bowel and associated fluid loss he believed. The sympathomimetic effect of endotoxin was blocked by chlorpromazine and dibenzyline and so flow was maintained through the capillaries. He went on to point out that if hypotension or endotoxin leads to vasospasm in the viscera it is easy to understand why there is no beneficial effect from the adrenergic drugs. In fact, the irreversibility could conceivably by encouraged by these latter agents.

Although there was no criticism with Lillehei's technique of giving the drugs at the time of endotoxin administration there was room for

arguement with those other investigators who gave antiadrenergics prior to shock induced by haemorrhage. In these instances animals lost less blood in acquiring the predetermined hypotensive level than did controls and therefore any survival could be accredited to a lesser insult to their vascular system rather than to protection with the agent. Nickerson and Zingg[113] attempted to correct this situation by administering the agent after bleeding had been completed. They used hydralazine, which is also an antiadrenergic drug. Although their dogs were not severly shocked treated dogs did show an improvement in absolute survival over controls in the ratio of 69% to 31% survival. They noted also that the treated dogs were able to withstand a lower blood pressure for a longer duration than untreated animals. This implied that systemic blood pressure was not a reliable indication of potential survival and also suggested that a flow of blood at tissue level as presumed to result from the use of a vasodilator was more important than a high axial pressure. This was quite revolutionary thinking indeed.

A comparison of hydralazine and Levophed was made by Webb et al.[103] recently under the same experimental conditions of shock as used by Nickerson and Zingg. While 5 out of 19 hydralazine treated dogs died in their series, 17 out of 21 Levophed infused animals survived. Webb argued that since lactate and pyruvate levels were up in the dogs receiving hydralazine there must be a lack of oxygen supply to the tissues. He neglected to point out the reverse implication, viz., that fewer of these substances would reach the systemic veins if capillary circulation is shut off as it no doubt is in Levophed treated animals. In his series of 10 control dogs 7 lived indicating a lack of severity of the shock technique. The significance of this will be dealt with in the discussion.

Mainly as a result of successful use of adrenal corticoids in clinical practice in cases of operative shock associated with hypovolemia there has been considerable laboratory exploration of these agents to find out how they affect the shock process.[51] At first there were reports that there was no significant effect of intramuscular cortisone on the course of haemorrhagic shock. Knapp and Howard found that intravenous hydrocortisone, 100 mg. given after 3 hours of hypotension and after reinfusion of blood into shocked dogs failed to revive them. Before this Frank[38] had noticed no improvement whatever in survival either with cortisone given prophylactically at the end of the shock period or after reinfusion or with A.C.T.H. However others have achieved notable success with corticoids in experiments. Connolly et al.[17] used a Wiggers' shock technique in dogs to produce a control animal mortality of 82%. By treating their test dogs with from 100 to 300 mg. of hydrocortisone they saved 26 out of 37 dogs. The striking point here was that this increase in survival resulted from the use of hydrocortisone alone without reinfusion of the shed blood. These workers found that the hydrocortisone was most effective if given soon after the appearance of severe shock. In fact if it was given more than 45 minutes after the pressure began to fall below 50 mm Hg. no favourable response occurred. The nature of the effect was an improvement and maintenance in blood pressure and this group concluded that the action was probably to potentiate circulating adrenergic drugs to maintain just enough vessel tone to permit circulation to all parts. Small et al.[96] attempted to verify this notion of potentiation. They suspected that corticoids sensitized the heart to the ionotropic effect of adrenergic drugs. They therfore used adrenalectomized animals and gave Levophed along with hydrocortisone. They found that when the blood pressure is being maintained

by Levophed there is no further effect from corticoid administration.

The explanation for favourable results of corticoids in haemorrhaged animals has eluded many investigators. While persons who are deficient in adrenal corticoids can be expected to go into shock from a much lesser insult than normal persons there is no good reason to explain why an individual with normal adrenal glands whould benefit from exogenous corticoids when he suffers haemorrhage. It has been suggested that perhaps in shock there is a failure of intermediary metabolism of adrenal corticoids which means that an effective end product is not appearing even though the glands are reacting normally to the stress.[62] Even if this were true however one must still account for the favourable action corticoids have on the shocked animal and this is the more difficult problem. This topic will be persued in the chapter on discussion.

Considerable work has been done totry to determine which corticoid fraction is the most important. Acting on the logical assumption that the mineralocorticoids would be the most important in the haemorrhagic shock state where fluid losses are great Swingle attempted to evaluate these separately from the glucocorticoids.[99,100] He shocked dogs to 40 mm Hg. for 30 minutes by bleeding then treated with desoxycorticosteroid and 2-methyl, 9-alpha fluorohydrocortisone. He found, surprisingly enough, that the mineralocorticoid did nothing while the glucocorticoid led to a marked improvement in blood pressure. He surmised that it acted by drawing fluid and electrolytes into the vascular compartment but did not suggest how this took place. An interesting observation was made by Swan[97] and his associates in respect to the conjugation and excretion of 17-hydroxy-corticosteroids. They found that when a patient was undergoing prolonged and extensive surgical trauma there was a continuing elevation of these

conjugates but when patients were rendered hypothermic prior to surgery there was a suppression of the adrenocortical secretion. This makes one wonder how important corticoids are since substantial amelioration is noted in hypovolemic shock when animals are cooled. The fact again observed here that in normothermia at least adrenal function is stepped up in response to trauma adds to previous evidence that these glands do play a role in shock or at least make an effort to take part.[62]

It was implied earlier that combinations of restorative agents have been used in the treatment of shock with success. In this laboratory the use of hydralazine in combination with overtransfusion met with encouraging results.[86] The premise underlying this work was that while the vasodilator is acting to expand the capillary bed one should ensure the flow thus encouraged by adding more than the normal blood volume.

Hypothermia in combination with autonomolytic agents has been investigated.[75] Using the Fine technique of producing shock, animals were given chlorpromazine alone or in combination with cooling. While cooling alone lead to significant improvement in survival time the best results were obtained when 100 mg. of chlorpromazine was given 2 hours before bleeding and cooling was induced down to 31°C. Such lytic cocktails have been endorsed by others and used along with hypothermia apparently produce a better distribution of blood to the viscera. The sympatholytic effect provides some resistance to acute total ishcaemia, Overton suggested.

LaBrie et al. used antibiotics in combination with hypothermia in dog experiments. They reasoned that since in previous experiments visceral hypothermia to 25° C. initiated after aortic occlusion protected animals from death but not from paraplegia and because precooling to 30° C. prevented

paraplegia but not death from shock, the two used together should be very beneficial. They found though that there was no additive effect of antibiotics given as treatment to precooled animals. Precooling alone and pretreatment with antibiotics alone were successful in promoting significant survival rates.

PART II

MATERIALS AND METHODS

CHAPTER III

EXPERIMENTAL SHOCK

The methods of producing experimental shock are legion. They include total body trauma by drumming, individual limb crushing, aortic or arterial occlusion, subjection to extremely low or high temperatures, administration of toxic substances, and haemorrhage. We have continued to emply the latter method for two main reasons. In the first place haemorrhage occurs in the majority of tramuatic injuries and is therefore a common denominator in shock. Secondly, in the laboratory the induction of shock by haemorrhage can be carried out with considerable accuracy. Another reason could be added, for the picture of shock pathogenesis created by haemorrhage is considered to be similar if not identical to the shock syndromes from other causes. In previous years the technique of Jacob Fine has been used in this laboratory.[29] Briefly this involves bleeding the experimental animal from a systemic artery, usually the femoral, into an elevated reservoir bottle through plastic or rubber tubing connections. The reservoir is raised or lowered as is necessary to keep the arterial pressure of the animal at 30 mm Hg. Eventually the animal reaches a maximum bleeding volume at this pressure and begins to take up blood from the reservoir. After 40% of the blood in the reservoir is absorbed the remainder is reinfused quickly. One then observes a rise in blood pressure because the blood volume is back to normal. However

this is not maintained and soon the pressure falls off. Fine and his coworkers learned from experience that when 60 mm Hg. has been reached in this decline irreversibility had ensued. With this technique their mortality has been 90% with a mean maximum bleeding volume of 53 cc/kg. Without doubt the method is severe and in our laboratory not one survival has occurred in all the control animals and in fact there has been a high percentage of acute deaths signifying that the technique would still produce 100% mortality were it made somewhat less severe and prolonged. Its advantage is, as Fine pointed out, that it is a physiological method of inducing shock; i.e., the bleeding time interval until uptake begins is determined by the individual animal. In this way every animal supposedly has been shocked to the same degree by the time he is reinfused. To arbitrarily set a time for bleeding, Fine argued, defeats the purpose of the experiment since one animal might be in severe shock and another in only moderate distress at the end of the predetermined interval.

However it is necessary, we believe, to have a technique somewhat less severe than that mentioned. In considering the method of Swan several points are to be noted. His technique consists of removing 35% or other percentage of the animal's blood volume as determined immediately before the experiment. He notes that by so doing all animals are shocked to exactly the same extent and should one dog have a small blood volume for his size he will be able to compensate to the same extent as an animal with a larger volume because the same fraction of blood is being removed. Swan claimed 82% mortality could be achieved with this method while 100% deaths resulted from withdrawl of 45% of the animal's blood volume. It must be remembered that this technique was being recommended when this group were doing work with hypothermia in haemorrhagic shock and in such

circumstances less blood is lost in reaching a hypotensive level than in normothermia. Some justification exists therefore for this method and others have advocated its use.[3] However Walcott et al.[101] and Wang et al.[102] have shown that after bleeding a certain percentage of the premeasured blood volume the residual blood volume still varies considerably. This is a reflection of the variability in compensatory power from one animal to another.

In attempting to devise a standard method of shock C.J. Wiggers tried many possibilities before arriving at his well known technique.[106] He made the very valid point that so often when an arbitrary hypotensive level is chosen for an arbitrary duration the investigator runs the risk of presuming irreversible shock has occurred when it has not and vice versa. He recognized that in order to produce irreversibility an element of duration and an element of severity are necessary and he introduced them in this order. His method which he admitted was arrived at simply by trial and error is simply to lower arterial pressure by bleeding from an artery to 50 mm Hg. for 90 minutes. A further 45 minutes at 30 mm Hg. is induced by withdrawing more blood and at the end of this period the entire volume of withdrawn blood is reinfused. This leads to an improvement of blood pressure for ½ to 1 hour then a steady decline terminating in death in about six hours. With this method, which by 1950 had been used on over 300 dogs, an 82% mortality rate resulted. Maximum bleeding volume averaged 40 - 45 cc/kg.

The obvious advantage to the Wiggers type of shock induction is that it can be well controlled and easily reduplicated. Wiggers however admitted that to guarantee irreversibility, as was his chief ambition, the technique had to be modified from time to time, even in his own laboratory. He also noted that the times and pressures were quite arbitrary and no

doubt because they are other investigators have chosen to change the technique while still employing the principle.[87,107] Such changes are necessary when certain facets of the problem of shock are being investigated or where a surgical procedure or other stress is being added to the haemorrhage insult. One such variation on the theme by Wiggers was composed by Nickerson and Zingg.[113] They reversed the order of the elements of severity and of duration and added a 'clamped period.' This latter innovation was very sensible because it forced the animal to rely on its own adjustment mechanisms to accomodate to the hypovolemic state. Their procedure was to render an animal hypotensive to 45 mm Hg. for a total of 40 minutes following with 70 mm Hg. for 45 minutes and then clamping the tubing between the reservoir and the animal for 1½ hours or 2 hours prior to reinfusion of all the blood in the reservoir. Such a technique gave a 69% mortality. One must question here the induction of a true irreversible state. While they recorded blood pressures and pulse rates they did not remark on the post mortem findings in the animals. This technique of Nickerson and Zingg for inducing shock appealed to us however because by providing a period wherein the animal neither receives nor loses blood it allows one to carefully estimate the value of a therapeutic agent at this time. As our aim was to assess the value of hydralazine, Levophed, and hydrocortisone as <u>treatment</u> agents it was necessary to give them after all bleeding had taken place. To do this with the pure Wiggers' technique one would have the conflicting effect of the reinfused blood to contend with in trying to evaluate the particular drug. The 'clamped period' gives the opportunity to measure the drug effect with no other variable in operation. However while we did not want to experience the hopelessly irreversible state of the Fine method we did feel obliged to stiffen the requirements

of the Nickerson technique so as to produce irreversibility. After all, we wished to know how these agents would succeed in redeeming an animal shocked beyond the point of saving by blood infusion alone. By experimenting with five pairs of dogs we were able to arrive at a very satisfactory experimental method which was employed with only one change for the remainder of the series. The experimental procedure was as follows: The dog was given a small dose of nembutal, usually no more than 5 cc's and the groins were shaved clean and painted with an antiseptic solution, Hibitane. The animal was weighed then placed on its back and held in position on the table by ties to the four legs. Endotracheal airways were inserted so that the tongue would not block the respiratory passage but the cuffs were not inflated nor was a respirator ever used. Using sterile instruments and technique, the femoral artery and vein on one side were exposed by sharp and blunt dissection. Ties were laid in place under the vessels and the latter clamped momentarily while they were opened and cannulated. In the case of the vein, polyethylene #205 tubing was threaded through the femoral vein lumen up into the inferior vena cava. It was possible to tell when this was properly placed by the pulsatile backflow of venous blood. In the artery a glass sidearm cannula was securely fastened. Distal ends of the vessels were permanently ligated. Before the clamp was removed from the artery the cannula was connected to the tygon tubing system which had previously been topped up with a 3% sodium citrate solution. The system lead from the artery to a glass 'Y' connector and thence to (a) a mercury manometer and to (b) the reservoir bottle which was suspended from an I.V. stand. Accompanying the reservoir bottle was intravenous solution of 5% glucose in saline which was allowed to drip slowly into the vein via the polyethylene tubing. This tubing was also connected to a water

manometer which permitted measurement of systemic venous pressure. The reservoir was equipped with an air vent so that the air pressure within the bottle would be constant irrespective of the volume of blood within and was also fitted with a pumping bulb and valve system to permit rapid reinfusion of the blood at the proper time. From the side arm of the glass cannula rigid polyethylene tubing lead to a Sanborn pressure transducer which in turn was mounted on and connected to a Sanborn Twinviso 60-1300 recording amplifier. In the line of tubing was a 3 way valve and a syringe to allow irrigation of this system with anticoagulant solution. When all connections had been made and clamps placed on the tubing to the transducer and that to the reservoir 0.4 mg/kg. of liquid heparin was given through the intravenous system. Within 5 minutes the arterial clamp was removed and the pulse wave moved through the system to the mercury manometer. Blood pressure, pulse, respiratory rate, and venous pressure were now measured and then the animal was allowed to stabilize for 20 to 30 minutes. During this interval the Sanborn machine was balanced.

The purpose of having this latter pressure recorder was so that the low arterial pressures could be accurately determined when the fluid damping effect rendered the mercury system unreliable. In addition it was possible to make a permanent record of the pressure curves with this electronic apparatus. The reason for having a mercury system at all was in order to expedite reading of pressures and pulses and also to allow reservoir level changes to be made quickly. It is important to note that when a pressure of 40 mm Hg. for example is observed on a mercury column connected by several feet of fluid filled tubing to an artery the mean pressure in that artery is actually about 43 mm Hg. and a manometer reading of 70 mm Hg. is really closer to 75 mm. arterial pressure. This is

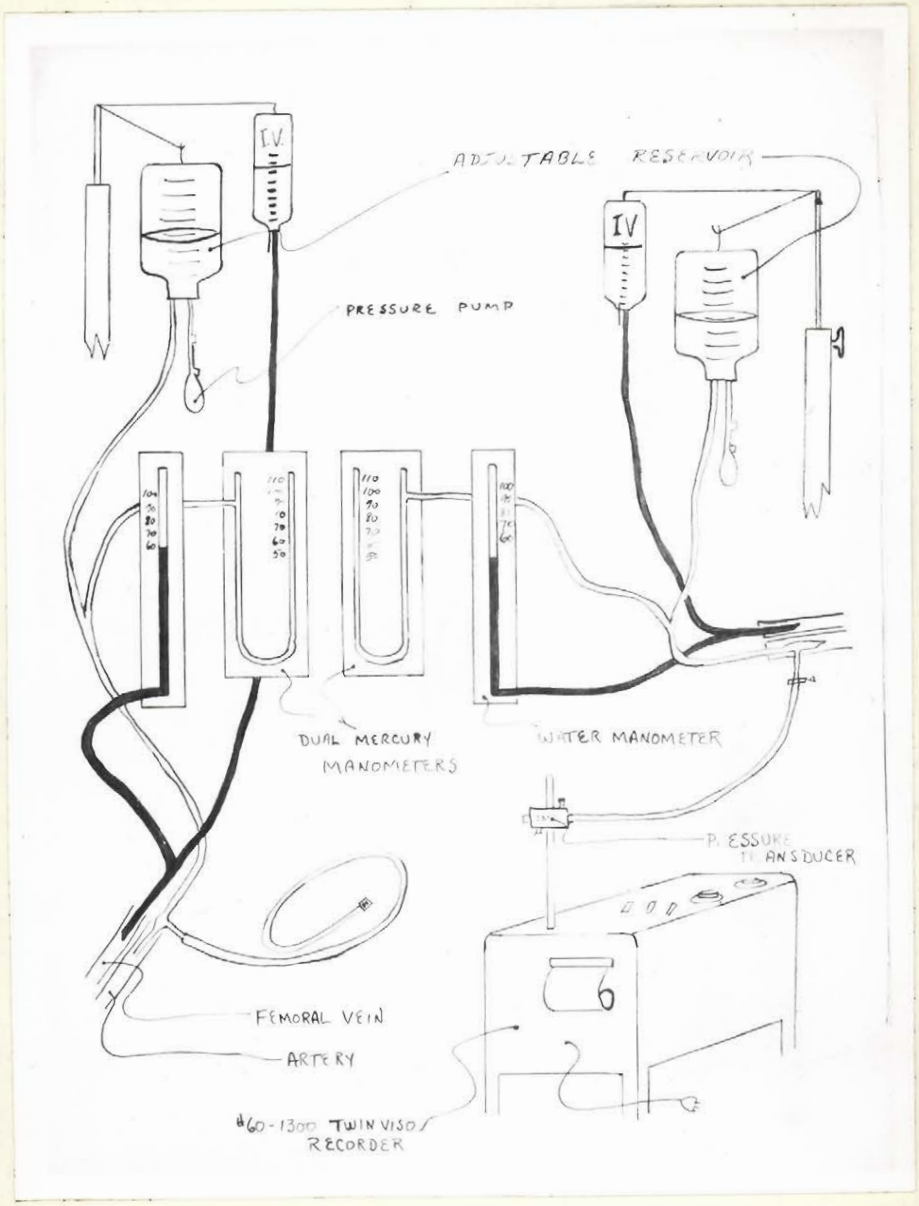


FIGURE 1.

Diagram of Apparatus Used in Paired Experiments.

due to the damping effects of the fluid column and of the mercury which similarly distorts pulse pressure readings. However this problem was overcome by having the two pressure recording systems. By means of a sliding scale on the mercury manometer the top of the meniscus could be set opposite 40 mm Hg. when the transducer was giving the true 40 mm.reading. In actual fact the meniscus should have been at about 37 mm Hg. when the pressure in the artery was 40 mm. Likewise, with the scale so set a true mean arterial pressure of 70 mm. showed as 70 mm Hg. on the manometer. The manometer would have been recording a pressure of 65 or 66 mm. if the scale had been fixed rather than sliding. With this dual system then it was possible to watch the mercury manometer for changes in pressure and pulse and then check these more thoroughly on the more accurate but harder to read Sanborn graph.

By the end of the stabilization interval the dogs were usually beginning to move about slightly as the small dose of anaesthesia had worn off. Now 10 cc's of venous blood was taken from each dog with sterile syringes and put into two vials. These samples were analyzed for plasma protein concentration, albumin/globulin ratio, haematocrit and haemoglobin. The experiment was then begun. The clamp was removed from the reservoir tubing and this allowed the dog to bleed freely into the bottle at a rate of between 40 and 60 cc/minute. The bottle was adjusted on the I.V. stand to a level which supported a pressure of 40 mm Hg. In general it took at least 5 minutes to attain the proper adjustment and from then on only minor changes in reservoir level were necessary as the pressure remained steady. An interval of one hour after 40 mm. had been reached was allowed for summer dogs and 1¼ hours for winter dogs. In addition to the four other measurements noted, bleeding volumes were recorded every 10 minutes. The reservoir was then elevated so as to increase the pressure head of the

fluid column and hence the animal's pressure to 70 mm Hg. This pressure, once attained, was held for 30 minutes in the case of summer dogs and 45 minutes for winter animals. Next a clamp was placed firmly across the reservoir tubing and the animal was not allowed to bleed out nor take up blood. This situation lasted for 90 minutes and was followed by a rapid reinfusion of the reservoir blood which had been warmed and gently agitated. Using the pressure system of the reservoir the shed blood was returned to the animal in between 7 to 10 minutes. All tubing was clamped off close to the animal and observations were continued now at 30 minute intervals. A second 10 cc. venous blood specimen was taken from each dog and sent down to the laboratory for a repeat analysis of the values mentioned before. The course of the animal's pressure and pulse was followed for two or more hours until a noticeable trend was observed. The slow drip of glucose and saline was maintained up until this point but then the animal was freed from cannulæ and tubing and was returned to a cage in the same room as the other member of the pair. Nothing was available for eating before the next day but a dish of water was left in the cage. The animal was checked the same evening and followed into subsequent days to note its state of health, ability to move around without falling, and response to light, touch, and sound. Dogs which died were autopsied. Also autopsies were done on some treated animals which passed the 48 hour survival time. These were sacrificed with a large dose of nembutal. At autopsy attention was given to the gross appearance of the liver, kidneys, and the spleen if present. The entire small and large bowel was then removed with its mesentery and examined grossly. The lumen was opened from one end to the other and the mucosa and wall were inspected. The number, size, and distribution of haemorrhagic lesions were noted and the amount of blood in the bowel lumen

estimated. Chests were opened for the purpose of ruling out lung abscesses or other disease as possible factors contributing to death.

It had been implied that a pair of animals were used in these experiments. This was the case. In an effort to reduce to a minumum the possibility that a variation of, for example, room temperature might influence the outcome of an experiment two animals were run at the same time. All procedures were duplicated exactly and measurements were made simultaneously. The lag between preparation of the first and second animal was compensated for by the stabilization period. In the majority of experiments a control animal was run opposite a test animal. In several instances when 3 pairs of dogs were being run in the same week each dog of one pair was treated, one with one agent and the other with a different drug of the test groups or with the same agent as the first animal. While the parameters discussed were felt to be important measurements the prime interest of these experiments was survival. After careful thought the interval of 48 hours following reinfusion was decided upon. An animal that lived to this time was considered to be a survival while those not, fatalities.

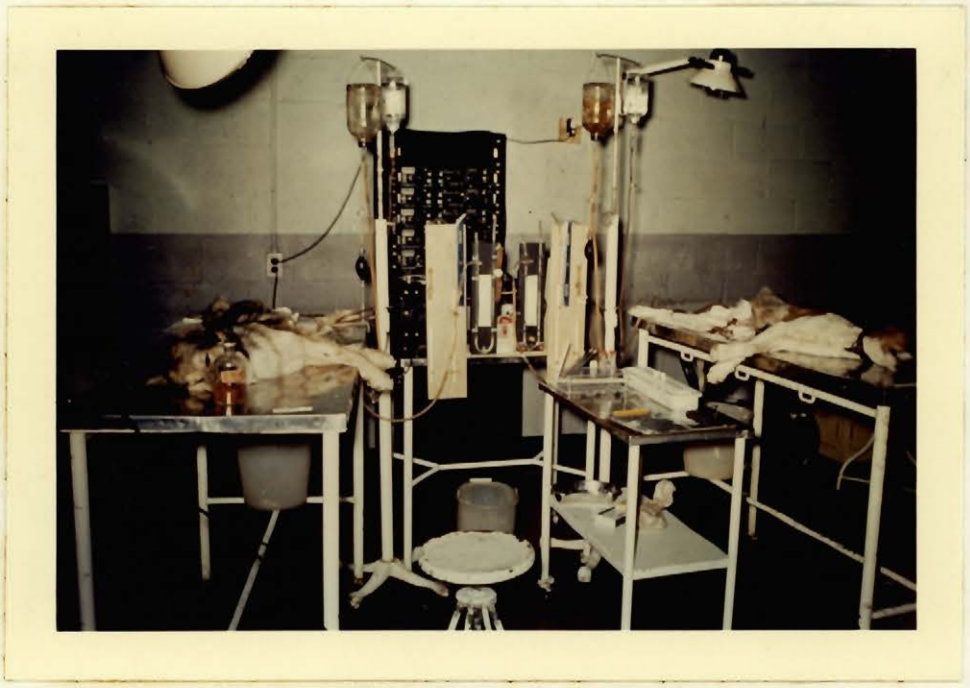


FIGURE 2.

Photograph of Paired Experiment
in Progress.

CHAPTER IV

TEST ANIMALS

Drug treatment was administered during the clamped period. The decision as to which of the pair would be the test animal was made by the toss of a coin. In no way was the course of the test dog altered from that of the control animal except for the specific agent being administered.

SECTION A. Hydralazine.

A 0.4 mg/kg. dose of hydralazine was given as a single injection via the intravenous catheter within 5 minutes of clamping of the reservoir tubing. Glucose and saline was allowed to drip at the same rate as with the control animal.

SECTION B. L-norepinephrine.

It was desired to maintain a low normal blood pressure with this drug and by trial it was found that a drip rate of between 150 and 250 ug/kg/hr. served this purpose. Eight mg. of Levophed was mixed with 500 cc's of 5% glucose and saline and the drip was continued at the above rate for the entire 90 minute period. After the first ten minutes it was rarely necessary to adjust the flow rate as the arterial pressure remained steady. Control animals were given an amount of 5% glucose and saline equal to that of the test dogs in this series. That is, the drips were regulated to the same rate. At the end of the clamped period the Levophed

drip was discontinued and a fresh bottle glucose and saline was put up in its place. This was run in slowly and the control drip was regulated to match it.

SECTION C. Hydrocortisone.

A single 200 mg. dose of Solu-cortef (Upjohn) was given through the intravenous tubing within 5 minutes of clamping. Glucose and saline was run in at a slow rate as with the control dog. No further measures were taken.

CHAPTER V

PREPARATION OF ANIMALS FOR EXPERIMENT

For these experiments mongrel dogs of both sexes which were considered to be in good health were used. The average weight was 12.7 kg. and ranged from 8.3 to 17.3 kg. The choice of experimental animal was made because of several factors. Dogs had been used in this laboratory previously and have also been employed by most men investigating the shock problem. While there are differences between dogs and human beings in respect to gross and microscopic anatomy and function of certain organs there probably is comparable behaviour in the vascular system in general terms. Pigs are apparently more analogous to man than are dogs in many respects but the availability of the latter make their use more convenient. Apropos the liver, there are some differences between man and dog which perhaps could be significant. The usual finding of large numbers of Clostridia organisms in the liver of dogs[69] suggests that in the presence of a reduced blood flow, such as is the case in shock, the dog is more susceptible to death from infection by these anaerobes. The suggestion that the Clostridia originate in the bowel and are simply trapped in the liver after reaching this organ by the portal vein bears reconsideration. The work of Culbertson[19] tends to disprove this idea since his portal vein cultures were consistently negative. It is reasonable that any anaerobe infestation of the liver could be controlled by penicillin therapy[48] and for this reason in all

but the first 7 pairs of our animals we administered 600,000 units of Bicillin C-R long acting penicillin two weeks prior to experiment. In this way we hoped to render the liver more nearly comparable to that of the human being apropos sterility.

The difference in architecture between the spleens of man and dog are well noted. The spleen of the dog is emptied not only by elastic retraction as in the human being but also by contraction of non-striated muscle and this function allows it to contribute to the circulation a considerable volume of blood. As far back as 1925 Barcroft[6] sought to determine whether there was a significant decrease in spleen size in emergency situations and found that at least an 8% shrinkage occurred in the dog spleen. The studies of Ebert and Stead[22] indicated that while there is little evidence to support the view that the spleen is a reservoir for red cells in man there is good proof that this organ contributes up to 16% of the animal's blood volume in a shock situation in the case of the dog. Some have claimed that the spleen of the dog can accomodate up to 1/5 of the total blood volume and of course this blood is rich in red cells.[55] Again Patek and Daland found that in man the administration of adrenaline does little to increase red cell count or haemoglobin concentration.

In order to eliminate the probable influence of this function in our shock experiments we decided to splenectomize our dogs and except for the first 7 pairs all animals underwent this operation. It is interesting to note that Hay also recommends this procedure in the study of haemorrhagic shock.[49] The dogs were chosen for surgery fifteen days before experiment and splenectomies were performed on a pair in the same morning. The particular pair were matched for weight and size as nearly as possible but choice of sex was completely random. They were fasted prior to operation.

At the time of surgery they were shaved and prepared with Hibitane solution. Nembutal anaesthesia was used and the animals were intubated so that the respirator could be used as necessary. It was seldom needed. The operation itself was carried out by the surgeon unassisted and took less than one hour. A left paramidline incision was employed in the upper abdominal wall and carried down to the peritoneum. Cautery was employed to control bleeding. The spleen was delivered and its mesentery opened. The main artery was clamped and the vein left open so that by gentle massage the spleen could be emptied of some of its blood. It is noteworthy that the nembutal used to anaesthetize the animals caused a marked engorgement of this organ. Next, the vessels in the mesentery were ligated and divided and the spleen removed. These organs were weighed after the operation. Chromic catgut #1 was used for ties and closure of all layers except the skin. Here wire was used. Post operative care consisted of no oral feeding until the next morning and included the administration of the long duration penicillin. The animals recovered quickly and generally without complications. Occasionally a mild upper respiratory tract infection developed but his was controlled by the penicillin. More than sixty splenectomies were performed but only one animal died acutely post operatively. It this case a tie had slipped from a vessel in the gastro splenic omentum and death resulted from haemorrhage within 4 hours of surgery.

For the remainder of the period before experiment the dogs were kept in pens rather than cages. Their diet was the regular kennel menu and they were allowed out on the run regularly. Sutures were removed in 7 days. In general the wounds were well healed by this time; if not, removal of the sutures encouraged scar formation so that by the time of experiment all wounds were closed. On the evening before the experiment the pair were checked but were not isolated in cages. Food and water were available to them.

CHAPTER VI

DRUG TREATMENT

SECTION A. Hydralazine.

L-hydrazmophthalazine is marketted by the Ciba company as "Apresoline" and is regarded as a moderately strong antihypertensive agent. It acts to lower both diastolic and systolic pressure in both hypertensive and normotensive individuals by a central effect on the vaso-motor area of the brain and by a peripheral effect in the manner of adrenergic blockade. It has been claimed by Reubi[85] and shown by Moyer[72] that renal blood flow is increased by this drug and the inference was made that splanchnic flow would be likewise increased. Because of this the drug appeared to have possibilities in the treatment of shock. The fact that it had an adrenergic blocking action and therefore reduced total peripheral resistance was important enough but in addition this agent was reputed to have a strong central action on the heart similar in effect to that of epinephrine. An increase in heart rate, stroke volume, and hence cardiac output results from its use. Because it was the premise of this group that the irreversibility of shock is due to a powerful pressor effect in the important splanchnic vessels with subsequent ischaemia and sequelae, an agent such as hydralazine with its purported ability to block afferent receptors and therefore act as an antiadrenergic and also to act centrally to increase the flow of blood seemed to be the ideal drug for this series. It was well known to us that certain pressor amines are capable of producing

the same ionotropic and chronotropic effect on the heart without increasing capillary flow. An agent which would act to cause visceral capillary dilation and hence allow an effective flow of blood at tissue level could prove to be the answer to the problem of irreversibility. If animals given this drug survived while controls died reversibility would be demonstrated and could perhaps be considered to be due to mesenteric vessel metarteriolar and precapillary sphincter dilation since no antitoxic effect has ever been accredited to the drug.[42] The duration of a single dose of hydralazine is thought to be up to 10 hours.

SECTION B. L-norepinephrine.

It was because according to our reasoning fatal ischaemia of the bowel supplied by the superior mesenteric artery is brought on and aggravated by a stimulation of circulating adrenergics we hypothesized that a further exogenous dose of such an adrenergic agent would simply add to the vasoexclusion already taking place. In no way could an elevation of systemic pressure help to bring blood to anoxic tissues when the terminal ramnification of the arterial network were shut down tightly. It was predicted that death would be hastened by giving l-norepinephrine to an animal which has been bled maximally.

L-norepinephrine is a naturally occurring pressor amine and has been identified as the mediating agent of the postganglionic sympathetic nerves.[42] It is found in other tissues too including the wall of arteries.[10] The drug acts to increase both systolic and diastolic blood pressure and often pulse pressure also by increasing total peripheral resistance. It has an effect on the heart to increase stroke volume but there is no improvement in cardiac output because of a reflex vagal bradycardia. Goodman and Gilman[42] note that peripheral resistance is increased in most vascular beds but in

the case of the coronary and cerebral arteries flow is maintained due to some selective vasodilation perhaps. The manufacturers of Levophed suggest that because of its strong peripheral vasoconstriction of precapillary sphincters and metarterioles it is useful in haemorrhage in order to mobilize stagnant blood. The view that this stagnation is secondary to arterial ischaemia is overlooked by them. This agent has a temporary effect and must be administered continuously.

SECTION C. Hydrocortisone.

The action of the adrenocorticoids on the vascular system is known by inference rather than as fact. It is known for example that in adrenocortical insufficiency there is an imbalance of sodium and water metabolism and this accounts for the hypotension associated with the disease. However when these elements alone are corrected the coexisting hypotension is not always improved as it is when corticoids are given. Obviously the corticoids or one of their fractions are responsible for a vasopressor effect.

Desoxycorticosterone is known to produce hypertension but this is in association with a positive sodium balance and an increase in circulating blood volume.

The statement is frequently made in order to explain the beneficial effect of corticoids in clinical haemorrhage states that these agents reestablish or potentiate the response to vasopressors[104] but his has not been borne out by experimental work.[96] The impression that there is a direct central nervous system action to increase motor irritability and thus vascular tone is likewise not proven to be the mechanism of action. Nonetheless striking results have been reported clinically of response in hypovolemic shock to corticoids, usually the glucocorticoids, and it was

the plan to include in this programme a series of hydrocortisone treated animals. It was desired to see what effect if any the intravenous form of hydrocortisone would have in the controlled framework of the experimental method outlined previously and then try to account for its action.

PART III

RESULTS

CHAPTER VII

CONTROL ANIMALS

The behaviour of animals subjected to the shock process as outlined was interesting and followed a course which repeated itself with only minor variations from one experiment to another. The recordings of vital sign changes are tabulated in the appendix and the other values are recorded in tables I, II, and III.

In general control animals behaved similarly whether they were splenectomized or not. It was not possible to det e ct any difference in the course of the experiment or in outcome except that the reservoir volumes of shed blood were less for splenectomized dogs than for intact animals of the same weight. Probably splenectomy does decrease the circulating blood volume. In this group of experiments all evidence indicated however that splenectomized animals withstand shock at least as well as intact animals. This does contradict some previous impressions.[57]

As the experiment began with removal of the reservoir clamp blood flowed rapidly into the bottle as pressure dropped towards 40 mm Hg. Within 10 minutes there were several hundred cc's in the reservoir. The difference between splenectomized and non-splenectomized animals of equal weights was seen at this point for an animal with intact spleen would force between 150 and 200 cc. more blood into the reservoir than a splenectomized dog in this early interval. From this time on the rate of flow would be paralleled so that at the end of either the 40 mm. or the 70 mm. period the

intact animal's shed volume would be 150 to 200 cc. more than that of the splenectomized animal. Apparently the initial hypotension acted as a stimulus for the emptying of the spleen and once this had occurred there was no subsequent resorption or extrusion of blood by this organ. Post mortem examination of the non-splenectomized series of animals consistently revealed small spleens of low weight. Bleeding, while rapid at first, slowed down in rate towards the end of the 40 mm. interval but rarely did it stop completely or did blood return to the animal. This continuing outpouring of blood reflected the animal's persisting adjustment in the manner of increased peripheral resistance. Always as soon as the reservoir was elevated to a higher level in order to raise the arterial pressure there was some uptake of blood, usually between 50 and 100 cc. Generally there followed a further rise in reservoir level and this often exceeded that attained at 40 mm Hg. This reflected continuing vasomotor effect in the smaller vessels and provided a very satisfactory result because by the end of the 70 mm. period the volume of shed blood began to level out and come very close, if not always up to maximum bleeding volume. This applied equally well to both splenectomized and intact animals. The end of the 70 mm. period saw the termination of bleeding since the tubing was now clamped. The blood pressure pattern during the clamped period was fairly typical. Usually a rise of a few points took place, in some instances to 100 mm Hg., in the early part of this period. Within a half hour a decline usually began which persisted until reinfusion. The depth of this decline was rarely below 40 mm Hg.

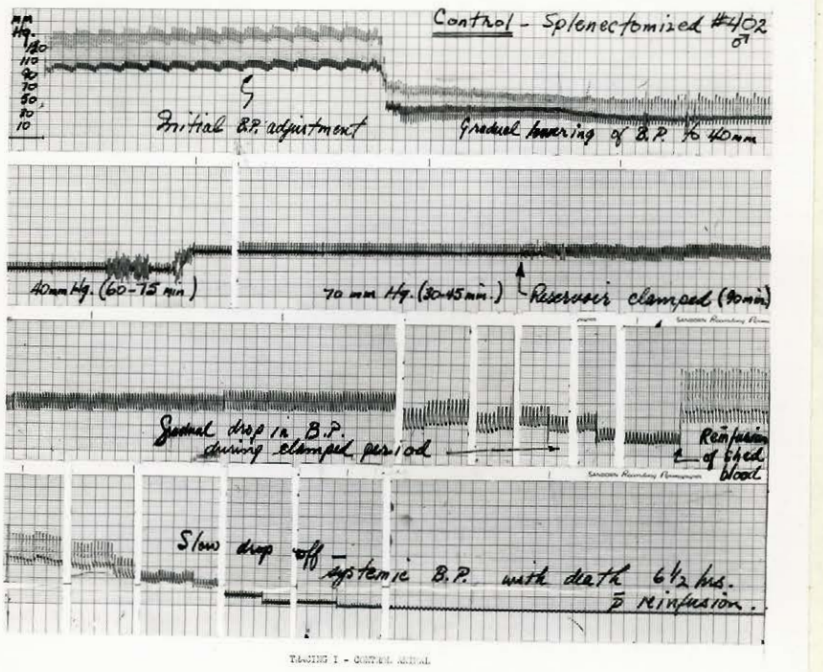
On reinfusion of blood no difficulty was experienced. The animals absorbed the shed blood volume easily when it was run in under slight pressure. Of prime interest of course was the blood pressure pattern

following reinfusion. Without exception it rose briskly immediately after replacement of blood to a level approximating that before experiment. This was only occasionally exceeded subsequently but was maintained for a variable length of time before beginning to decline. This falling off was generally gradual but in the case of some of the animals was sudden. (Note Tracing #I).

Pulse and respiration patterns during the experiment were irregular but generally these two paralleled one another. During the 40 mm. period both increased gradually. On elevating the pressure to 70 mm., pulse and respiratory rate slowed somewhat but remained above normal values. At the commencement of the clamped period a further slowing was general but as this period progressed an acceleration was common. Often there was a dysrhythmia of pulse and respiration during the last half hour of the clamped period. This was associated either with an acceleration or deceleration of the pulse and these changes were taken to indicate that the animal was having difficulty in maintaining circulation to vital centres.

With reinfusion both rates returned to near normal values only to increase again gradually then either speed up markedly or slow down drastically prior to death. Venous pressures did not show any particular trend although it was common for these values to be much higher after reinfusion than at any previous interval.

Other phenomena were noted in control animals. It was very common for a bowel movement to occur at some time during the clamped period, usually towards the end. This discharge was short of explosive but was forceful enough to indicate more than simply sphincter relaxation. Possibly a parasympathetic discharge was occurring. The stools were never bloody but were commonly loose and watery. Less frequently spontaneous



TRACING I.

Twin-viso Recording of Blood Pressure Changes during an Experiment with a Control Splenectomized Animal.

emptying of the bladder occurred at some stage of the experiment. On occasion Cheyne-Stokes breathing occurred in late stages following reinfusion.

As a rule there was an apparent improvement in the animal's condition in the period immediately following reinfusion. In addition to a more normal approximation of vital signs the dogs were more alert and aware of their situation. During the hypotensive and clamped periods although the animals were awake they moved about very little on the tables. Reinfusion obviously stimulated their nervous systems. Occasionally at this stage an animal would become active and require one or two cc's of nembutal. Whenever this was given the other member of the pair received an equivalent dose based on his weight.

As has been implied previously a difference in response to haemorrhage was noted in dogs coming from the farm in winter versus those arriving in the warm summer and autumn months. Dogs brought into the laboratory at McGill from the farm in mid-winter invariably withstood the shock better. That is to say, after any given time interval in the bleeding procedure their volumes of shed blood would be less than those of warm weather animals. For the months of January, February, and March therefore an extra 15 minutes was added to both the 40 mm. and 70 mm. intervals. This was found by experience to produce a bleeding volume comparable to the animals run in October, November, and December. Although April was not a cold month dogs run at this time were subjected to the longer periods of hypotension because they seemed to have retained their resistance to shock. The necessity for this change in procedure was worrisome to the investigators but a perusal of the literature revealed that the situation was not new; in fact it is regarded as a normal feature of experimentation with dogs in climates where

temperature changes are marked from one season to another. Remington[82] noticed that winter experiments had to be modified to produce results similar to summer series. It was noted by Cleghorn [15] and others[63,64] that climate changes greatly affected the response to haemorrhage. Wiggers[106] remarked that, "dogs appear to be less resistant . (to stress) . . in summer than in winter."

In two instances animals were disqualified from the experiment after showing an unexplained fall in blood pressure to subnormal levels prior to bleeding. This phenomenon occurred soon after cannulation and was attributed to either an idiosyncratic response to nembutal or a vagal reflex due to tissue handling. In one instance there was acute death prior to reinfusion. One hour after clamping dog #37 died. Because at post mortem typical bowel changes were seen this death was attributed to the shock of haemorrhage and reflected, it was felt, the severity of the procedure. In the case of dogs #382, 393, and 395 death occurred before the animals left the experimental tables. Dogs #156, 329, and 498 were observed continually until death although pressure recording had been discontinued. All other deaths occurred in the cages of the kennel rooms. The mean time of death for control animals was 12.3 hours post reinfusion in the case of intact dogs and 13.2 hours in the case of splenectomized animals.

Post mortem examination proved most interesting. The livers and kidneys were usually dusky in colour and moderately engorged but spleens, when present, were small and pale. Most attention was focussed on the bowel and this was carefully examined after being removed from the abdomen and opened longitudinally from duodenum to rectum. Without exception in control animals mucosal ulceration was obvious and the stool within the lumen was bloody. Both of these phenomena varied to some extent. Ulcers were sometimes

discrete and occupied as little as half the mucosal surface. Occasionally they were more concentrated toward one or other end of the bowel but most frequently the terminal small bowel and ascending colon exhibited the greatest concentration of ulcers. Grossly these appeared to have ragged borders but deep bases covered with a fibrinous exudate. In other instances ulcers ran together and produced a large area of sloughed mucosa. Again fibrin was present. The amount of blood in the bowel lumen varied but there was always no doubt that bleeding had occurred. (Note Figure #3). Stools, in addition to being blood tinged or composed mainly of blood, were unformed. Frequently the content was of an opaque, fawn colour with the consistence of cooked starch. Bowel walls were consistently thicker than those of dogs dying from other causes and they demonstrated extensive bruising and haematoma development which did not necessarily correspond to the position of mucosal ulcers.

Mesenteric vessels generally appeared to be constricted but his was not deemed to be a significant finding at this time.

Out of 31 control dogs not one animal lived beyond the established 48 hour survival time and therefore mortality can be given as 100%. In the case of the dogs used as controls in the hydralazine series the evidence of death from irreversible haemorrhagic shock was most convincing. The same can be said for the control dogs run in the hydrocortisone series. However, during the two winter months when Levophed was under trial post mortem examinations of controls revealed in addition to the typical bowel changes evidence of pulmonary disease in 3 dogs. Dogs #13, and 435 showed pulmonary empyemas and #483 had multiple small abscesses in both lungs. It was interesting that these animals had relatively long survival times and this made one wonder if a certain resistance is developed to shock by a preceeding

FIGURE 3.

Photograph of the Small and Large Bowel of Control Animal #438. Arrow Indicates an Ulcer.

or concurrent illness. While it is possible that these animals would have lived had they been free from the chest complications it is not probable. Nonetheless for the sake of reliability of results these three should not be considered as shock death. The method shock employed can they be safely said to give a mortality of between 90 and 100% in untreated control animals. (Note Figure#10).

The laboratory findings in control animals are tabulated in the appendix. No specific trend was seen between preshock and postreinfusion samples, either in total proteins or the albumin and globulin fractions. Haemoglobin and haematocrit values were remarkable in their similarity in the two samplings.

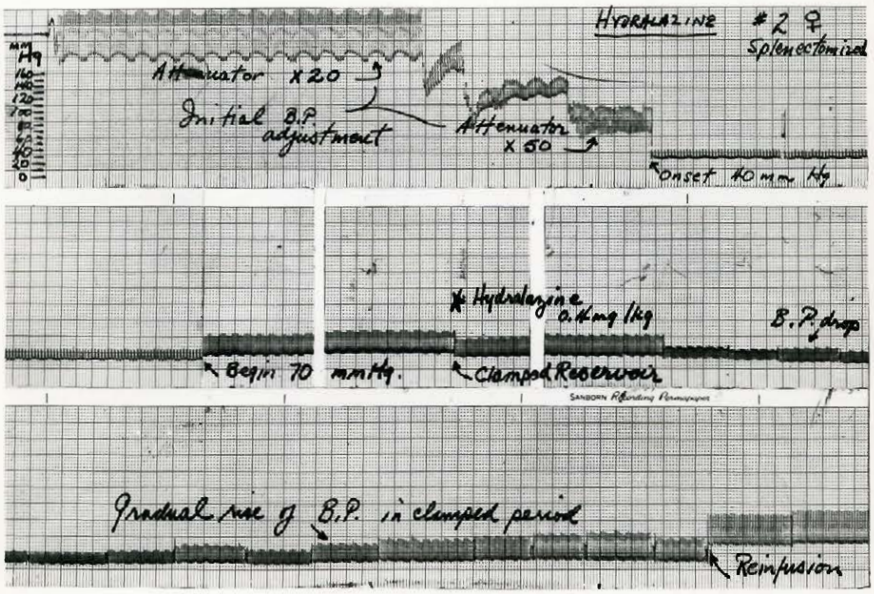
CHAPTER VIII

TREATED ANIMALS

SECTION A. Hydralazine Treated.

Sixteen animals were treated with hydralazine. Fifteen of these survived and one died. This includes 7 non-splenectomized and 8 splenectomized survivals. The fatality, dog #424, lived 44 hours and was of the splenectomized group. This animal was slow to arouse after the experiment and did not appear to have full mental control. He staggered about the cage in an ataxic manner and did not eat. Autopsy revealed no more bowel necrosis than was typical for this group nor was any complicating lesion found.

The behaviour of hydralazine animals followed a characteristic pattern. For ten minutes following administration of the drug at the beginning of the clamped period the blood pressure remained at around 70 mm Hg. Often there was a slight rise to 75 or 80 mm. and occasionally a fall to 65mm. Within 10 minutes the pressures, both systolic and diastolic, began to drop and they fell steadily for an hour to as low as 26 mm Hg. Pulse pressures were often more than in control animals. During the last 20 to 30 minutes of the clamped period the pressure began to rise slightly but evenly as shown in Tracing II and Figure #4. The mean pressure for the clamped period was 59 mm Hg. Reinfusion of blood brought the pressure up of course but rarely to the preexperiment level. Over the next hour a



TRACING II - HYDRALAZINE TREATED DOG

TRACING II.

Twin-viso Recording of a
Hydralazine Treated
Animal.

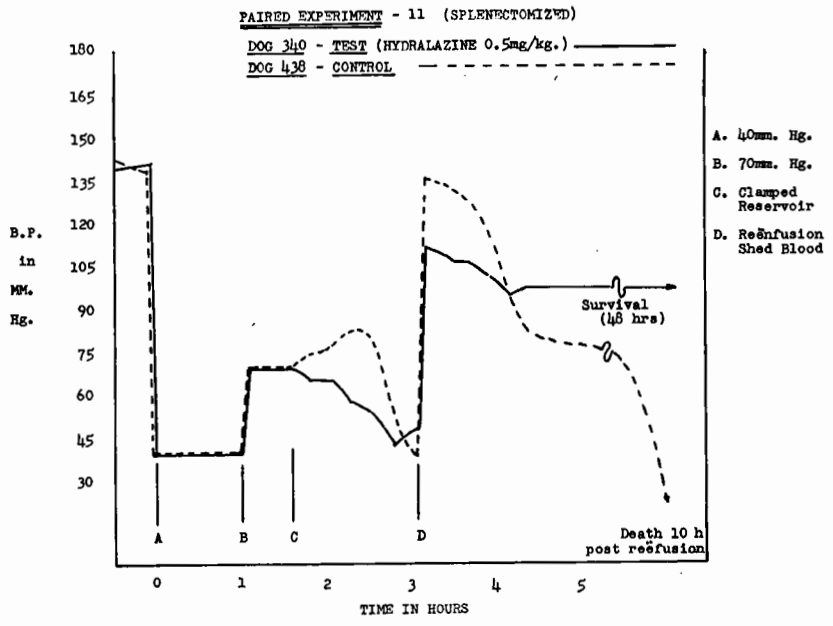


Figure 1.

FIGURE 4.

Graphical Representation of Blood Pressure Changes during Experiment XI. A Hydralazine Treated and a Control Animal were Used. Both Were Splenectomized.

slight decline of 10 to 20 mm Hg. occurred but from this time on very little if any fall was noted. Usually the pressure stayed steady or rose a few points.

Pulse and respiratory rate were increased following hydralazine so that they exceeded control rates by 10 to 20%. Upon reinfusion, little difference existed between the rates of the two animals. As a rule systemic venous pressure was not markedly reduced after drug administration and values were higher than control levels during the clamped period. On reinfusion it increased but not to a higher level than controls.

Following reinfusion it was almost the rule that these hydralazine treated dogs voided but in no case was a bowel movement noted either at this stage or earlier. The increased urine production seemed to verify the claim for improved renal blood flow.[72]

In subsequent hours these animals responded normally to external stimuli and began to eat at as early times as control dogs. However several of these animals appeared to be dizzy and weak on the following day. This situation improved in all and by the 3rd day these dogs were as active as the others.

Autopsies were done following sacrifice and showed a mild amount of liver and kidney engorgement and small pale spleens in those intact animals. The bowel picture was interesting indeed. While ulceration was not entirely absent one was impressed by the sparsity of the necrotic patches. Ulcers were small and scattered in a fairly even distribution. Stools were formed but occasionally blood tinged. The bowel wall was thin and the bruising effect seen in controls was absent. The mesenteries did not look any different from those of controls. (Note Figure #5).

Laboratory results were not convincing of any trend. Haemoglobin

FIGURE 5.

Photograph of the Small and Large Bowel of an Hydralazine Treated Animal - #414.

(The small amount of necrotic change is noteworthy)

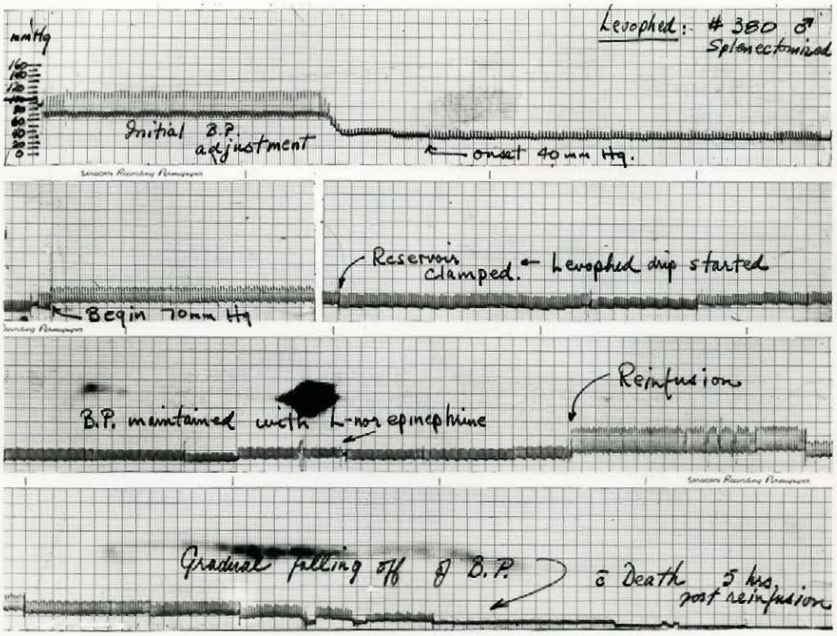
and haematocrit varied very little from first to second sample and while plasma proteins did drop a little between prehaemorrhage and reinfusion this was the same as in controls. Albumin/globulin ratios were similar too. Occasionally there was a rise in the globulin fraction in the 2nd sample but his phenomenon was observed in control animals too.

The improvement in survival was striking to the investigator. Repeatedly when the cages were checked on the evening or morning following experiment the hydralazine dog would be alive and active while the control was dead. The value of this agent certainly was apparent.

SECTION B. L-norepinephrine Treated.

Thirteen snimals were tested with this drug. The results are not convincing but are only suggestive that the agent is actually harmful in hypovolemic shock. There were three 48 hour survivals in this group, #'s 314, 450, and 491. With the 10 animals which died the mean time of death was 11.5 hours from reinfusion. As these were all splenectomized animals this compares with 13.2 hours mean time of death in controls. The "t" test applied to these figures for the time of death gives a value of 0.626 which is not significant.

Blood pressures during the clamped period were being sustained with the Levophed drip as outlined and at the rate of flow used were held to low normal values. The mean blood pressure was 88 mm Hg. during this period. When the vasopressor drip was stopped in order to study the effect within 20 to 30 seconds a precipitous drop of 30 to 40 mm. occurred. Reopening of flow brought the pressure back to the original level. Pressures approximated prehaemorrhage levels immediately following reinfusion; some were higher and some, lower. The nature of the decline of blood pressure



TRACING III - L-NOREPINEPHRINE TREATED DOG

TRACING III.

Twin-viso Recording of an Animal
Treated with
L-norepinephrine.
(Levophed)

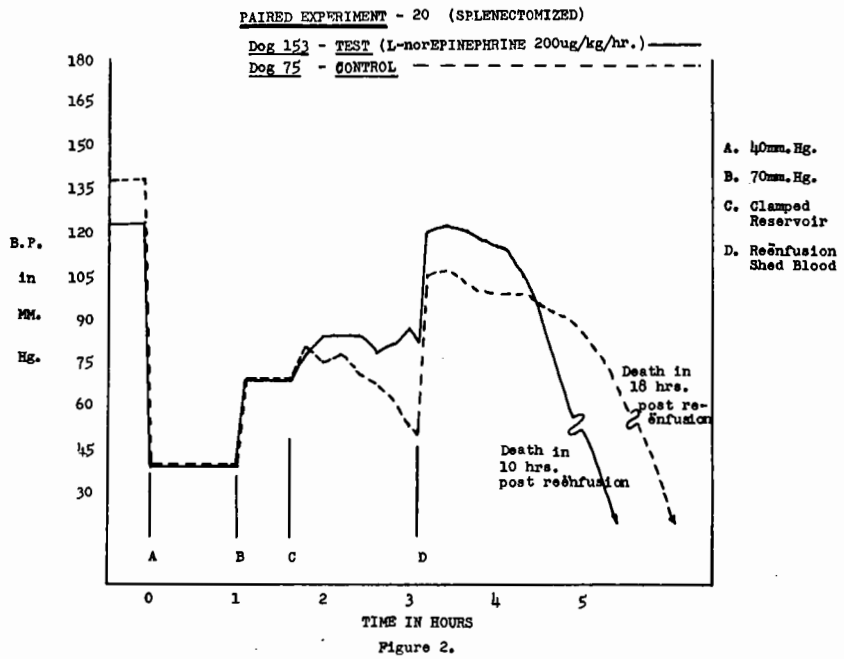


Figure 2.

FIGURE 6.

Graphical Representation of Blood Pressure Changes during Experiment XX. This Includes a Control and a L-norepinephrine Treated Animal.

in the succeeding hours was no different from controls except that it occurred more quickly on the average. There was nothing distinctive about the pressures of the three survivors at any time.

While pulses and respiratory rates increased slightly with the administration of Levophed the greatest rise came following reinfusion of shed blood and considerably exceeded those of control animals. Venous pressures were up over control values during the clamped period as would be expected and they stayed up at values comparable to controls following return of blood.

Voiding was a common but not universal feature of these animals and it occurred late in the clamped period as a rule. Watery bowel movements occurred in about half of the dogs which died. A bloody stool was seen in one animal only, # 459.

Postmortem examinations were informative. It was rare to find discrete ulcer formation in the bowel mucosa because the necrosis was widespread. Large sloughs of mucosa with blood sausage attached were frequently seen. (Note Figure #7). Although these were isolated they did involve in toto as much as 1/3 of the bowel surface. In some animals the bowel walls seemed to be split as though by a dissecting aneurysm and frequently the walls were ½" thick filled with blood and fluid for distances of 4 to 6". The severity of the necrotic lesions was obvious although occasionally a length of bowel would be completely spared of ulceration of any kind. Although kidney appearance did not differ very much from control animals, livers were smaller and more pale than others.

Laboratory results did not add anything to the picture. When this series is compared statistically with the 24 splenectomized control animals a chi^2 corrected value of 3.33 is calculated. This is not significant and

FIGURE 7.

Photograph of the Small and Large Bowel of an Animal Treated with L-norepinephrine. This Was Dog #492.

(Note the segment containing submucosal blood).

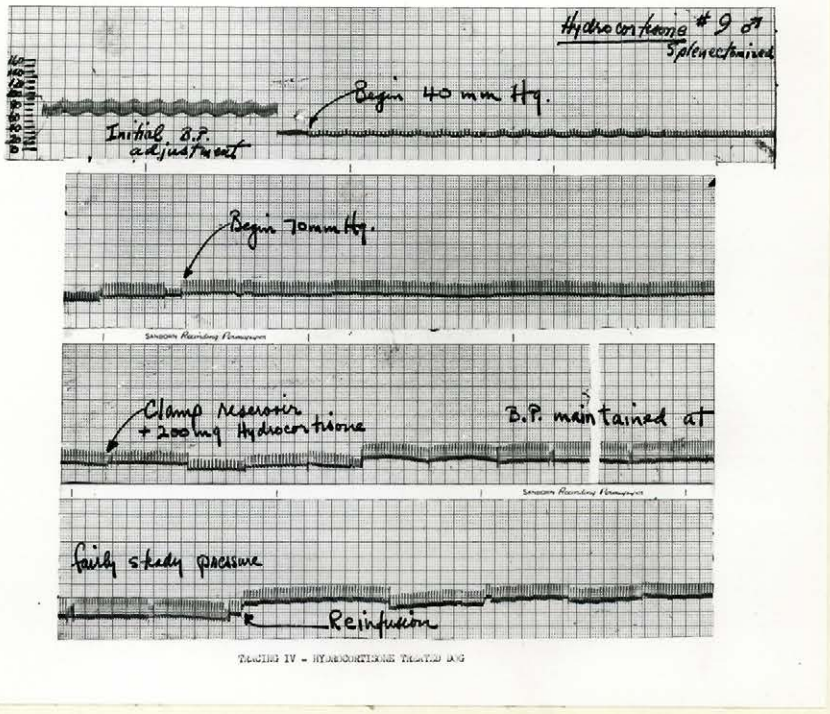
indicates that the three survival should really not be attributed to the effect of Levophed. However a significant figure would appear if the control splenectomized series had been only slightly larger and it is reasonable to say that survival was in some way related to the effect of the agent.

SECTION C. Hydrocortisone Treated.

The intravenous preparation was used to treat 13 dogs. Of this number 11 survivors are reported. (Note Tables I,II, and III). The two dogs which did not survive, #151 and #214 died in 42 and 34 hours respectively from the time of reinfusion. All animals were splenectomized.

With this group a characteristic blood pressure curve was observed in almost all the animals. Following the administration of 200mg. hydrocortisone early in the clamped period one noticed the usual slight rise in pressure but following this there was no falling off in arterial tension. However there was no marked increase either. Rather, the pressure was maintained just above the 70 mm Hg. level throughout the 90 minute period. Actually pressures ranged between 74 and 88 mm. in all but one case. With dog #342 the pressure dropped to 58 mm. in the last 20 minutes of the clamped period. The mean pressure was 80 mm Hg. for the clamped period. Following reinfusion pressure rose to levels approximating pre-haemorrhage values or slightly more. Generally a slight drop followed in the next hour but in several instances a moderate rise took place before the pressure levelled off. All post infusion pressures were more than 100 mm Hg. as shown in Figure #8.

Hydrocortisone produced no increase in pulse and respiratory rate. A mild degree of acceleration occurred during the clamped period but this



TRACING IV - HYDROCORTISONE TREATED DOG

TRACING IV.

Twin-viso Recording of a
Hydrocortisone Treated
Animal.

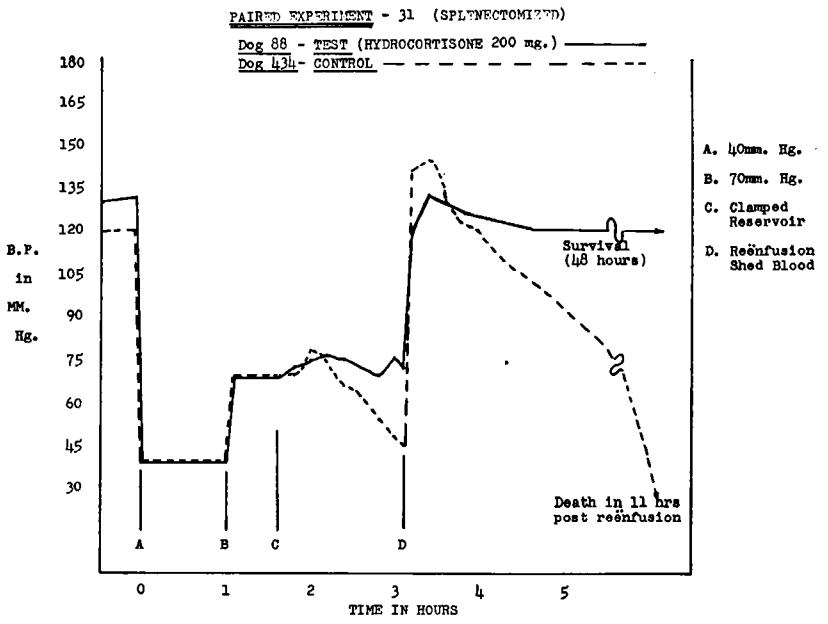


Figure 3.

FIGURE 8.

Graphical Representation of Blood Pressure Changes during Experiment XXXI. A Control and a Hydrocortisone Treated Animal Were Used.

was considerably less than with control animals. It is noteworthy that the effect of any of this drug on pulse and respiratory rate was to slow them or at least prevent rapid acceleration and probably this was secondary to the blood pressure maintenance effect. Venous pressures rose a little after reinfusion but less than those of control animals.

Voiding and defecation were not features of this group. Recovery of these animals was probably quicker than those of the hydralazine treated group. Within 6 to 8 hours they were eating and standing up and by the next day were able to be allowed out on the run.

Post mortem examination was carried out on the two fatalities and on several others of the group following the 48 hour time limit. Again, grossly, the liver and kidneys were not remarkable. The bowel was found in all to be quite similar to those of the hydralazine group. If anything ulcer formation was less widespread and the craters themselves were smaller, measuring 1/8 to 1/4 " in diameter rather than 1/2". Their depth was comparable and fibrinous exudate was present in the bases. Stools present were soft and mucous covered. In some isolated spots bloody exudate was stuck to the mucosa. (Note Figure #9).

Laboratory findings showed no special trend between prehaemorrhage and reinfusion samples. A drop of 0.5 gms% total protein was common but not universal.

The striking improvement in recovery from the severe shock situation with the use of this drug is noted. The general well being of the animals too was remarkable and exceeded that of the hydralazine treated group.

FIGURE 9.

Photograph of the Small and Large Bowel of an
Animal Treated with Hydrocortisone.
This Was Dog #342.

(Note the sparsity of haemorrhagic mucosal lesions).

TABLE I.

RESULTS OF HAEMORRHAGIC SHOCK EXPERIMENTS
NON-SPLENECTOMIZED ANIMALS

	Number of Dogs	Mean Weight in kgs.	Bleeding Volume in cc's/kg.	Mean B.P. during clamped Period-mmHg.	Number Fatalities	Number Survivals	Survival Time in hours from Reinfusion	Mean Weight Spleens Grams
CONTROLS	7	13.6	55.4	67	7	0	12.3	73
HYDRALAZINE 0.4 mg/kg.	7	13.2	65.6	60	0	7	(48)	

TABLE II.

RESULTS OF HAEMORRHAGIC SHOCK EXPERIMENTS
SPLENECTOMIZED ANIMALS

	Number of Dogs	Mean Weight in kgs.	Bleeding Volume in cc's/kg.	Mean B.P. during clamped Period-mm Hg	Number Fatalities	Number Survivals	Survival Time in hours from Reinfusion	Mean Weight Removed Spleens - Gms.
CONTROLS	24	12.4	46.2	67	24	0	13.2	71
HYDRALAZINE 0.4 mg/kg.	9	13.8	48.6	58	1	8	(44)	73
L-NOREHNEPHRINE 150-250 ug/kg/hour	13	12.6	49.6	88	10	3	11.5	77
HYDROCORTISONE 200 mg.	13	12.3	49.2	80	2	11	(38)	78

TABLE III.

RESULTS OF HAEMORRHAGIC SHOCK EXPERIMENTS
INCLUDING NON-SPLENECTOMIZED AND
SPLENECTOMIZED ANIMALS

	Number of Dogs	Mean Weight in Kilograms	Bleeding Volume in cc's/kg.	Mean Blood Pressure during clamped Period in mm Hg.	Number of Fatalities	Number of Survivals	Survival Time in Hours after Reinfusion	Mean Weight Spleens in Grams
CONTROLS	31	12.6	48.3	67	31	0	12.8	71
HYDRALAZINE 0.4 mg/kg.	16	13.6	56.0	59	1	15	(44)	73
L-NOREPINEPHRINE 150-250 ug/kg/hour	13	12.6	49.6	88	10	3	11.5	77
HYDROCORTISONE 200 mg.	13	12.3	49.2	80	2	11	(38)	78

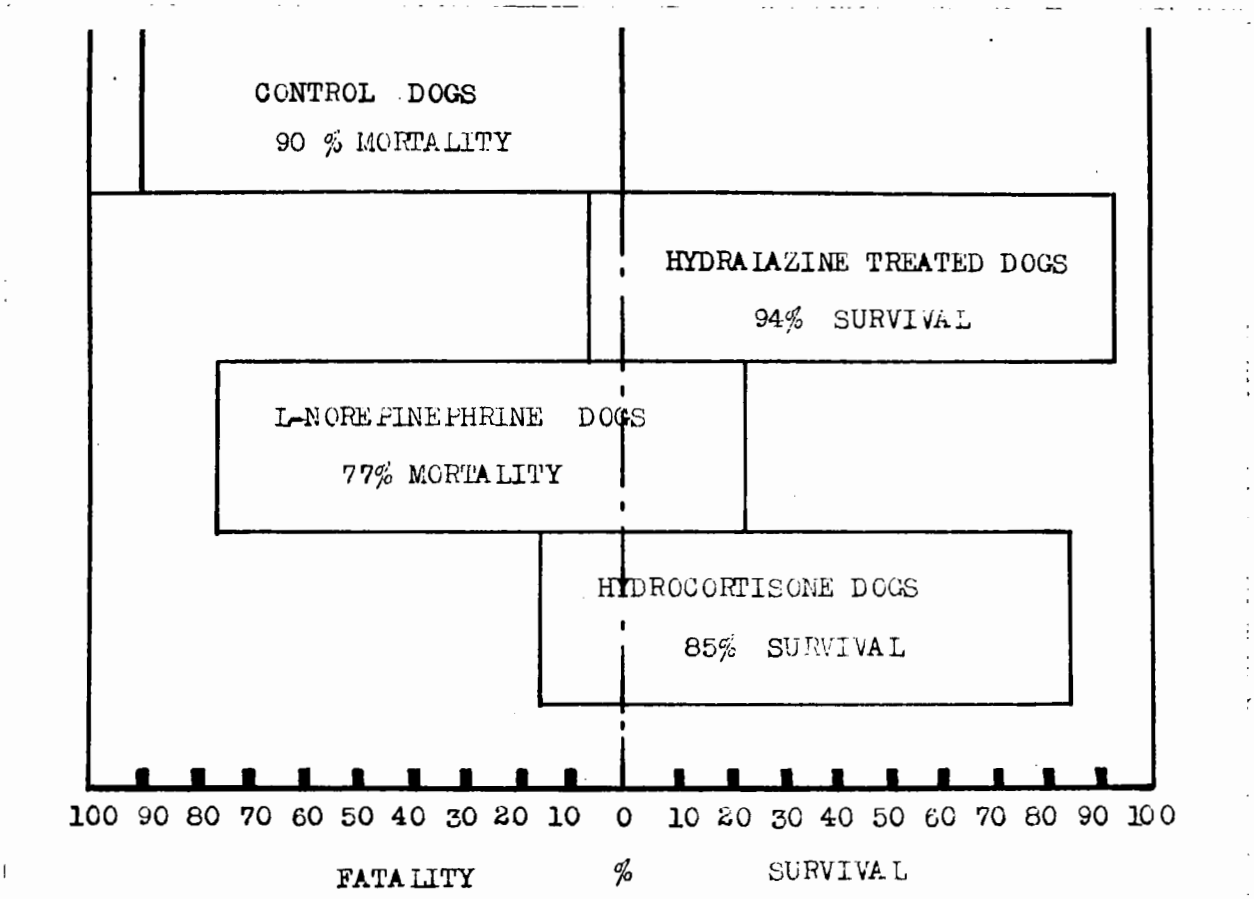


FIGURE 10.

Graphical Representation of All Paired Experiments. Included Are Splenectomized and Non-splenectomized Animals. Percentages are for 48 Hour Survival.

PART IV

CONCLUSIONS

CHAPTER IX

DISCUSSION

SECTION A. Experimental Method.

The reasons for employing a Wiggers' type of shock inducing technique rather than the Fine method have been enumerated. Briefly, they include ease of control and ability to reduplicate the stress situation. The additional advantage of the clamped period as introduced by Nickerson and Zingg was explained but it was noted that their method as it stood did not produce a severe enough stress since only 69% of controls died. Through good fortune and with the use of a small number of dogs for trial purposes it was possible for us to arrive at a combination of hypotensive pressures and time intervals which would present a severe stress and guarantee a high mortality. The close approximation to maximum bleeding volume at the end of the second hypotensive period was regarded as a further advantage of this shock technique. To achieve this volume is a reliable indication of severity. In actual fact the bleeding volumes were high considering that the animals were splenectomized. Those intact dogs poured out slightly more blood during the shock period than did Fine's dogs and yet they were not apparently so severely shocked as his. The difference probably lies in the duration of shock rather than the variance of pressures. While the bleeding volumes were comparable these were accomplished in a shorter interval in the present

series than with Fine's animals. Possibly this gives less chance for more terminal vessels to close down.

The clamped period offered a chance to observe the effect of therapeutic agents without the presence of other variables. It is noted that when an animal receives a ganglionic blocking drug before haemorrhage, less bleeding occurs in reaching the degree of hypotension demanded than in an untreated animal.[83] Hence the valid arguement that a lesser stress has been imposed can be made should the pretreated animal survive and the control one die. Although we did not wait until irreversibility occurred before rendering treatment as have others[29] (this point was presumed to occur late in the clamped period) we did give our agents only after the insult to the animals had been completed. This,it is believed,is important because in drawing the parallel with a human being involved in an accident and sustaining blood loss and hypotension it is obvious that bleeding would be stopped by a first-aid attendant before a pharmacological agent is administered by a physician. To carry the analogy further, the clamped period represents the interval before cross matching and administration of blood by transfusion. A drug then to be practical should exert a favourable influence on the vascular system after the bleeding insult has occurred but before blood volume has been replenished.

The use of an intravenous glucose and saline drip throughout the experiments was not thought to alter the course of shock to any appreciable extent. Both animals received equivalent amounts based on their weights and this never exceeded one pint. There was no particular reason for choosing glucose and saline over glucose and water as both serve as diluents for Levophed.

While the use of other chemicals such as nembutal, heparin, and

sodium citrate in the experiment can be questioned for their possible influence on the course of the shocked animals it should be noted that both animals of the pair received these agents. Great care was taken to ensure that they were administered in doses which considered the size and weight of the animals and so amounts as nearly equivalent as possible were given. Nonetheless there has been criticism of the use of barbiturates for anaesthetizing animals prior to cut-down procedures. The V.E.M. and V.D.M. theories of Shorr suffered a setback when Fine et al. were unable to demonstrate the vasodepressor substance in the blood of shocked dogs which had not been anaesthetized with barbiturate. Of course V.D.M. had been isolated from shocked animals and identified as ferritin.[70,71] As a result of the finding Fine began to use morphine as premedication for cut-down procedures instead of barbiturates.

While the possibility of disturbances of the vascular system and alteration of body fluids distribution by anaesthetic agents has been raised no experimental evidence is available to show that such alterations could affect resistance to blood loss or modify the animal's compensation to this. Lawson and Rehm[64] noted that movement of water to and from tissues and blood stream in shock is just as effective in anaesthetized animals as in others. C.J. Wiggers did extensive comparisons of tolerances to haemorrhage and resulting bleeding volumes in unanaesthetized dogs and those given a barbiturate. His conclusion was that, "data . . . reveal such surprising similarity between unanaesthetized and barbitalized dogs that any significant effect of these anaesthetics on production of haemorrhagic shock must be seriously questioned." While Hume[52] found that nembutal anaesthesia reduces the secretion of epinephrine and nor-epinephrine he found that nembutal plus trauma resulted in no change in epinephrine

secretion and a slight rise in nor-epinephrine and corticosteroid levels.

The effect of heparin is to increase bleeding of course and so its use in a haemorrhagic shock situation may be considered important. However in healthy animals the only loss of blood other than into the closed reservoir system was at the cut edges of tissue in the cut-down region. This latter was minimal because ties were applied to severed vessel ends at the time of preparation. It was essential to use this anticoagulant to guarantee freedom from clotting of the blood shed into the reservoir.

Less than 50 cc. of 3% sodium citrate was used to provide a fluid column between the animals and manometer and the animal and reservoir. Of this perhaps 30 cc. was returned to the animal with the reinfused blood and this amount was not considered harmful. It can be restated than both animals of the pair being run received equivalent amounts of heparin and citrate in proportion to their weights.

It is perhaps worthwhile to comment briefly on rates of bleeding and reinfusion. As it was noted in the protocol, animals were bled into the reservoirs from normal pressures of about 130 mm Hg. to 40 mm. in a 5 to 10 minute period and likewise reinfusion of blood was carried out in a similar time interval. It is a well known fact that an animal can withstand removal of a greater volume of blood when this is carried out over a matter of hours or days rather than minutes.[7,14,24] At one time it was thought that vasoconstriction mechanisms did not act efficiently in the case of rapid haemorrhage but his idea was not supported by physiological principles. Our guide in this matter has been the work of Wiggers[106] and Price.[79] The former especially did extensive experiments with different types of bleeding and three rates. He found that bleeding volumes were very comparable whether bleeding was at the rate of 3 or 50 cc/minute.

Price analyzed his own experiments and concluded that acute haemorrhage affects blood pressure in the same way whether bleeding occurs rapidly or slowly, continuously or intermittently. Our animals were allowed to bleed out into the reservoirs at between 40 and 60 cc/minute.

In their work on arterial versus venous transfusion Hampson, Scott, and Gurd,[46] showed that animals can withstand rapid transfusion even when blood volumes are not appreciably diminished. Even if there exists a state of small vessel constriction as in hypovolemic shock the vascular system seems to be able to accomodate large volumes of blood with ease. Possibly this means that arteriolar and perhaps A-V communicating channels are dilating.

Although the double system of blood pressure measurement may seem clumsy to the reader in actual practice it worked extremely well. It was a simple matter to move a Kelly clamp from the tubing channels in order to divert flow from one machine to the other. The advantages of easy reading on the one hand and accuracy on the other made the system worthwhile.

To have perfect control of an experiment such as that of shock it would be necessary to use animals of the same litter which had been reared in the same environment. While this is possible with rats and rabbits there are certain disadvantages to using such small animals for haemorrhage experiments per se. Certain isolated features of the syndrome can be studied with them.[30] The advantages of using dogs in shock experiments are obvious but one is faced with the problem of ignorance of previous stresses, past illnesses, and even the age of the animal. Paired experiments with one dog being used as a control and the other as test animal cannot equate the past environment. The many environmental and procedural factors related to the experiment can be controlled by pairing animals however and undoubted-

ly this is very important when a treatment form is being analyzed.

The reasons for splenectomy have been given and the mechanics of the operation itself have been outlined. The decision to wait only two weeks after splenectomy before challenging the animals may deserve a word of comment. Others have chosen to wait up to six weeks believing that this amount of time was necessary for recovery from surgery. It was the experience in this laboratory this year that no advantage was gained in waiting beyond 2 weeks. By this time dogs were in good health whereas if kept in the kennel any longer many developed upper respiratory tract infections. This situation existed in non-operated animals too when they were kept indoors for long periods of time. The splenectomy operation was relatively simple, corresponding in duration and difficulty to an appendectomy in a human being. Blood loss was minimal and haemoglobin and haematocrit values on experiment days failed to reveal any marked anaemia. The question as to whether or not an operation or similar stress renders an animal more resistant to haemorrhage as suggested by Culbertson is really quite theoretical. As mean survival time of splenectomized controls was 13.2 hours as opposed to 12.3 for non-splenectomized controls one may agree or disagree with the statement. The difference is not significant. Nonetheless both members of the experimental pair had undergone the same stress and even if the individual response to stress varied somewhat it is doubtful that the outcome of the experiment would have been affected.

The need to set a time interval for survival is fairly obvious. Certainly the possibility of death from anuria for example is likely following an insult such as severe haemorrhagic shock. However this does not occur before at least several days following experiment.[90,91] Similarly death from hepatic insufficiency is not acute.[81] Edwards[23] was most emphatic

in his denunciation of liver damage from ischaemia being responsible for the lethal outcome of shock. Likewise the morbidity and mortality from gangrene due to femoral vessel occlusion will take longer to develop. On the other hand one cannot safely presume that an animal living 18 hours after shock has survived because while the average time of death from shock is less than this the range includes it. Some research teams[103] have chosen 24 hours as the survival time while others[66] have felt that 48 hours is more reliable and also more impressive should it be attained. The establishment of this time simply infers that an animal passing the mark has survived the lethal effect of severe bleeding. It does not mean that he will live for another month or even a week. The problems of long term survival are being explored by other workers. It is the elusive answer to the acute haemorrhage question for which we are searching here.

Post mortem examinations as described were not complete. The gross picture of the small bowel and large intestine interested us primarily. Careful microscopic examination of bowel lesions could be carried out to see if there is evidence of deposition of intravascular fibrinoid material which might be associated with haemorrhage and necrosis and hence signify a reaction similar to that described by Schwartzman.

SECTION B. Control Animals.

The bleeding out pattern observed in these experiments, although interesting, is probably not too unusual or surprising. The initial rapid flow followed by a slower but steady rate of bleeding during the 40 mm. period was normal. The slight uptake of blood when the reservoir was raised and arterial pressure elevated to 70 mm Hg. can be understood by surmising that this increase in arterial tension would force open arteriolar

channels in one or other region or organ. The point should be enlarged here that total peripheral resistance may fall during progressive shock but this does not mean that the regional resistances are not increased.[106] It is reasonable to expect that the vasculature of some organs is more responsibe than others. Subsequent mounting of the reservoir volume reflects normal cardiac response and additional contributions of blood to the central circulation by organs and tissues but as the maximum bleeding volume at the particular pressure is approached flow slows into the bottle indicating that because of lowered circulating blood volume and hence decreased venous return and cardiac output the animal cannot keep up an arterial pressure of more than 70 mm Hg. In fact some animals were obliged to take up some blood in order to maintain this pressure. In this respect it is most interesting to note the pattern of blood uptake in dogs #'s 366, 432, and 329. An increase in venous return apparently occurred in these animals from the resorption of blood from the reservoir and this in turn lead to a maintenance of pressure by improving cardiac output. It is possible that the larger channels, such as the arterioles and A-V capillaries, dilated to accept this return flow of reservoir blood. In the case of #329 which was left untreated death occurred within 6 hours implying that the uptake of blood was of no benefit to the animal. Perhaps this means that proper rerouting of the blood to the capillaries did not occur but that it remained in more central channels.

In the case of the non-splenectomized animals volumes of shed blood were higher during both hypotensive periods than with splenectomized dogs signifying that contraction of this organ occurs soon after the haemorrhage begins. The difference in volumes of blood shed between these two groups of animals approximates 15% of total blood volume and therefore corroborates

the view of Ebert and Stead.[22] The fact that our splenectomized animals fared as well as intact dogs points up the idea that the volume of blood remaining in the animal after haemorrhage is more significant than the volume it possessed originally. In other words the extra blood contained in the spleen of intact animals was of no use because it was lost into the reservoir and by the time this additional amount of blood was reinfused irreversible changes had taken place. It would be unreasonable to expect the spleen to hold onto its blood while haemorrhage was occurring to discharge it only when haemorrhage had ceased. It could be argued that the presence of a spleen is actually harmful because upon reinfusion this organ would take up blood that otherwise might supplement the general circulation. This is not sound however because as we and others have noticed at autopsy spleens are small and pale, not engorged. A final theoretical point can be raised. The non-splenectomized animals received no penicillin whereas those operated upon did. It is known that dogs are susceptible to death from clostridial infections when blood supply is diminished. This danger is alleviated by penicillin. Considering that we were using a long duration type of penicillin and giving it 2 weeks before experiment it is possible that the presence of a spleen in intact animals balanced the protective effect of antibiotics in splenectomized dogs. While this might explain survivals it does not account for death among controls.

The patterns of pulse and respiratory rates during haemorrhage were not outstanding. The increase in heart rate and reduction of pulse pressure reflect a less efficient heart action with decreased stroke volume. The lowering of venous pressure follows. As haemorrhage continues and shock progresses the heart accelerates more and pulse pressures decrease further along with output. Pressure is maintained without the need for

elevation of the column of fluid in the reservoir by progressive increases in resistance through small vessel channels in various organs and tissue regions. Pressure fall during the clamped period must indicate inability of the heart to maintain a satisfactory output in the face of reduced venous return. It is also possible that arterioles are dilating or A-V shunts are opening due to humoral influences.[13] Filling of the central vascular channels by reinfusion naturally improves venous return and cardiac output. The briefness of the pressure rise is not well understood but can be accounted for by several possibilities. No doubt continuing loss of blood volume through the bowel apertures is of some importance although as Richards[86] has shown even over-transfusion does not correct the irreversible process.

Poor cardiac output even with a high right atrial pressure indicates weakening of the myocardium and this could result from cellular ischaemia. Irregularities of pulse may be due to interference with ventricular conduction but a central defect might be suspected since respiratory abnormalities are note also. No doubt cerebral and brain stem anoxia exists and can perpetrate these dysrhythmias.

Liver venule sphincter tone is thought to be increased and hence there is a restriction of outflow of blood from the liver. This reluctance of the liver to allow portal flow to make a contribution to venous return probably aggravates the situation.

Bowel movements occurring during the later periods of the experiments represented more than relaxation of sphincters it was felt. The stools were loose and bulky suggesting considerable content in the bowel lumen. Never were stools made up entirely of blood as has been reported by some[29] but they were often blood tinged and sometimes contained large

amounts of clotted blood. The cause for defecation is probably due to the content in the bowel and possibly due to autonomic nervous stimuli. This latter may reflect a temporary parasympathetic overtone resulting from a predilection for sympathetic activity in the vascular tree.

Bladder emptying could be explained in the same way although micturition resembled an overflow type of voiding rather than that caused by vigorous bladder muscle contraction.

The post mortem bowel changes seen in control animals reflect the procession of events occurring in the vascular system supplying this organ, it is felt. They are due it is believed to necrosis following anoxia, a condition favoured by vasoconstriction of precapillary sphincters and metarterioles belonging to the mesenteric artery network. Because bowel changes are found from mid-duodenum to rectum the superior and inferior mesenteric arteries are incriminated and the coeliac is exonerated. The implication being made here is not that these arteries themselves differ from others particularly but that their end vessels, perhaps by virtue of their repeated branching and relatively unsupported state in the mesenteries and bowel walls, are more susceptible to sympathogenic stimuli and therefore respond early to hypovolemia. The endotoxin which is believed to be elaborated in the ulcer craters by anerobic metabolism gains access to the venous side of the vascular network and slowly permeates the general circulation. Its action, it is believed, is to potentiate the body's adrenergic drugs, epi-and nor-epinephrine which are in the circulation and attached to vessel endothelium. Further vasoexclusion of tissues results and endotoxin production continues. Cerebral ischaemia and myocardial damage develop and the cardio-vascular and respiratory systems are imperilled. In addition fracturing of end vessels along the lines cementing

cells together is thought to occur allowing loss of plasma and blood into the bowel lumen and submucosal layers.[30] It should be made clear that while the vasospastic state becomes more and more widespread and involves more and more capillaries and metarterioles some capillary channels, either those branching from the metarterioles or the direct A-V anastomotic capillaries,are open and allow an ever diminishing circulation. It is believed that death results from several factors not the least of which is secondary loss of fluid from the vessels into the bowel. However replacement of blood even at a rate greater than what may be lost from the vascular system either through the bowel or by liver damming does not help to promote survival. One is obliged to assume that tissue impairment from anoxia becomes more and more grave and eventually myocardial function and central nervous system action,for example,are no longer sufficient to maintain the life of the organism and the balance is so tipped.

It is reasonable to believe that a small amount of anoxic necrosis is compatible with reversibility. The lethal effect of a toxic substance must be a matter of degree. Presuming that it is possible to arrest production of such a substance by reestablishing blood flow to the tissues and thereby discouraging anaerobic metabolism the deleterious developments can be halted. If circulation is not returned to the tissues and anoxia persists the situation becomes irreversible.

The small pale spleens seen at autopsy of the first 7 pairs of dogs confirm the suspicion of Wiggers that this organ, once it has contracted and contributed its volume of blood to the general circulation does not perform a similar function again. Even after reinfusion it fails to serve as a sponge but rather its vessels remain constricted,and for all intents and purposes it excludes itself from any participation in the vascular

system adjustments. This also bears out the impression gained in these experiments that splenectomized animals withstand shock as well as intact ones.

While many other biochemical and metabolic changes take place in shock we have dealt in our considerations with what is felt to be the most important cause of death, vascular system alterations.

Current thinking on the subject of haemorrhagic shock incriminates an endotoxin as being partly responsible for irreversibility. A toxin theory of death from irreversible shock is needed because it has not yet been possible to explain why reinfusion of blood does not save shocked animals. The toxin is thought to be a product of anaerobic metabolism of organisms normally resident in the gastrointestinal tract and its nature is likely that of a lipopolysaccharide. The effect of this endotoxin is felt to be potentiation of the vasospastic effect of normally circulating adrenergic drugs with subsequent aggravation of bowel ischaemia, necrosis of mucosa, and loss of blood and plasma into the wall and bowel lumen. The synergistic effects of anoxemia of other organs, with poor cellular function resulting, in hastening death is not denied by the endotoxin theory.

SECTION C. Treated Animals.

Subsection 1. Hydralazine. The prolongation of life provided by this drug must be accounted for. Up until the clamped period test dogs and control animals behaved in a similar fashion. Indeed the decision as to which animal would be used as a control or test was not made until the time of clamping. It is characteristic of the drug, we have seen, to produce hypotension and acceleration of heart rate with an increase in

pulse pressure and indeed these finding were noted. The drop in pressure results of course from vasodilation and herein lies the crux of the matter. It is our idea that because of its sympatholytic action hydralazine opens first metarterioles and then,with the aid of inflowing blood from these vessels, opens the precapillary sphincters. It is well known that while capillary flow is usually determined by the column of blood in the proximal arteriole and metarteriole, capillaries can control their own flow by adjustment of precapillary sphincters.[13] (As was previously pointed out,Zweifach observed that norepinephrine acted on the precapillary sphincters before the metarterioles). The return of blood flow through the capillaries is not restricted to only the bowel but here it is probably very vital that flow be reinstituted. Flow through these end vessels is assisted by the improved cardiac output which hydralazine encourages. At this point a debatable question arises. How can tissues be perfused when systemic blood pressure is as low as we have observed, viz., less than 30 mm Hg.? When this question is raised it is usually to the kidney that one's attention is directed and it is true that there must be at least 70mm. of pressure to effect glomerular filtration. It is also true that other tissues such as the bowel do not require high pressures for adequate perfusion. For normal exchange of solutes and fluids they do require that capillaries be open however. The temporary disturbance of renal function may be deleterious but this itself is questionable if the hypotension is short lived. In any case renal dysfunction has no bearing on the outcome of acute shock. Its influence on the body after shock has been survived is really another problem.

The tendency for an increase in blood pressure before the end of the clamped period suggests the acquisition of a balance of blood flow rather than a wearing off of the drug effect it is felt. It is presumed that

initially large numbers of terminal capillary channels are opened by the d g but later as tissue requirements are met some rerouting of blood through direct A-V communications occurs and directly assists venous return to the heart. The fact that in hydralazine treated animals the blood pressure did not reach as high values after reinfusion as it did in control dogs suggests that the drug was still acting to cause selective vasodilation. It is of special interest to note the patterns of bleeding and uptake of dogs #s366 and 432. Both absorbed all of their shed blood by the end of the second hypotensive period signifying a need for additional volume to support the systemic pressure. It was out of curiosity and interest but with some reluctance that these animals were given hydralazine because their situation seemed bad enough without the addition of hypotension. Nonetheless both survived whereas a third such animal with no blood for reinfusion, # 329 was left as a control and did succumb. The view is hereby supp o rted that it is the effective tissue flow which is all important in survival and that maintenance of a high axial pressure is secondary in importance.

The hypothesis that bowel damage could be arrested by adrenolytic action was borne out on post mortem examination. Although necrotic lesions were not prevented from developing their magnitude was greatly reduced over those of control animals. A logical explanation for their presence at all is that the process was underway before the clamped period and drug administration began. This idea should be corroborated of course by sacrifice of animals immediately following the haemorrhagic insult. It is necessary to attempt an explanation for the apparent lack of success with this drug by Webb and for the fact that Nickerson and Zingg had 31% fatalities with it. These results are puzzling but it must be noted that

the degree of shock induced by the method which both used is not severe and indeed there was a high percentage of surviving controls. It is entirely possible that a drug powerful enough to open precapillary sphincters in severely shocked animals where adrenergic effect is strongly established and allow an effective tissue flow will so markedly dilate these vessels in a moderately or mildly shocked preparation that widespread pooling of blood will result and cause a collapse of the circulation.

The theories regarding the action of hydralazine on precapillary sphincters and metarterioles have been formulated on the basis of the known pharmacological characteristics of the drug and according to the established patterns set by other autonomolytic agents. It is our intention to verify these ideas by direct microscopy of the bowel and mesenteries and of other organs while the drug is being used.

Subsection 2. L-norepinephrine. The outcome of these experiments is somewhat confusing. On the one hand there were three 48 hour survivals which infers that Levophed has a beneficial effect in shock because for all intents and purposes no control animals survived. On the other hand there was a more rapid demise in the 10 animals which died than in controls. More important in the case of the fatalities was the bowel necrosis and intraluminal haemorrhage which was remarkably more severe than that seen elsewhere even in control animals. It was not infrequent to find a blood sausage so thick and firm that it had caused intussussception of the bowel. Considering the 10 fatalities, support is given to the thesis that exogenously administered vasopressor agent simply aggravates a situation created by hypovolemia. It adds its effect to circulating adrenergics which themselves are being potentiated, it is thought, by endotoxin. The result of this sympathomimetic activity is to isolate a greater number of

capillaries by closing their sphincters and producing spasm in the metarterioles which feed them. Since "the circulation conducts its affairs at the capillary," [94] crystalloids, and other solutes are not carried to the cells and these die in greater numbers than ever. The resulting necrosis in the bowel is worse than usual.

It is not difficult to understand why vasopressor therapy should receive recommendation in shock. After all the term 'shock' itself is almost synonymous with hypotension and in the face of this condition the natural tendency is to do all possible to restore blood pressure. Certainly one is reluctant to use an agent which further lowers the blood pressure! The work shock however is not synonymous with <u>hypovolemia</u> and here is where the thinking of many clinicians stops. Certainly when shock is normovolemic as in spinal anaesthesia there is need for a vasopressor. Here vasodilation causes a decrease in total peripheral resistance and the correction of the situation depends on increasing vasomotor tone. Again in severe septicemic shock while a vasopressor in small doses may be helpful the underlying condition must be remedied with antibiotics if the shock is to be alleviated. The basic problem in hypovolemic shock is heightened tone in end arteries and capillaries causing tissue anoxia and the duty here is to mitigate this situation, not aggravate it. High arterial tension in the large vessels is no guarantee at all that there will be an effective blood flow at tissue level. We really want an increased nutritive flow to the cells not a well-functioning by-pass system.

The work of Erlanger and Gasser in 1919 is apropos this arguement. They produced the same picture of bowel mucosa congestion and necrosis as is seen in dogs dying of irreversible haemorrhagic shock by administering repeated doses of adrenalin. In Lillehei's work with endotoxin shock,

aramine and Levophed were used to keep blood pressures at over 80 mm Hg. but with no improvement in survival of the treated animals.

To account for the three surviving animals is difficult. The results show that these survival occurred at a time of the year when control animals were living longer than the mean time. Yet control animals did not survive 48 hours and these Levophed treated animals did. It has been confirmed by Jamieson[35] that the sphincters of the hepatic veins, in the dog at least, are relaxed by epinephrine and nor-epinephrine in adequately large doses. Such relaxation means that a large volume of blood being held in the liver will be released into the circulation. It is conceivable that this augmentation of circulating blood volume occurred in these three animals at a time when it could be utilized by the capillary circulation to prevent tissue anoxia. This would imply that the irreversible process was late in commencing in these animals since capillary shut down had not taken place on a wide scale.

Subsection 3. Hydrocortisone. The effectiveness of this drug in severe shock is demonstrated by the experimental results. The reason for its action is difficult to account for. The maintenance of blood pressure during the clamped period is certainly significant and demonstrates that the corticoids act directly or indirectly to improve vascular tone of the central channels; the arteries, arterioles, A-V communications, and venules. Survival in association with minimal changes in the bowel mucosa indicates that they act in some way to guarantee patent channels also in terminal vessels; the metarterioles and capillaries.

That corticoids potentiate the effect of adrenergic agents is a debated question and one for which experimental evidence is bilateral.

It is extremely interesting to note that the mean blood pressure during the clamped period was 80 mm Hg. as opposed to 88 mm Hg. with the Levophed treated animals. The implication is strong that while the effect of these two drugs on the blood pressure is similar the mode of action or the site of action must be different since the variance in survival time is obvious.

A well known action of corticoids is to cause retention in the blood stream of sodium and water. This knowledge has been the basis for the suggestion that the mechanism of corticoids given to shocked animals is to support the circulation by drawing from the interstitial space sodium and water. Naturally the mineralocorticoids would be expected to have a more marked action in this respect than the glucocorticoids. This is not the case according to Connolly[17] who found better elevations of blood pressure with glucocorticoids. Swingle et al. demonstrated a notable restoration of blood pressure and fluid and electrolyte balance in previously adrenalectomized dogs treated with 2-methyl, 9-alpha fluorohydrocortisone.[99] This fraction is a powerful glucocorticoid but the shift of fluid effect took place only after 48 to 60 hours, a period much too slow by haemorrhagic shock standards to assist the hypovolemic state. In later work Swingle and his colleagues corroborated the idea that glucocorticoids are more important than mineralocorticoids in effecting fluid shifts. The important point they made was that this action occurs when animals are deficient in hormone to begin with and are given no external water or electrolytes. They implied that in the normal animal where fluid compartments are completely balanced mineralocorticoids,such as aldosterone, control the retention and excretion of ions and water. Nonetheless desoxycorticosterone has been shown to cause an elevation in blood pressure in man and has done this in the absence of increased sodium or fluid intravascularly.[77] The mechanism of this has

not been clarified.

The question of whether there is a deficiency of corticoid production by a shocked animal is raised. This is quite problematical because the response to surgical injury for example is invariably a rise of corticoid fractions in the urine. This has been shown by several investigators.[62,80,97] The levels are found to remain high for 2 to 7 days. While adrenocorticoid levels may be low in insufficiency states there is little reason to believe they are low in normal shocked animals. What is a little more likely is that in haemorrhage when blood flow to allorgans is impaired a relative deficiency of hormone production results. This means that the demands of the stressed organism outstrip the rate of corticoid production. This view would still be consistent with the fact that urine levels are elevated above normal. The corollary to this is that the high urine levels reflect an inability of the shocked organism to use the preparation being elaborated by the body.[68] Perhaps the externally administered product is more easily utilized by the animals and this effects an improvement which should really be brought about by the body itself. A further possibility is that since adrenal cortical compounds are carried by plasma albumin and globulin there is indeed a deficiency of them as plasma volume is certainly diminished in haemorrhage. Again this does not account for the mode of action of the corticoids.

It is known that glucocorticoids interfere with chemical changes in polysaccharides. Should the endotoxin be in fact a lipopolysaccharide as has been suggested[30] it is conceivable that hydrocortisone exerts its effect by disrupting the elaboration or release from the tissues of this toxin.

It is well accepted that any severe direct injury to cells with

impairment of their metabolism is in part alleviated by corticoids.[51] Corticoids increase the ability of the body to withstand any stress for that matter.

The value of these latter notions and generalizations depends on the assumption that in haemorrhagic shock the adrenals are not able to produce enough of the rightkind of extract to meet the organisms needs and hence the exogenous supply has a beneficial effect. These are only suppositions and the nature of the mechanism of action remains obscure. The value of such a therapeutic dose does seem to have been borne out in these experiments however.

SECTION D. Discussion Arising from the Literature.

This includes an opinion as to the value of hypothermia and antibiotics. While cooling,carried out at the proper time,has been proven beneficial there has been doubt raised about the value of hypothermia and hydrocortisone therapy together. This was an indirect result of Swan's work.

Lillehei's work with endotoxin shock must be closely viewed. He claimed that sterilization of the bowels prior to giving the endotoxin did nothing to protect the animals. This only means however that the endotoxin extraneously administered killed the animals. It does not disprove the value of antibiotics in controlling the proliferation of bacteria and production of toxin by resident organisms. There is no reason whatsoever to suspect that bowel sterilization would protect his animals from a large dose of endotoxin given to them from without. Nor of course is there reason to presume that resident bacteria under the proper stimulus of anoxaemia and without the threat of antibiotic are not able to overpower their host.

CHAPTER X

SUMMARY

The haemorrhagic shock syndrome has been reviewed in order to acquaint the reader with current beliefs in respect to the pathogenesis of this condition.

A review of the literature dealing with restorative procedures and treatment agents was made. It was by this means that the changing views concerning the shock syndrome were surveyed since the revelation of new facts has generally been represented by the recommendation of certain treatment methods. Particular attention was given to pharmacological agents.

Experimental shock production has received brief consideration and the advantages of different methods were discussed. A technique has been described which was devised in this laboratory. Its advantage has been that it regularly produces irreversible shock but not to the irrevocable extent that had been experienced with other methods previously employed. Its design also permitted an assessment of the effects of pharmacological agents without the entry into the experiment of variables.

Reasons for conducting paired experiments and for using splenectomized dogs have been considered.

Three pharmocological agents; hydralazine, l-norepinephrine, and hydrocortisone have received close attention in this work. Their action

and effects on hypovolemic animals have been studied and an evaluation has been made of their influence on survival. Detailed records have been kept of vital sign changes and alterations of certain blood chemistry values under the influence of these drugs.

Post mortem changes,particularly of the bowel,were described and photographed.

Graphical representation has been made of some typical experiment from each group and a characteristic tracing for an animal of each series is exhibited.

The discussion has been concerned with an attempt to account for the behaviour of animals at different stages of shock and to explain the effects on the cardiovascular system of severe hypovolemia. An explanation of the influence of the drugs employed on different organs and systems has been attempted. Some suggestions have been offerred to account for the alterations which are thought to occur in the vascular system in particular.

Conclusions based on the experimental work and on the review of the literature are enumerated.

CHAPTER XI

CONCLUSIONS

1. An haemorrhagic shock technique has been devised and employed throughout the course of the experiments. It employs a combination of bleeding intervals at hypotensive levels and a'clamped' period at which time the animal is isolated from its shed blood. The method has proven to provide at least 90% mortality from irreversible shock in untreated animals. The administration of drug therapy at the beginning of the clamped period or during it has allowed us to study the effects of pharmacological agents when no other variables are acting on the situation. While the most favourable time for administration may be later in the clamped period this has yet to be determined.

2. The experiments in this laboratory have demonstrated no greater susceptibility to haemorrhage because of splenectomy either in control or test animals. It is felt that while the spleen indeed serves a reservoir function in the dog the emptying action takes place early in the bleeding process and does not occur subsequently even when blood is reinfused. The small size of spleens observed at autopsy confirms the notion that this organ isolates itself from the general circulation once it has contracted initially. Under the conditions of this experimental method the volume of blood delivered by splenic contraction is lost to the animals circulation.

3. The post mortem findings in control animals of ulcerated bowel mucosa, thick engorged bowel wall, and blood or bloody fluid in the lumen of the bowel attest to the severity of the shock procedure. The necrotic bowel changes are regarded as reflecting a state of anoxaemia stemming from vasoconstriction of precapillary sphincters and metarterioles of the terminal branches of the mesenteric vessels, in particular the superior mesenteric artery. The depletion of blood volume from loss of fluid into the necrotic bowel wall and lumen in all likelihood contributes to death from cardio-vascular failure but the added effects of severe ischaemia in several vital organs must be important in the demise of the animal.

4. Results of these experiments show decided amelioration of the lethal trend with the drug hydralazine. Its significant role is conjectured to be in reversing the otherwise fatal progression of events following upon small vessel constriction. It is submitted that by its antiadrenergic action hydralazine overcomes the vasospastic state that the majority of precapillary sphincters and infeeding vessels throughout the organs of the body are in and thereby allows a perfusion of blood and exchange of solutes with vital tissue cells. Its action on the heart to increase output has not been ignored but it is felt that the vascular action is of prime importance. That the irreversible trend has not proceeded is demonstrated in post mortem bowel specimens. These showed minor ischaemic changes but without evidence of blood or fluid loss. The lessened severity of ischaemic changes at this site as compared to control animals is thought to reflect spared condition of other organs also. The ideal time for administration of the drug in clinical situations remains to be determined. The experimental evidence suggests that the optimum time is as soon as possible after bleeding has occurred.

5. Although the results are somewhat conflicting in the L-norepinephrine series we believe that there has been some proof gained that it is a policy of questionable merit to use norepinephrine to combat the hypotension which results from blood loss. Here the tissues are already ischaemic from small vessel constriction and increasing the constriction with this adrenergic drug, although it supports the blood pressure, still further embarrasses the peripheral circulation. The post mortem findings of extensive mucosal sloughing and blood in the bowel lumen indicate that while L-norepinephrine has maintained venous return and central pressure this has been at the expense of tissue flow.

6. From the experimental circumstances of this work proof has been attained that hydrocortisone effects reversal of severe haemorrhagic shock otherwise unmodified by blood transfusion and thereby produces surviving animals in a large percentage of cases. Several possibilities for the beneficial action of this agent are considered. The suggestion that in haemorrhage there is a relative lack of a form of corticoid easily utilized by the body seems to be a plausible explanation for the benefit of exogenously administered hydrocortisone. The mode of action thought to be most likely is that of detoxification of the endotoxin by interference with chemical changes involved in its elaboration by organisms or liberation from tissues. A role such as this no doubt would best be regarded as a part of the well known action of corticoids to restore body homeostasis.

7. If the analogy is made between experimental hypovolemic shock and haemorrhagic shock in a person sustaining a severe injury it is perhaps in order to recommend an agent to be used in treatment of this patient. On the basis of this experimental work carried out on dogs the most

impressive results were with hydralazine and the next with hydrocortisone. From the point of view of the medical profession probably hydrocortisone is more acceptable for use than the hypotensive agent. The distinct value of sympatholytic action, even while this may be accompanied by low central pressures, should not be overlooked however. The doubtful value of L-norepinephrine and the obvious improvement afforded by the sympatholytic agent in these experiments offers strong proof that in the first place a vasospastic condition exists in shock, especially in late stages, and secondly this is a harmful thing to the animal.

8. From the literature review it is safe to conclude that some benefit accrues from cooling a hypovolemic animal. Whether this is just a stalling procedure which when discontinued allows the irreversible process to continue or not remains to be decided. The ideal method of cooling and the optimum temperature to avoid cardiac complications is not definite yet and bears further investigation.

9. The proof afforded by other workers that antibiotics protect animals in hypovolemic shock cannot be ignored and it seems obvious that such therapy should be part of the management of severe haemorrhagic shock. The implication is hereby made that the management of severe shock resulting from haemorrhage should include as restorative measures the use of an antiadrenergic agent, an antibiotic effective against gram negative organisms and hypothermia along with, of course, blood transfusion. An alternative to this regime would be hydrocortisone, an antibiotic, and blood. The exact times of administration and posology for greatest effectiveness have still to be worked out.

APPENDIX A

TABLES OF VITAL SIGNS AND RESULTS OF PAIRED EXPERIMENTS

HYDRALAZINE SERIES

INCLUDING NON-SPLENECTOMIZED AND SPLENECTOMIZED ANIMALS

DATE of Experiment	TEST ANIMAL - Treatment Agent Employed DOG NUMBER SEX (M or F) WEIGHT in Kilograms				
TIME in Minutes	Blood Pressure in mm's of Mercury	Reservoir Volume in cc's	Pulse in beats/minute	Respiratory Rate /min.	Venous Pressure cm's water
	STABILIZATION PERIOD 20 - 30 MINUTES.				
	INITIAL PERIOD OF HYPOTENSION. 40 mm Hg. 1 HOUR - SUMMER DOGS. 1 1/4 HOURS - WINTER DOGS.				
	SECOND HYPOTENSIVE PERIOD. 70 mm Hg. 1/2 HOUR - SUMMER DOGS. 3/4 HOUR - WINTER DOGS.				
	CLAMPED PERIOD of 1 1/2 HOURS. TREATMENT GIVEN AT THIS TIME. IN THE CASE OF HYDRALAZINE AND HYDROCORTISONE, AT THE BEGINNING OF THE PERIOD; WITH L-NOREPINEPHRINE, DURING THE ENTIRE INTERVAL.				
	REINFUSION AND FOLLOW UP INTERVAL.				
OUTCOME	SURVIVAL OR DEATH WITH TIME OF DEATH FOLLOWING REINFUSION. BOWEL NECROSIS INDICATED AS: 1-Mild; 2-Moderate; 3-Severe.				
SPLEEN WEIGHTS	GIVEN IN GRAMS.				
BLEEDING VOLUME	EXPRESSED AS cc/kg. BODY WEIGHT. # - SIGNIFIES IF MAXIMUM BLEEDING VOLUME WAS ATTAINED.				
CHEMISTRY	Haemoglobin gms.%	Haematocrit ,%	Total Protein gms,%	Albumin gms.%	Globulin gms.%
BEFORE HAEMORRHAGE					
AFTER REINFUSION					

FIGURE 11.

Key to the Tables of Vital Signs and Results Included in the Appendices.

TABLE A - I. PAIRED EXPERIMENT I. NON-SPLENECTOMIZED.

21 OCT. 1959	TEST - HYDRALAZINE # 404 F 13.6					CONTROL # 393 M 14.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	155		130	10	6.0	130		150	9	6.5
-10	150		132	9	5.9	135		150	9	6.0
0	40	700	140	15	4.2	40	650	140	14	4.7
10		750	142	16	4.2		710	144	14	4.6
20		800	142	16	4.2		750	148	16	4.6
30		830	144	16	4.1		800	150	16	4.5
40		850	146	17	4.0		820	150	16	4.5
50		875	148	18	4.1		830	154	18	4.4
60		920	150	18	4.0		850	156	18	4.3
65	70	840	146	17	4.2	70	830	152	16	4.5
75		850	142	16	4.2		870	148	16	4.5
85		860	142	16	4.2		890	144	15	4.6
95		860	140	16	4.2		870	144	16	4.5
100	75		146	18	5.0	72		142	15	4.6
120	60		150	18	5.2	82		136	16	4.6
140	52		152	20	5.2	78		140	16	4.5
160	48		156	22	5.0	66		148	17	4.4
180	54		154	20	5.0	46		156	18	4.3
200	160		132	16	7.2	110		142	16	4.8
230	152		126	14	5.6	102		146	17	4.6
260	145		124	14	5.5	98		152	18	4.5
290	142		129	14	5.5	90		160	20	4.3
320	140		120	14	5.4	82		180	22	4.2
Outcome	SURVIVAL 48 Hours.					DEATH - 3 Hours. '2'				
Spleen Weight						70 Grams.				
Bleeding Volume	63.2 cc/kg. #					61.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - II. PAIRED EXPERIMENT II. NON-SPLENECTOMIZED

28 OCT. 1959	TEST - HYDRALAZINE #261 F 13.6					CONTROL #301 M 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	130		140	20	6.5	130		120	22	4.4
-10	135		136	18	6.4	130		124	18	4.4
0	40	600	140	20	4.8	40	500	132	20	2.8
10		640	142	22	4.6		510	136	22	2.9
20		700	144	24	4.6		550	140	24	2.8
30		750	144	26	4.5		625	142	26	2.6
40		770	146	28	4.4		675	142	26	2.7
50		790	142	27	4.5		700	142	26	2.6
60		800	140	26	4.5		700	140	25	2.6
65	70	750	136	24	4.6	70	500	132	24	2.7
75		760	132	24	4.6		520	130	24	2.6
85		770	130	22	4.5		510	132	25	2.6
95		770	132	22	4.5		500	132	26	2.5
100	75		144	24	4.8	70		132	24	2.7
120	78		148	32	4.9	78		128	22	2.9
140	74		152	42	4.8	75		132	22	2.8
160	68		156	48	4.8	67		136	24	2.7
180	80		152	48	4.8	58		140	24	2.7
200	130		140	36	5.2	120		132	20	3.3
230	122		132	28	5.0	110		134	22	3.2
260	120		124	22	5.0	110		136	24	3.1
290	118		120	16	5.1	106		136	25	3.1
320	120		120	16	5.0	104		136	26	3.0
Outcome	SURVIVAL - 48 Hours.					DEATH - 15 Hours. '2'				
Spleen Weight						74 Grams.				
Bleeding Volume	58.8 cc/kg. #					51.5 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - III. PAIRED EXPERIMENT III. NON-SPLENECTOMIZED

6 NOV. 1959	TEST - HYDRALAZINE #348 M 14.5					CONTROL #498 M 15.4				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	150		180	14	4.8	175		170	18	6.4
-10	150		176	16	4.6	172		166	18	6.2
0	40	460	155	20	3.5	40	470	110	20	4.3
10		540	158	24	3.3		490	112	26	4.2
20		625	160	24	3.3		550	116	32	4.2
30		670	168	26	3.4		610	124	36	4.1
40		720	180	30	3.4		680	136	36	4.2
50		740	180	32	3.3		760	132	36	4.1
60		740	178	32	3.2		750	130	36	4.0
65	70	650	185	30	3.6	70	590	145	26	4.2
75		700	182	28	3.5		560	142	28	4.2
85		720	180	26	3.6		600	142	26	4.1
95		720	178	26	3.6		640	136	26	4.1
100	80		150	36	4.2	75		150	30	4.4
120	72		158	38	4.3	80		148	32	4.3
140	55		164	42	4.4	76		144	34	4.3
160	40		172	44	4.4	80		148	36	4.3
180	28		190	46	4.3	72		160	38	4.2
200	112		140	34	5.4	92		144	37	4.1
230	116		146	34	5.3	84		140	40	4.0
260	114		150	35	5.3	72		130	44	3.9
290	108		160	36	5.2	60		130	50	3.8
320	110		152	30	5.4	50		130	50	3.7
Outcome	SURVIVAL - 48 Hours.					DEATH - 6 Hours. '3'				
Spleen Weight						62 Grams.				
Bleeding Volume	51 cc/kg. #					49.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - IV. PAIRED EXPERIMENT IV. NON-SPLENECTOMIZED

11 NOV. 1959	TEST - HYDRALAZINE #425 F 13.6					CONTROL #156 M 11.0				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	124		180	12	7.0	130		140	12	2.2
-10	126		174	11	6.8	135		135	10	2.2
0	40	770	180	54	3.5	40	480	150	20	1.2
10		820	166	57	4.0		550	160	24	1.5
20		940	170	56	4.0		570	160	32	1.2
30		960	176	54	3.8		600	160	30	0.8
40		1000	185	54	3.8		650	162	28	0.6
50		1050	185	52	3.8		680	160	28	0.4
60		1040	186	54	3.8		670	160	28	0.3
65	70	950	186	40	5.2	70	640	170	26	1.1
75		960	180	42	5.1		650	172	26	1.4
85		960	178	40	5.0		630	170	24	1.5
95		960	180	36	5.0		600	156	24	1.7
100	65		180	45	5.0	70		160	26	2.4
120	60		185	50	4.9	80		160	26	2.5
140	58		190	50	4.8	75		180	28	2.6
160	58		180	52	4.8	60		174	26	2.8
180	50		185	50	4.4	50		176	34	2.6
200	136		160	36	10.3	140		156	26	7.8
230	120		150	32	6.4	124		148	14	3.4
260	112		154	24	5.7	116		155	16	2.8
290	104		162	32	5.3	108		164	20	2.4
320	106		160	26	5.2	98		90	18	2.4
Outcome	SURVIVAL - 48 Hours.					DEATH - 9 Hours. '2'				
Spleen Weight						46 Grams.				
Bleeding Volume	78 cc/kg. #					61.8 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - V. PAIRED EXPERIMENT V. NON-SPLENECTOMIZED.

16 NOV. 1959	TEST - HYDRALAZINE #419 F 13.2					CONTROL #370 M 16.8				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	104		140	36	4.2	155		160	8	7.3
-10	110		140	36	4.1	150		160	9	7.2
0	40	600	120	66	1.8	40	470	140	16	8.3
10		660	132	72	1.9		500	140	24	7.5
20		700	140	70	1.6		540	140	26	7.3
30		730	144	70	1.7		570	144	28	7.5
40		760	150	70	1.8		590	144	28	7.7
50		770	150	70	1.7		610	144	30	7.5
60		780	152	70	1.8		640	144	30	7.6
65	70	700	152	64	0.3	70	620	164	24	6.8
75		750	156	60	0.2		650	162	20	6.9
85		800	160	56	0.2		690	164	18	6.9
95		780	160	52	0.1		720	162	16	7.2
100	74		152	64	0.3	80		158	28	7.3
120	62		150	70	0.6	72		164	28	7.4
140	56		165	70	0.6	62		168	20	7.3
160	60		166	66	0.7	54		168	18	7.0
180	76		160	64	0.8	46		168	14	6.3
200	125		132	90	8.5	155		168	8	9.0
230	120		120	72	8.3	150		160	14	9.0
260	120		120	72	8.0	130		168	13	8.6
290	110		120	64	8.0	124		168	14	8.8
320	116		120	60	8.0	122		166	15	8.6

Outcome	SURVIVAL 48 Hours.	DEATH - 18 Hours. '2'
Spleen Weight		75 Grams.
Bleeding Volume	60.6 cc/kg. #	42.8 cc/kg.

Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - VI. PAIRED EXPERIMENT VI. NON-SPLENECTOMIZED.

20 NOV. 1959	TEST - HYDRALAZINE # 7 F 11.0					CONTROL # 427 M 14.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	155		168	8	4.4	160		160	18	6.8
-10	154		170	10	4.6	162		160	18	6.9
0	40	550	120	16	0.8	40	740	160	28	2.2
10		700	124	18	0.6		800	172	32	2.2
20		790	132	20	0.4		850	176	36	2.6
30		810	136	20	0.2		900	180	40	2.6
40		870	144	20	0.5		920	180	40	2.8
50		900	152	22	0.7		930	180	38	2.8
60		900	158	22	0.6		930	184	38	3.2
65	70	810	176	22	1.2	70	820	180	42	3.5
75		850	176	22	1.3		850	180	38	3.6
85		890	192	24	1.4		870	190	38	3.7
95		890	190	24	1.6		850	195	40	3.8
100	58		200	24	2.1	80		170	38	3.7
120	54		200	26	2.2	70		180	40	3.6
140	46		200	28	1.8	50		190	40	3.6
160	38		192	24	2.2	38		196	40	3.6
180	46		196	28	2.4	25		195	38	3.6
200	145		168	24	4.5	116		132	34	4.1
230	144		166	20	4.4	120		136	32	7.2
260	142		164	18	4.4	98		140	40	7.6
290	140		164	16	4.3	100		120	40	7.1
320	140		160	15	4.3	100		124	16	6.3
Outcome	SURVIVAL 48 Hours.					DEATH - 12 Hours. '2'				
Spleen Weight						70 Grams.				
Bleeding Volume	82 cc/kg. #					64 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - VII. PAIRED EXPERIMENT VII. NON-SPLENECTOMIZED.

25 NOV. 1959	TEST - HYDRALAZINE #407 F 9.1					CONTROL #382 F 9.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		160	20	4.0	128		132	16	4.4
-10	140		152	18	3.8	126		128	14	3.8
0	40	500	120	32	0.4	40	380	108	28	3.3
10		520	124	34	0.3		440	110	30	3.0
20		550	132	36	0.2		510	112	30	2.8
30		570	140	36	0.1		540	116	28	2.6
40		580	144	38	0.2		540	120	28	2.7
50		580	152	40	0.1		540	124	28	2.7
60		570	156	40	0.1		520	128	28	2.6
65	70	350	160	34	0.1		380	128	20	3.2
75		470	160	32	0.1		400	128	20	3.4
85		510	160	28	0.1		420	128	20	3.8
95		500	160	30	0.3		370	130	20	3.6
100	70		144	36	2.4	72		132	16	4.0
120	84		148	40	3.0	76		128	20	4.3
140	64		152	44	3.0	68		100	16	4.2
160	56		160	36	2.8	64		100	18	4.1
180	44		164	38	2.8	60		106	18	4.0
200	100		160	32	4.8	120		120	16	4.1
230	104		160	28	4.2	116		140	16	4.4
260	96		166	24	3.0	114		140	18	4.5
290	98		152	22	2.8	110		148	20	4.4
320	108		140	20	3.0	87		160	16	2.8

Outcome	SURVIVAL 48 Hours.	DEATH - 3½ Hours. [3]
Spleen Weight		114 Grams.
Bleeding Volume	63.7 cc/kg. #	56.9 cc/kg. #

Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.										
After Reinfus.										

Maximum Bleeding Volume attained.

TABLE A - VIII. PAIRED EXPERIMENT VIII. SPLENECTOMIZED.

27 NOV. 1959	TEST - HYDRALAZINE # 448 M 15.9					CONTROL # 37 M 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	163		160	10	5.6	150		130	10	4.8
-10	160		160	12	5.7	145		130	12	4.8
0	40	670	160	24	3.2	40	400	132	16	3.5
10		720	164	32	3.1		460	136	20	3.3
20		770	166	34	3.0		500	140	24	3.3
30		780	172	36	3.0		550	140	26	3.2
40		800	176	38	3.0		600	142	28	2.8
50		830	180	40	3.0		620	140	28	2.9
60		850	180	40	3.0		630	140	30	2.8
65	70	800	152	34	4.1	70	600	132	28	3.1
75		820	156	32	4.0		650	134	30	3.3
85		850	160	34	4.0		670	136	30	3.3
95		850	164	36	3.9		670	140	30	3.2
100	68		180	40	5.8	88		140	28	3.0
120	40		180	42	5.6	90		142	24	2.8
140	36		180	44	5.6	90		140	16	2.1
160	42		180	46	5.6	50		100	10	1.0
180	54		176	50	5.7	0		0	0	0
200	140		144	44	6.1					
230	140		142	36	6.0					
260	136		132	28	6.0					
290	134		124	24	5.8					
320	136		120	22	5.8					
Outcome	SURVIVAL 48 Hours.					DEATH 1 Hr. clamping. '2'				
Spleen Weight	58 Grams.					62 Grams.				
Bleeding Volume	53.5 cc/kg. #					49.3 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.1	46%	6.5	3.5	3.0	12.6	39%	6.9	3.9	3.0
After Reinfus.	13.7	42%	5.8	3.6	2.2	12.0	36%	5.8	3.4	2.4

Maximum Bleeding Volume attained.

TABLE A - IX. PAIRED EXPERIMENT IX. SPLENECTOMIZED.

30 NOV. 1959	TEST - HYDRALAZINE # 381 F 12.7					TEST - HYDRALAZINE # 366 F 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	108		126	18	4.8	113		144	24	1.8
-10	115		124	22	4.6	110		136	22	1.6
0	40	450	144	44	3.1	40	290	100	28	0.8
10		490	142	44	3.0		300	104	32	0.7
20		530	146	42	3.0		350	103	34	0.9
30		540	148	42	3.1		370	102	36	0.9
40		540	150	40	3.2		340	104	36	0.8
50		510	150	40	3.1		300	102	34	0.7
60		500	150	42	3.0		270	102	32	0.7
65	70	420	142	42	3.6	70	120	124	34	1.1
75		430	148	40	3.4		120	124	34	1.2
85		420	152	40	3.4		110	126	34	1.1
95		410	160	40	3.3		0	130	34	1.0
100	74		148	50	3.8	70		136	40	1.8
120	68		152	52	3.9	46		120	44	2.0
140	54		160	54	3.9	26		114	46	2.0
160	50		160	46	4.0	32		114	40	2.0
180	62		160	46	3.9	40		124	32	2.1
200	106		140	36	4.7	56		130	36	2.2
230	114		132	32	4.6	62		126	34	2.1
260	108		124	26	4.6	75		136	28	2.1
290	84		132	34	4.4	82		140	30	2.2
320	86		126	28	3.8	86		140	26	2.2
Outcome	SURVIVAL 48 Hours. '1'					SURVIVAL 48 Hours. '1'				
Spleen Weight	84 Grams.					80 Grams.				
Bleeding Volume	42.5 cc/kg. #					22 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.5	44%	6.6	3.8	2.8	11.7	34%	6.1	3.6	2.5
After Reinfus.	13.5	40%	5.9	2.9	3.0	10.8	33%	5.8	3.3	2.5

Maximum Bleeding Volume attained.

TABLE A - X. PAIRED EXPERIMENT X. SPLENECTOMIZED.

2 DEC. 1959	TEST - HYDRALAZINE # 414 M 12.7					CONTROL # 395 M 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	126		188	24	6.0	144		144	20	7.0
-10	126		180	22	6.1	144		140	24	7.0
0	40	550	114	40	5.8	40	650	144	60	6.6
10		560	120	40	4.6		660	160	56	6.7
20		600	126	42	4.6		700	168	52	6.7
30		630	132	44	4.5		700	166	46	6.8
40		630	136	40	4.4		730	164	42	6.7
50		620	136	38	4.4		730	166	42	6.7
60		620	140	36	4.4		730	168	40	6.7
65	70	500	146	36	5.0	70	710	165	40	6.4
75		450	150	36	5.6		690	184	40	6.4
85		410	150	36	5.7		650	182	36	6.5
95		400	160	34	5.6		630	180	36	6.6
100	50		162	40	5.8	54		180	38	6.7
120	42		140	44	5.7	48		168	40	6.8
140	48		145	48	6.3	50		168	44	7.0
160	64		160	44	5.8	42		176	40	7.4
180	80		160	42	5.1	30		144	15	7.0
200	116		150	30	8.2	102		120	40	10.6
230	120		140	24	7.1	90		120	40	10.8
260	116		136	24	6.3	85		128	40	10.4
290	112		120	24	6.2	63		152	40	10.0
320	116		120	24	6.2	30		164	42	8.0
Outcome	SURVIVAL 48 Hours.					DEATH - 3 Hours. '3'				
Spleen Weight	50 Grams.					56 Grams.				
Bleeding Volume	49.6 cc/kg. #					53.6 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.5	42%	6.6	3.6	3.0	12.6	38%	6.2	3.3	2.9
After Reinfus.	11.9	40%	5.8	3.5	2.3	11.7	36%	5.4	3.0	2.4

Maximum Bleeding Volume attained.

TABLE A - XI. PAIRED EXPERIMENT XI. SPLENECTOMIZED.

7 DEC. 1959	TEST - HYDRALAZINE #340 M 11.8					CONTROL #438 F 11.4				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	132		100	6	5.0	145		170	10	4.5
-10	140		100	6	5.3	140		175	8	5.0
0	40	410	110	26	1.5	40	400	160	8	4.8
10		490	112	30	3.5		410	160	14	5.0
20		520	118	30	3.5		430	160	20	6.5
30		530	124	30	4.0		500	172	20	6.5
40		540	124	30	4.0		510	176	20	6.5
50		560	126	32	4.5		540	176	20	6.5
60		590	126	32	4.5		570	170	22	6.5
65	70	500	136	20	6.2	70	550	170	16	8.0
75		530	140	22	6.7		570	166	18	8.3
85		550	136	24	7.0		590	175	18	8.5
95		550	138	24	7.0		570	176	18	8.3
100	65		146	28	7.5	75		170	14	9.5
120	62		150	30	7.4	80		176	16	9.8
140	52		160	36	6.6	74		180	18	9.5
160	45		168	42	6.2	60		190	22	8.7
180	50		168	42	6.2	42		186	24	7.5
200	110		146	32	8.1	138		156	12	9.0
230	108		156	30	8.2	130		154	12	8.3
260	104		160	38	8.0	116		162	28	7.8
290	102		160	38	8.5	98		166	26	7.8
320	104		156	40	8.5	88		174	24	7.8
Outcome	SURVIVAL 48 Hours.					DEATH - 11 Hours. '2'				
Spleen Weight	70 Grams.					64 Grams.				
Bleeding Volume	50 cc/kg. #					51.8 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.7	48%	6.2	4.0	2.2	11.0	38%	6.2	3.0	3.2
After Reinfus.	14.6	50%	5.8	3.6	2.2	11.2	35%	6.0	3.0	3.0

Maximum Bleeding Volume attained.

TABLE A - XII. PAIRED EXPERIMENT XI. SPLENECTOMIZED.

9 DEC. 1959	TEST - HYDRALAZINE # 424 M 14.7					CONTROL # 417 F 14.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	146		172	16	6.6	126		154	14	4.2
-10	148		172	16	6.4	128		154	16	4.2
0	40	570	150	36	4.3	40	450	96	20	3.3
10		600	150	37	3.5		490	100	20	3.2
20		680	156	38	3.5		540	110	21	3.1
30		710	160	38	3.4		570	120	22	3.0
40		750	180	36	3.7		580	132	22	3.1
50		790	180	40	3.7		560	144	22	3.0
60		760	180	40	3.7		520	160	24	3.4
65	70	690	172	36	4.2	70	450	144	22	4.0
75		660	164	40	4.3		470	152	24	4.2
85		670	172	40	4.4		480	164	24	4.3
95		640	176	40	4.5		460	162	26	4.2
100	50		180	50	5.4	65		168	26	4.4
120	38		178	44	5.0	60		156	28	4.6
140	28		172	44	5.0	54		160	30	4.5
160	35		160	36	6.0	56		160	30	4.3
180	48		160	36	6.1	53		166	30	4.4
200	104		168	36	9.1	98		158	44	6.9
230	100		174	44	9.4	106		144	22	5.5
260	98		176	36	9.5	112		130	20	5.3
290	92		168	36	9.1	114		132	18	5.4
320	90		170	34	9.0	116		146	32	4.6
Outcome	DEATH - 44 Hours. '1'					DEATH - 18 Hours. '2'				
Spleen Weight	79 Grams.					71 Grams.				
Bleeding Volume	51.4 cc/kg. #					40 cc /kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.9	45%	4.6	2.8	1.8	14.1	43%	6.4	3.4	3.0
After Reinfus.	12.5	43%	3.8	2.4	1.4	14.0	42%	6.2	3.4	2.8

Maximum Bleeding Volume attained.

TABLE A - XIII. PAIRED EXPERIMENT XIII. SPLENECTOMIZED.

11 DEC. 1959	TEST - HYDRALAZINE # 432 M 12.3					TEST - L-NOREPINEPHRINE # 314 F 11.8				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	124		112	9	6.5	116		116	8	5.9
-10	124		118	10	6.5	116		110	8	6.8
0	40	430	110	13	4.6	40	500	100	14	4.2
10		420	118	14	4.7		430	106	14	4.3
20		430	118	14	4.7		490	108	14	4.3
30		420	116	14	4.7		530	120	15	4.2
40		430	118	16	4.8		570	132	16	3.8
50		430	116	16	4.8		640	136	18	3.2
60		430	116	17	4.8		680	140	20	3.2
65	70	260	106	13	6.3	70	600	146	18	3.6
75		170	108	14	6.6		660	144	19	3.6
85		100	112	15	6.3		700	142	20	3.5
95		0	116	16	6.2		720	144	22	3.4
100	75		108	16	6.5	90		152	20	5.2
120	62		110	15	6.4	90		148	18	5.4
140	52		116	16	7.0	94		148	18	5.5
160	45		118	17	7.2	104		150	19	5.3
180	50		118	17	7.4	108		160	20	6.0
200	70		104	16	7.6	130		120	18	8.8
230	88		102	16	7.6	112		116	18	6.2
260	96		102	16	7.5	110		115	18	5.8
290	100		100	16	7.5	110		115	18	5.5
320	104		102	16	7.7	108		116	18	5.8
Outcome	SURVIVAL - 48 Hours. '1'					SURVIVAL - 48 H ours. '1'				
Spleen Weight	108 Grams.					120 Grams.				
Bleeding Volume	35 cc /kg. #					61 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.5	43%	6.5	3.5	3.0	13.8	41%	6.3	3.4	2.9
After Reinfus.	12.2	37%	5.7	2.9	2.8	12.6	35%	5.2	3.2	2.0

Maximum Bleeding Volume attained.

TABLE A - XIV. PAIRED EXPERIMENT XIV. SPLENECTOMIZED.

14 DEC. 1959	TEST - HYDRALAZINE # 406 M 17.3					CONTROL # 402 M 9.1				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	118		150	30	5.6	120		140	12	4.3
-10	122		150	26	5.4	118		136	13	4.3
0	40	480	108	48	0.2	40	190	100	16	4.1
10		510	116	44	0.1		220	100	18	4.1
20		560	118	40	0.1		260	104	18	4.1
30		560	122	56	0.1		310	108	18	4.2
40		590	128	56	0.1		340	110	18	4.2
50		620	134	56	0.1		360	120	18	4.1
60		640	140	50	0.1		360	128	18	4.1
65	70	550	138	40	0.3	70	260	126	16	4.6
75		500	154	42	1.2		270	124	16	4.4
85		550	160	43	1.1		290	132	16	4.2
95		520	164	42	1.1		310	136	16	4.1
100	78		128	48	1.0	78		124	16	4.4
120	60		146	48	1.0	80		120	16	4.4
140	52		142	60	0.8	70		100	12	4.6
160	45		146	62	0.8	56		108	14	5.3
180	38		150	60	0.8	32		120	16	5.2
200	110		140	50	3.0	110		100	16	7.8
230	114		132	42	3.1	100		108	16	6.4
260	120		130	40	3.0	82		120	18	6.2
290	120		130	40	3.0	74		128	20	5.8
320	116		124	36	2.8	60		140	24	4.6
Outcome	SURVIVAL - 48 Hours.					DEATH - 6½ Hours. '2'				
Spleen Weight	80 Grams.					43 Grams.				
Bleeding Volume	37 cc/kg. #					39.5 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	11.7	41%	6.9	3.4	3.5	12.1	36%	5.1	2.8	2.3
After Reinfus.	11.4	43%	6.3	3.3	3.0	11.0	34%	4.6	2.7	1.9

Maximum Bleeding Volume attained.

TABLE A - XV. PAIRED EXPERIMENT XV. Ssplenectomized.

16 DEC. 1959	TEST - HYDRALAZINE # 2 F 12.7					TEST - L-NOREPINEPHRINE # 478 F 11.0				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		180	20	7.9	142		160	15	5.3
-10	144		168	20	10.5	146		160	14	4.2
0	40	470	140	28	9.1	40	420	150	22	4.7
10		560	140	28	9.0		500	142	28	3.5
20		640	156	32	8.4		500	146	30	3.5
30		700	164	36	8.2		500	146	28	3.7
40		750	172	36	8.0		510	150	28	3.9
50		770	180	40	7.8		520	160	28	3.9
60		800	188	42	7.6		530	160	30	3.8
65	70	750	190	44	8.2	70	490	172	32	4.2
75		800	200	44	8.2		490	166	32	4.2
85		880	188	40	8.8		480	172	32	4.2
95		850	192	40	8.7		460	184	30	4.2
100	75		200	46	8.1	78		178	30	4.2
120	60		200	44	7.6	70		184	30	4.2
140	48		196	44	7.6	74		176	28	4.3
160	27		200	42	7.2	94		168	24	6.0
180	35		192	40	7.4	95		164	26	5.5
200	120		160	32	7.6	110		172	22	6.9
230	112		164	28	7.6	108		182	26	6.3
260	110		168	28	7.4	104		180	20	6.4
290	108		172	32	7.6	96		180	24	6.2
320	112		160	24	7.2	86		180	26	6.0
Outcome	SURVIVAL - 48 Hours.					DEATH - 19 Hours. '3'				
Spleen Weight	150 Grams.					63 Grams.				
Bleeding Volume	71 cc/kg. #					47.2 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	15.1	44%	5.8	3.2	2.6	10.3	39%	4.1	2.6	1.5
After Reinfus.	13.3	38%	5.5	2.8	2.7	10.3	36%	3.3	2.0	1.3

Maximum Bleeding Volume attained.

APPENDIX B

TABLES OF VITAL SIGNS AND RESULTS OF PAIRED EXPERIMENTS

L-NOREIPNEPHRINE SERIES

SPLENECTOMIZED ANIMALS

TABLE B - I. PAIRED EXPERIMENT XVI. SPLENECTOMIZED.

6 JAN. 1960	TEST - L-NOREPINEPHRINE # 321 F 14.5					CONTROL # 496 F 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	124		100	14	4.3	136		140	8	3.1
-10	124		120	16	5.2	136		128	10	3.5
0	40	600	150	46	2.7	40	590	95	10	1.4
10		670	152	42	2.6		590	100	8	1.7
20		690	156	44	2.6		590	100	10	1.6
30		730	160	46	2.6		630	100	12	1.5
40		760	168	38	3.0		640	100	12	1.6
50		770	168	40	2.8		660	100	12	1.5
60		770	172	38	2.7		670	114	14	1.6
70		760	172	42	2.6		660	112	16	1.5
80	70	740	166	36	3.2	70	540	112	10	1.8
90		730	160	36	3.4		540	120	10	2.2
100		720	160	36	3.4		520	116	9	2.1
110		710	164	38	3.3		500	120	11	2.0
120		700	168	42	3.2		500	120	12	2.1
130	80		174	52	3.4	88		120	8	2.0
150	85		172	50	3.4	80		120	9	2.0
170	80		180	48	3.2	75		140	10	2.3
190	75		164	40	3.2	70		140	12	2.3
210	65		152	34	2.7	55		140	12	2.0
230	120		114	32	5.4	140		120	16	5.2
260	140		116	22	5.6	124		94	12	5.7
290	160		106	20	5.5	118		90	12	4.2
320	120		104	20	7.2	106		120	10	3.8
350	115		100	18	7.0	100		120	10	3.6
Outcome	DEATH - 7 Hours. '3'					DEATH - 20 Hours. '2'				
Spleen Weight	58 Grams.					38 Grams.				
Bleeding Volume	53.0 cc/kg. #					48.5 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	11.4	40%	5.0	3.0	2.1	11.4	41%	4.8	3.0	1.8
After Reinfus.	12.9	46%	5.3	3.1	2.2	11.9	41%	4.7	2.9	1.8

TABLE B - II. PAIRED EXPERIMENT XVII. SPLENECTOMIZED.

11 JAN. 1960	TEST - L-NOREPINEPHRINE # 492 F 13.6					TEST - L-NOREPINEPHRINE # 397 M 14.1				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	118		130	20	5.6	132		122	11	2.8
-10	120		130	16	5.4	136		126	15	3.4
0	40	550	132	20	4.0	40	480	124	28	2.6
10		600	130	22	3.8		500	120	20	2.5
20		620	130	24	3.9		540	118	20	2.1
30		630	130	23	3.6		590	116	20	1.5
40		650	136	20	3.7		620	124	30	0.7
50		680	140	22	3.7		650	134	28	0.4
60		700	144	22	3.6		670	144	32	0.4
70		700	142	20	3.6		660	144	34	0.3
80	70	640	130	18	4.0	70	610	160	22	1.2
90		650	124	16	4.2		640	160	20	1.2
100		650	128	16	4.4		630	168	19	1.5
110		660	128	16	4.4		640	176	18	2.4
120		660	130	16	4.3		640	172	18	2.1
130	84		140	18	6.2	115		160	10	2.5
150	88		144	20	6.6	112		164	16	2.7
170	86		140	20	6.8	108		170	16	1.9
190	82		140	24	6.6	104		160	15	2.2
210	87		150	26	6.5	108		156	16	2.1
230	120		150	24	7.0	150		94	11	6.4
260	130		144	22	6.6	130		100	18	4.0
290	120		140	22	6.4	120		116	21	3.6
320	110		136	20	6.4	110		116	24	3.4
350	104		136	24	6.6	100		124	24	3.0
Outcome	DEATH - 7 Hours. '3'					DEATH - 13 Hours. '2'				
Spleen Weight	83 Grams.					120 Grams.				
Bleeding Volume	51.5 cc/kg. #					47.5 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.6	41%	5.3	3.6	1.7	16.3	50%	6.0	4.1	1.9
After Reinfus.	11.7	37%	5.4	2.9	2.5	15.8	48%	5.4	3.7	1.7

TABLE B - III. PAIRED EXPERIMENT XVIII. SPLENECTOMIZED.

15 JAN. 1960	TEST - L-NOREPINEPHRINE # 450 F 13.6					CONTROL # 483 M 15.9				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	112		150	20	6.3	138		156	10	4.8
-10	112		144	22	5.8	130		160	12	8.0
0	40	450	120	28	5.0	40	120	120	12	8.5
10		440	120	26	5.1		150	120	14	8.8
20		440	120	32	4.9		270	120	14	8.4
30		460	124	36	4.8		310	120	14	8.5
40		500	132	36	4.7		350	122	14	8.6
50		550	140	40	4.5		400	132	18	8.5
60		570	144	40	4.5		440	140	20	8.0
70		570	142	40	4.3		460	138	22	8.0
80	70	510	140	33	4.4	70	300	144	22	8.5
90		500	140	38	5.3		320	140	22	9.0
100		480	146	48	4.8		320	148	20	9.2
110		500	150	45	4.8		330	150	20	9.2
120		500	152	46	4.7		340	152	20	9.1
130	110		156	48	4.7	75		160	22	8.3
150	98		160	52	4.9	90		160	18	9.0
170	102		180	56	5.0	90		162	16	8.5
190	96		190	56	5.2	100		180	16	8.5
210	102		190	52	5.2	87		180	14	7.9
230	128		144	62	6.7	140		150	28	6.5
260	126		128	54	5.5	100		160	26	5.8
290	124		124	50	5.0	86		165	24	5.6
320	120		130	52	5.3	84		170	26	5.6
350	120		130	52	5.2	82		172	28	5.5
Outcome	SURVIVAL 48 Hours.					DEATH - 23 Hours. '2'				
Spleen Weight	76 Grams.					100 Grams.				
Bleeding Volume	43.4 cc/kg. #					27.7 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.9	45%	6.2	3.2	3.0	11.7	35%	5.4	3.3	2.1
After Reinfus.	13.5	42%	5.4	3.1	2.3	11.7	35%	5.5	3.5	2.0

TABLE B - IV. PAIRED EXPERIMENT XIX. SPLENECTOMIZED.

20 JAN. 1960	TEST - L-NOREPINEPHRINE # 459 M 13.2					CONTROL # 435 M 9.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	158		180	12	4.7	134		176	12	5.3
-10	160		180	14	4.8	1 36		168	16	5.2
0	40	400	136	14	4.2	40	350	180	22	0.4
10		450	150	16	2.5		380	164	28	1.2
20		500	170	21	2.9		410	168	33	1.4
30		520	175	24	3.6		430	166	38	1.2
40		530	170	24	4.2		450	162	40	1.0
50		550	174	24	4.5		480	174	40	1.1
60		550	172	24	4.4		490	168	40	1.0
70		540	172	25	4.3		500	170	40	1.1
80	70	510	174	18	4.6	70	440	164	36	1.6
90		520	172	19	5.0		440	164	34	1.5
100		530	168	20	4.9		470	166	32	1.4
110		530	170	20	5.6		480	168	31	1.4
120		530	170	21	5.6		480	170	30	1.4
130	82		170	28	5.1	78		174	32	0.9
150	85		176	36	5.3	78		174	32	0.9
170	82		176	36	5.5	98		168	26	1.5
190	90		170	40	6.2	90		170	30	1.7
210	94		170	38	6.3	86		176	32	1.6
230	100		168	24	7.3	144		132	24	7.9
260	115		140	26	6.9	124		128	20	2.3
290	100		146	25	7.0	118		136	20	1.6
320	90		150	30	5.8	110		140	24	1.4
350	70		160	32	4.0	87		150	26	1.0
Outcome	DEATH - 6 Hours. '3'					DEATH - 19 Hours. '2'				
Spleen Weight	72 Grams.					82 Grams.				
Bleeding Volume	41.6 cc/kg. #					52.6 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	15.2	47%	6.2	3.3	2.9	11.6	35%	6.1	2.8	3.3
After Reinfus.	13.9	43%	4.8	2.7	2.1	11.0	33%	6.1	2.6	3.5

TABLE B - V. PAIRED EXPERIMENT XX. SPLENECTOMIZED.

25 JAN. 1960	TEST - L-NOREPINEPHRINE # 153 F 12.7					CONTROL # 75 F 8.3				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	124		132	26	7.5	136		144	26	2.6
-10	125		130	26	7.0	130		140	26	2.8
0	40	670	128	24	4.5	40	370	112	26	5.9
10		700	120	24	5.0		400	116	27	4.9
20		720	122	26	4.8		380	116	28	4.5
30		800	124	26	4.6		360	116	28	4.5
40		830	128	27	4.0		400	116	30	4.0
50		860	144	24	3.2		410	116	28	3.5
60		900	142	25	3.8		400	120	29	3.5
70		900	144	26	3.9		400	120	30	3.4
80	70	840	148	28	3.8	70	335	144	26	3.8
90		880	150	28	3.9		350	142	24	4.2
100		890	146	26	4.1		350	140	24	4.5
110		880	146	26	4.0		340	144	24	4.4
120		870	148	24	4.0		340	144	26	4.4
130	85		160	28	5.8	80		150	24	4.9
150	85		160	28	5.7	76		150	25	5.0
170	85		160	29	5.8	78		144	26	5.1
190	76		168	30	5.6	72		144	26	5.0
210	88		170	26	5.2	65		146	28	5.0
230	122		144	24	6.8	90		136	18	4.2
260	122		132	24	6.8	80		132	19	5.6
290	120		120	24	6.8	80		136	18	5.1
320	125		120	24	6.8	78		140	19	5.0
350	124		120	25	6.7	68		142	19	5.0
Outcome	DEATH - 10 Hours. '3'					DEATH - 18 Hours. '2'				
Spleen Weight	80 Grams.					102 Grams.				
Bleeding Volume	71 cc/kg. #					49.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.9	38%	4.6	2.9	1.7	15.4	48%	4.5	2.9	1.6
After Reinfus.	12.1	36%	4.2	2.7	1.5	12.9	41%	3.3	2.2	1.1

TABLE B - VI. PAIRED EXPERIMENT XXI. SPLENECTOMIZED.

29 JAN. 1960	TEST - L-NOREPINEPHRINE # 308 F 12.3					CONTROL # 364 M 12.3				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	110		156	6	1.9	136		160	12	9.5
-10	112		152	9	3.2	134		164	11	9.4
0	40	240	118	9	1.5	40	480	126	32	4.1
10		290	118	9	1.5		500	126	32	4.1
20		400	91	10	2.3		580	108	36	4.0
30		400	100	10	2.0		620	114	38	3.9
40		410	106	10	1.6		660	118	40	3.7
50		460	120	12	1.4		720	124	40	3.7
60		490	120	14	0.8		750	132	40	3.5
70		520	132	16	0.5		790	140	40	3.4
80	70	470	140	12	0.9	70	720	142	36	4.0
90		460	142	12	0.8		700	144	29	4.4
100		460	142	12	0.7		700	144	32	4.6
110		460	142	12	0.7		700	144	36	4.4
120										
130	110		144	11	1.6	88		132	26	3.3
150	114		158	15	1.3	95		156	32	2.9
170	108		156	14	1.4	98		156	32	2.8
190	110		160	16	1.4	106		158	30	2.9
210	114		160	16	1.3	90		152	32	2.8
230	130		160	18	4.6	136		164	32	8.8
260	124		132	18	4.2	130		160	30	8.4
290	110		132	18	4.0	128		156	28	8.0
320	102		126	20	3.8	124		160	30	7.9
350	98		128	22	3.8	120		148	30	7.8
Outcome	DEATH - 30 Hours. '2'					DEATH - 12 Hours. '2'				
Spleen Weight	40 Grams.					40 Grams.				
Bleeding Volume	42.3 cc/kg.					64 cc /kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.9	46%	5.3	2.9	2.4	14.5	49%	5.2	2.8	2.4
After Reinfus.	14.1	48%	5.0	2.4	2.6	13.7	48%	5.0	2.8	2.2

TABLE B - VII. PAIRED EXPERIMENT XXII. SPLENECTOMIZED.

3 FEB. 1960	TEST - L-NOREPINEPHRINE # 491 M 12.3					CONTROL # 329 M 11.0				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	134		176	10	1.6	102		106	30	5.9
-10	134		176	11	1.7	106		108	32	5.8
0	40	400	168	24	1.3	40	360	110	18	0.6
10		400	172	24	1.2		350	100	24	1.2
20		410	180	25	1.0		320	90	25	1.8
30		450	190	26	0.8		330	86	22	1.6
40		460	200	26	0.5		310	86	22	1.6
50		480	200	26	0.4		310	86	22	1.7
60		490	200	28	0.4		300	86	22	1.6
70		470	200	28	0.3		300	86	24	1.5
80	70	470	200	28	0.6	70	300	86	22	2.2
90		420	200	28	0.6		240	86	22	2.2
100		415	200	28	0.6		200	86	20	2.3
110		410	200	32	0.6		100	86	20	2.1
120		400	200	32	0.5		40	86	20	2.0
130	116		152	19	0.9	100		90	18	2.7
150	114		170	22	0.8	95		88	20	2.6
170	120		160	26	0.8	98		96	20	2.5
190	112		160	36	0.8	96		95	20	2.3
210	110		176	36	0.7	94		98	20	2.2
230	112		160	46	2.0	108		120	18	3.0
260	110		160	42	2.0	104		110	16	3.1
290	108		162	42	1.8	100		114	16	3.0
320	104		164	40	1.7	98		116	16	2.8
350	100		150	40	1.6	94		114	16	2.7

Outcome	SURVIVAL 48 Hours. '2'	DEATH - 6 Hours. '3'
Spleen Weight	86 Grams.	76 Grams.
Bleeding Volume	40 cc/kg. #	32.7 cc/kg. #

Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	13.7	43%	5.8	2.7	3.1	14.2	44%	6.5	3.5	3.0
After Reinfus.	13.3	41%	5.6	2.8	2.8	14.0	41%	6.3	3.4	2.9

TABLE B - VIII. PAIRED EXPERIMENT XXIII. SPLENECTOMIZED.

10 FEB. 1960	TEST-L-NOREPINEPHRINE # 327 F 11.4					CONTROL # 13 F 18.2				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		140	22	3.0	145		140	22	4.8
-10	135		140	22	3.1	145		140	20	4.9
0	40	530	130	28	0.5	40	630	154	29	0.6
10		580	130	26	1.0		690	168	40	0.5
20		620	144	22	1.8		740	170	40	0.4
30		630	148	26	1.4		780	176	40	0.4
40		670	154	28	0.8		800	180	42	0.3
50		690	160	26	1.0		820	184	36	0.6
60		690	172	24	1.8		850	184	36	0.9
70		690	172	24	1.6		860	180	32	0.8
80	70	630	180	20	2.8	70	850	188	32	1.8
90		670	180	20	2.9		850	180	30	2.0
100		640	170	22	3.3		880	180	30	2.1
110		620	172	22	3.2		870	180	28	2.0
120		620	176	24	3.2		860	182	30	2.0
130	105		164	26	2.6	65		200	36	1.9
150	114		168	24	3.7	54		210	40	4.2
170	118		166	23	3.0	44		224	40	1.7
190	110		164	22	2.3	36		220	40	1.4
210	112		162	20	2.3	38		210	40	1.4
230	140		160	28	5.9	135		180	24	5.3
260	135		164	30	5.2	120		190	28	4.4
290	130		164	30	5.1	110		190	28	4.2
320	124		160	28	5.0	100		190	30	4.0
350	120		162	28	5.0	98		192	32	3.9
Outcome	DEATH - 25 Hours. '2'					DEATH - 21 Hours. '2'				
Spleen Weight	50 Grams.					50 Grams.				
Bleeding Volume	60.5 cc/kg. #					47.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	11.4	32%	5.3	3.1	2.2	11.0	31%	5.7	3.3	2.4
After Reinfus.	13.3	39%	5.3	3.1	2.2	10.6	29%	5.7	3.2	2.5

TABLE B - IX. PAIRED EXPERIMENT XXIV. SPLENECTOMIZED.

19 FEB. 1960	TEST - L-NOREPINEPHRINE # 452 F 9.1					CONTROL # 384 M 13.2				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	130		140	8	4.5	155		150	12	6.8
-10	126		140	10	4.4	160		150	12	6.3
0	40	320	112	12	3.0	40	480	160	20	5.4
10		350	112	16	2.8		550	162	22	6.0
20		430	112	24	2.2		590	164	24	6.4
30		460	112	28	2.0		620	164	24	6.4
40		510	124	30	1.8		650	170	25	6.2
50		530	136	32	1.6		680	172	26	6.1
60		550	140	32	1.4		710	174	24	6.5
70		600	140	32	1.2		720	180	24	6.8
80	70	500	148	22	3.6	70	690	180	20	8.1
90		480	152	22	3.5		700	180	20	8.3
100		510	150	23	3.0		700	180	24	8.5
110		540	140	24	2.9		690	180	24	8.5
120		520	142	26	2.7		680	180	24	8.3
130	88		156	26	2.6	80		188	20	8.8
150	100		160	26	2.4	68		190	24	8.6
170	98		160	20	2.2	40		180	24	7.4
190	106		88	12	2.7	30		170	20	6.8
210	102		90	11	2.8	27		172	18	6.6
230	130		136	20	4.6	140		156	24	8.4
260	120		120	16	4.1	124		172	26	8.6
290	114		120	18	4.2	120		160	26	8.4
320	108		124	20	4.4	116		156	30	8.2
350	96		132	16	3.2	102		180	30	6.8
Outcome	DEATH - 11 Hours. '3'					DEATH - 12 Hours. '2'				
Spleen Weight	100 Grams.					70 Grams.				
Bleeding Volume	66 cc/kg. #					55.5 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.8	48%	5.5	3.0	2.5	14.9	44%	5.2	3.3	1.9
After Reinfus.	14.1	44%	5.0	3.0	2.0	13.7	42%	5.0	3.1	1.9

TABLE B - X. PAIRED EXPERIMENT XXV. SPLENECTOMIZED.

24 FEB. 1960	TEST - L-NOREPINEPHRINE # 380 M 13.2					TEST - HYDROCORTISONE # 461 F 13.2				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	136		136	32	10.5	132		160	12	5.5
-10	140		120	20	9.1	135		160	13	5.3
0	40	500	118	22	8.0	40	500	140	16	5.5
10		520	116	22	8.0		600	144	16	5.5
20		610	124	24	7.5		610	144	18	5.3
30		660	132	24	7.5		650	144	20	5.1
40		690	136	24	7.5		730	150	20	4.9
50		700	148	26	7.6		750	160	20	4.5
60		710	150	26	7.7		800	160	20	4.5
70		750	156	28	7.8		810	160	20	5.0
80	70	660	164	26	7.9	70	740	164	18	5.1
90		700	164	26	7.9		760	164	16	5.0
100		690	170	24	7.9		770	168	16	4.9
110		670	170	25	7.9		760	170	16	5.0
120		660	172	26	7.9		740	172	16	5.0
130	80		140	28	8.0	76		164	20	4.9
150	82		160	34	8.2	66		168	20	5.0
170	76		170	36	8.9	74		170	18	5.1
190	80		172	40	9.5	82		160	16	4.9
210	86		180	42	10.0	76		160	12	5.6
230	140		152	52	13.5	108		120	12	5.5
260	136		144	46	12.5	112		122	10	5.6
290	106		136	48	11.6	116		124	9	5.7
320	86		148	42	10.8	126		128	9	5.8
350	56		152	38	8.8	124		124	10	5.8
Outcome	DEATH - 5 Hours. '3'					SURVIVAL 48 Hours.				
Spleen Weight	55 Grams.					85 Grams.				
Bleeding Volume	56.8 cc/kg. #					61.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	11.7	35%	5.0	3.0	2.0	11.0	31%	5.7	3.0	2.7
After Reinfus.	11.4	35%	4.6	2.8	1.8	11.0	31%	5.4	2.8	2.6

APPENDIX C

TABLES OF VITAL SIGNS AND RESULTS OF PAIRED EXPERIMENTS

HYDROCORTISONE SERIES

SPLENECTOMIZED ANIMALS

TABLE C - I. PAIRED EXPERIMENT XXVI. SPLENECTOMIZED.

2 MAR. 1960	TEST - HYDROCORTISONE # 214 M 12.3					CONTROL # 180 M 12.7				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		158	13	2.3	112		170	20	5.2
-10	145		160	12	2.2	110		168	19	5.2
0	40	330	118	20	0.9	40	240	120	30	4.1
10		350	118	20	0.9		280	124	32	4.0
20		370	120	20	0.8		310	130	36	4.0
30		390	120	20	0.7		350	132	40	3.6
40		390	120	20	0.6		350	130	36	3.6
50		390	122	20	0.5		350	130	34	3.4
60		400	124	20	0.4		360	130	32	3.2
70		400	126	20	0.4		400	128	30	3.2
80	70	370	124	18	0.9	70	130	160	24	4.7
90		400	120	17	1.0		160	160	24	4.6
100		430	120	16	1.0		150	156	22	4.4
110		440	120	17	1.0		170	156	22	4.3
120		440	120	18	1.0		180	152	24	4.2
130	84		124	16	0.7	68		148	22	4.2
150	82		120	16	0.8	70		150	24	4.1
170	80		124	18	0.8	75		158	22	4.4
190	84		124	20	1.0	72		160	24	4.6
210	82		124	20	1.0	68		160	22	4.6
230	120		126	18	2.0	84		118	14	4.7
260	130		128	19	2.0	80		120	16	4.5
290	115		130	20	2.0	78		120	16	4.3
320	110		128	20	1.9	76		124	18	4.1
350	100		136	20	1.9	70		130	18	4.0
Outcome	DEATH - 34 Hours. '1'					DEATH - 12 Hours. '2'				
Spleen Weight	67 Grams.					53 Grams.				
Bleeding Volume	35.8 cc/kg.					31.5 cc /kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	15.4	49%	6.9	3.3	3.6	12.1	36%	6.9	2.2	4.7
After Reinfus.	12.5	40%	5.7	2.9	2.8	10.3	32%	6.2	2.0	4.2

TABLE C - II. PAIRED EXPERIMENT XXVII. SPLENECTOMIZED.

14 MAR. 1960	TEST - HYDROCORTISONE. # 151 F 12.7					CONTROL # 396 M 14.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	108		140	12	3.5	134		160	20	5.4
-10	115		150	20	3.5	136		160	36	6.0
0	40	470	140	16	1.0	40	350	120	48	6.2
10		550	140	16	0.9		310	120	72	6.1
20		570	160	18	0.6		400	126	68	6.0
30		580	160	20	0.8		470	126	66	6.0
40		560	160	20	1.0		500	132	64	5.8
50		540	160	20	1.0		530	136	68	5.8
60		510	162	20	1.1		540	140	68	6.0
70		530	158	20	1.2		560	148	68	6.1
80	70	480	168	20	1.1	70	500	148	50	6.0
90		490	166	20	1.1		500	154	50	6.1
100		500	166	20	1.1		520	154	50	6.1
110		520	164	20	1.1		540	152	48	6.3
120		540	172	20	1.3		560	150	48	6.4
130	84		160	20	3.8	76		144	46	6.4
150	86		148	20	3.0	76		144	42	6.4
170	92		156	20	2.6	80		154	46	6.4
190	92		142	20	2.3	88		160	44	6.2
210	90		144	20	2.1	64		168	48	6.0
230	116		100	12	4.0	140		120	20	8.5
260	120		90	12	2.7	160		120	32	9.0
290	124		96	12	2.6	150		126	32	8.0
320	120		96	14	2.8	140		130	36	8.6
350	110		98	16	3.0	120		130	32	8.0
Outcome	DEATH - 42 Hours. '1'					DEATH - 14 Hours. '2'				
Spleen Weight	95 Grams.					65 Grams.				
Bleeding Volume	45.6 cc/kg. #					38.8 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	13.3	41%	4.9	2.8	2.1	11.0	33%	4.7	2.7	2.0
After Reinfus.	13.2	39%	5.0	2.7	2.3	10.6	32%	4.5	2.8	1.7

TABLE C - III. PAIRED EXPERIMENT XXVIII. SPLENECTOMIZED.

18 MAR. 1960	TEST - HYDROCORTISONE. # 3 M 13.6					CONTROL # 292 F 11.8				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	142		150	20	6.6	118		126	24	4.5
-10	140		152	20	6.5	120		124	26	4.4
0	40	470	164	26	1.3	40	430	120	40	3.4
10		510	136	20	0.6		460	124	44	3.3
20		570	120	22	0.1		480	120	44	3.4
30		600	108	24	0.1		470	120	44	3.3
40		670	120	24	0.1		450	124	43	3.4
50		740	144	24	0.1		440	128	38	3.6
60		760	152	26	0.3		410	128	36	3.7
70		770	160	28	0.5		400	128	36	3.9
80	70	620	164	26	1.2	70	150	120	24	4.0
90		630	164	24	1.3		150	116	28	4.1
100		720	164	24	1.4		300	118	30	4.2
110		740	164	24	1.4		280	120	30	4.2
120		740	164	24	1.4		280	124	30	4.2
130	84		164	26	1.6	78		124	30	4.5
150	80		156	22	2.0	84		120	28	4.7
170	86		160	26	2.5	85		120	30	4.8
190	84		160	24	1.8	82		120	30	4.8
210	86		160	24	1.6	80		116	32	4.6
230	112		120	22	7.0	116		92	20	5.2
260	118		120	20	6.2	85		108	24	4.8
290	120		110	18	6.0	60		132	32	4.1
320	124		108	16	6.0	54		136	38	4.0
350	120		110	16	6.0	50		142	40	3.8
Outcome	SURVIVAL 48 Hours.					DEATH - 5 Hours. '3'				
Spleen Weight	94 Grams.					72 Grams.				
Bleeding Volume	56.6 cc/kg. #					40.7 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.5	41%	5.2	3.5	1.7	16.8	50%	6.0	4.0	2.0
After Reinfus.	11.0	36%	5.4	2.9	2.5	15.4	47%	5.3	3.7	1.6

TABLE C - IV. PAIRED EXPERIMENT XXIX. SPLENECTOMIZED.

21 MAR. 1960	TEST - HYDROCORTISONE # 228 M 11.4					CONTROL # 331 M 11.4				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		156	16	4.8	118		120	17	6.5
-10	145		160	16	4.9	120		120	16	6.4
0	40	300	160	36	1.6	40	530	148	32	0.4
10		300	160	36	1.4		700	148	30	1.6
20		350	156	32	1.4		730	156	28	2.6
30		360	152	32	1.3		750	152	28	3.6
40		390	160	28	1.2		760	152	28	4.0
50		410	164	28	1.2		770	156	26	4.0
60		420	168	24	1.2		760	152	24	4.0
70		440	172	24	1.2		760	152	24	4.0
80	70	420	172	28	1.6	70	730	160	20	4.6
90		440	170	26	1.8		670	160	20	4.8
100		440	168	26	1.9		680	160	20	4.9
110		430	166	24	1.8		650	160	20	4.8
120		420	164	22	1.8		640	160	18	4.6
130	84		160	28	2.1	60		146	18	5.1
150	70		164	26	1.9	50		152	20	4.8
170	60		168	24	1.6	42		154	20	4.9
190	84		164	24	2.3	40		152	18	5.1
210	90		160	24	2.7	34		150	16	5.2
230	126		172	28	3.6	120		132	20	8.0
260	115		164	26	3.4	124		126	18	7.8
290	118		160	24	3.4	126		120	12	7.6
320	112		144	20	3.3	130		84	8	7.4
350	116		136	20	3.2	116		78	8	6.6

Outcome	SURVIVAL 48 Hours. '1'	DEATH - 12 Hours. '2'
Spleen Weight	65 Grams.	46 Grams.
Bleeding Volume	38.8 cc/kg. #	67.5 cc/kg. #

Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	11.0	32%	6.4	3.9	2.5	10.3	31%	5.9	3.6	2.3
After Reinfus.	12.5	39%	6.0	3.8	2.2	10.3	33%	5.9	3.7	2.2

TABLE C - V. PAIRED EXPERIMENT XXX. SPLENECTOMIZED.

25 MAR. 1960	TEST - HYDROCORTISONE # 129 M 13.6					CONTROL # 174 F 11.8				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	150		164	20	7.0	120		156	20	7.2
-10	150		160	20	10.4	120		152	20	8.6
0	40	290	140	52	5.8	40	550	148	24	6.0
10		340	146	56	6.0		570	152	30	5.0
20		370	152	60	6.2		610	160	40	4.8
30		390	156	58	6.1		620	172	36	3.7
40		400	156	56	6.1		650	180	36	3.5
50		410	160	56	6.0		680	182	36	3.5
60		420	164	58	6.0		700	184	36	3.5
70		440	176	62	6.0		720	184	40	3.3
80	70	400	180	56	6.5	70	600	180	32	5.3
90		400	180	56	6.4		630	180	34	5.2
100		500	172	52	6.5		680	180	33	4.9
110		480	166	56	6.5		700	180	34	4.7
120		450	160	60	6.5		690	180	34	4.7
130	82		180	56	6.2	64		172	32	4.1
150	86		180	52	6.1	54		172	34	4.1
170	84		180	48	6.1	48		170	34	3.8
190	84		176	48	6.0	42		172	33	3.6
210	82		180	48	6.0	34		172	32	3.0
230	140		144	20	6.4	110		128	20	5.3
260	135		142	20	6.4	108		130	22	5.2
290	130		140	20	6.3	102		132	22	5.1
320	124		140	19	6.3	96		140	24	4.6
350	120		140	18	6.2	90		140	24	4.2
Outcome	SURVIVAL 48 Hours.					DEATH - 6 Hours. '3'				
Spleen Weight	74 Grams.					108 Grams.				
Bleeding Volume	33 cc/kg.					61 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.7	45%	6.3	4.0	2.3	11.0	37%	6.0	2.8	3.2
After Reinfus.	14.5	44%	5.6	3.4	2.2	11.0	39%	6.0	3.3	2.7

TABLE C - VI. PAIRED EXPERIMENT XXXI. SPLENECTOMIZED.

28 MAR. 1960	TEST - HYDROCORTISONE # 88 F 13.6					CONTROL # 434 M 14.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	130		176	16	7.1	120		128	8	8.4
-10	132		180	16	7.0	124		130	10	8.2
0	40	350	132	16	5.3	40	420	132	16	0.8
10		360	132	16	5.9		500	136	16	0.5
20		370	140	16	5.4		510	140	16	1.0
30		380	130	16	5.0		520	140	17	1.3
40		410	128	16	5.0		530	138	18	1.2
50		430	132	16	4.7		520	140	20	1.2
60		480	140	16	4.1		560	144	20	1.2
70		510	152	16	4.0		600	160	20	1.1
80	70	480	168	12	4.1	70	590	162	16	2.5
90		460	170	14	4.2		600	156	16	1.9
100		460	170	16	4.3		640	150	16	1.7
110		470	170	16	4.4		630	150	16	1.7
120		430	170	16	4.4		650	146	16	1.6
130	90		152	16	4.3	74		140	14	1.9
150	80		144	16	4.3	72		136	13	1.9
170	85		150	15	4.5	66		130	12	1.8
190	78		160	14	4.7	62		120	12	1.7
210	72		164	15	4.7	54		116	11	1.6
230	120		148	16	5.9	140		88	12	14.5
260	132		160	16	5.8	144		84	13	10.3
290	130		152	16	5.7	130		88	14	6.4
320	120		132	14	5.4	122		100	14	4.1
350	124		128	15	5.5	109		124	16	3.8

Outcome	SURVIVAL 48 Hours.					DEATH - 11 Hours.				
Spleen Weight	55 Grams.					61 Grams.				
Bleeding Volume	39.7 cc/kg.					44.9 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.5	40%	6.2	3.6	2.6	12.3	37%	6.1	3.3	2.8
After Reinfus.	11.9	35%	5.7	3.3	2.4	10.8	33%	5.3	2.9	2.4

TABLE C - VII. PAIRED EXPERIMENT XXXII. SPLENECTOMIZED.

4 APR. 1960	TEST - HYDROCORTISONE # 23 M 12.7					CONTROL # 252 M 12.3				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		148	12	3.0	134		146	16	4.0
-10	144		150	14	3.0	138		150	20	4.3
0	40	490	106	14	1.1	40	410	88	40	4.0
10		500	108	16	1.1		400	84	38	4.1
20		570	140	24	1.1		410	96	40	4.2
30		610	160	28	1.1		430	98	40	3.6
40		690	156	28	1.5		470	108	40	3.2
50		720	160	28	1.7		500	124	40	2.9
60		760	164	30	2.3		550	132	40	2.5
70		780	168	32	2.8		560	134	40	2.4
80	70	740	172	24	3.0	70	450	132	30	5.2
90		760	176	20	3.4		450	132	28	5.6
100		780	176	22	3.5		420	130	30	5.8
110		760	176	24	3.6		420	128	32	6.2
120		770	180	24	3.6		380	128	32	6.0
130	76		156	20	3.5	74		120	32	5.9
150	86		156	22	3.0	84		124	30	6.4
170	86		160	24	2.6	112		140	28	6.3
190	82		160	26	2.2	106		142	26	7.1
210	86		160	28	2.1	98		144	24	8.1
230	138		146	26	6.8	140		128	22	7.5
260	150		112	20	3.3	158		96	20	5.9
290	150		112	20	3.2	156		80	28	4.0
320	146		110	20	3.1	150		80	32	3.8
350	144		108	18	3.0	144		80	36	3.6

Outcome	SURVIVAL 48 Hours.					DEATH - 24 Hours. †2†				
Spleen Weight	97 Grams.					68 Grams.				
Bleeding Volume	62.1 cc/kg. #					46.4 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.1	45%	6.5	3.5	3.0	12.5	38%	6.8	3.9	2.9
After Reinfus.	13.7	41%	5.5	3.3	2.2	11.0	32%	5.8	3.4	2.4

TABLE C - VIII. PAIRED EXPERIMENT XXXIII. SPLENECTOMIZED.

6 APR. 1960	TEST - HYDROCORTISONE # 9 M 11.4					CONTROL # 441 F 11.4				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	120		120	14	5.0	130		92	10	4.4
-10	130		140	14	5.0	134		104	12	4.2
0	40	470	112	20	4.0	40	370	68	8	2.9
10		540	112	20	4.0		410	68	9	2.5
20		550	120	22	3.0		420	72	10	1.5
30		590	128	24	2.8		450	84	10	1.2
40		650	136	26	1.3		470	110	10	0.7
50		720	148	28	0.6		510	116	10	0.5
60		740	160	24	0.3		520	132	12	0.4
70		790	160	20	0.1		540	148	12	0.1
80	70	760	164	28	0.5	70	460	140	14	2.4
90		770	164	28	0.5		460	136	14	2.4
100		780	168	28	0.6		470	142	15	2.6
110		790	172	28	0.7		490	144	16	2.7
120		780	176	30	0.6		480	144	16	2.5
130	76		148	28	1.1	74		144	20	2.8
150	66		156	28	1.6	68		140	28	2.2
170	83		164	32	1.5	76		136	26	3.1
190	84		172	28	1.6	64		124	16	3.2
210	80		164	24	3.5	54		120	14	3.7
230	140		132	20	4.2	150		70	6	5.0
260	136		132	20	4.4	140		80	7	4.6
290	120		140	18	4.7	134		68	6	4.7
320	120		144	20	4.8	130		70	8	4.8
350	120		148	22	4.0	118		72	8	4.8
Outcome	SURVIVAL 48 Hours.					DEATH - 21 Hours. '2'				
Spleen Weight	140 Grams.					74 Grams.				
Bleeding Volume	69 cc/kg. #					47.4 cc/kg.				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	13.3	41%	6.4	3.5	2.9	14.1	45%	6.3	3.3	3.0
After Reinfus.	12.1	37%	5.8	3.4	2.4	13.7	39%	5.8	3.0	2.5

TABLE C - IX. PAIRED EXPERIMENT XXXIV. SPLENECTOMIZED.

11 APR. 1960	TEST - HYDROCORTISONE # 342 F 9.1					CONTROL # 307 M 9.5				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		80	16	4.4	154		152	20	3.6
-10	142		160	20	3.5	148		152	12	2.9
0	40	240	130	40	1.4	40	420	150	20	0.5
10		260	128	40	1.3		450	152	20	0.5
20		350	136	42	0.7		500	152	22	0.5
30		360	140	44	0.3		520	156	24	0.5
40		400	144	44	0.2		550	160	22	0.4
50		420	152	44	0.1		570	160	24	0.3
60		460	156	45	0.1		590	176	26	0.2
70		450	160	46	0.1		580	176	26	0.1
80	70	440	184	40	0.2	70	570	180	24	0.6
90		430	182	40	0.2		590	180	24	0.4
100		430	184	38	0.3		540	180	24	0.4
110		430	180	38	0.3		550	184	24	0.6
120		430	176	36	0.3		560	182	24	0.6
130	64		160	34	0.3	80		172	26	0.5
150	84		148	32	0.3	56		164	26	0.5
170	78		148	34	0.2	44		172	28	0.4
190	68		160	36	0.3	42		168	28	0.3
210	58		164	36	0.4	36		184	28	0.2
230	124		140	28	3.3	124		148	20	5.5
260	126		136	20	3.1	128		144	18	3.3
290	124		132	20	3.6	120		156	20	2.1
320	124		128	20	3.8	110		160	24	1.5
350	126		124	20	3.8	108		164	26	1.3
Outcome	SURVIVAL 48 Hours.					DEATH - 12 Hours. '2'				
Spleen Weight	84 Grams.					56 Grams.				
Bleeding Volume	50.6 cc/kg. #					62.2 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.5	44%	6.3	2.8	3.5	11.7	33%	6.1	3.4	2.7
After Reinfus.	12.5	39%	5.8	2.5	3.3	10.6	33%	5.8	3.3	2.5

TABLE C - X. PAIRED EXPERIMENT XXXV. SPLENECTOMIZED.

13 APR. 1960	TEST - HYDROCORTISONE # 487 M 11.8					CONTROL # 16 F 13.6				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	140		160	12	4.4	150		144	12	4.7
-10	144		160	18	6.3	154		156	16	6.1
0	40	350	160	24	1.1	40	500	124	30	3.5
10		360	160	24	1.0		570	124	30	3.4
20		400	150	26	0.9		600	126	32	3.3
30		430	140	26	0.9		670	128	36	3.2
40		480	152	26	0.8		690	136	34	3.3
50		500	156	26	0.7		730	144	34	3.4
60		540	160	27	0.8		740	148	34	3.5
70		550	160	28	0.8		760	144	34	3.6
80	70	520	168	24	1.4	70	710	160	32	4.0
90		500	164	24	1.3		730	162	30	4.5
100		510	166	24	1.2		710	164	28	4.7
110		490	168	24	1.2		690	164	28	4.6
120		490	172	26	1.1		690	164	28	6.0
130	72		164	28	1.4	80		148	26	4.5
150	70		168	28	1.3	90		160	32	4.3
170	66		180	30	1.2	82		144	32	4.2
190	62		164	28	1.4	80		152	34	4.9
210	76		168	24	1.6	61		160	32	4.0
230	126		144	20	8.0	132		144	20	4.8
260	124		148	20	6.2	128		150	24	5.0
290	122		140	20	4.8	124		156	26	5.4
320	120		140	18	3.8	106		160	26	5.1
350	118		142	16	3.8	80		172	28	4.8

Outcome	SURVIVAL 48 Hours.					DEATH - 6 Hours. '3'				
Spleen Weight	54 Grams.					86 Grams.				
Bleeding Volume	46.6 cc/kg. #					55.9 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	12.9	40%	6.0	3.6	2.4	14.3	44%	6.5	3.6	2.9
After Reinfus.	10.3	32%	5.4	3.0	2.4	14.1	43%	6.2	3.4	2.8

TABLE C - XI. PAIRED EXPERIMENT XXXVI. SPLENECTOMIZED.

25 APR. 1960	TEST - HYDROCORTISONE # 494 F 13.2					CONTROL # 152 F 11.4				
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	124		152	12	2.6	106		128	12	4.0
-10	122		150	12	2.8	110		124	14	5.8
0	40	290	92	14	1.1	40	390	96	20	2.2
10		330	92	14	1.1		420	94	22	2.0
20		350	96	16	1.2		450	116	24	1.4
30		390	100	18	1.3		490	120	26	1.0
40		420	100	20	1.3		500	122	28	0.5
50		450	102	20	1.2		500	124	28	0.5
60		480	110	20	1.1		500	120	30	0.7
70		510	116	20	1.0		500	120	30	0.6
80	70	460	148	24	1.5	70	400	140	26	1.7
90		500	148	24	1.5		400	136	26	1.8
100		540	144	24	1.6		390	132	26	1.9
110		580	140	24	1.6		400	132	26	1.8
120		600	140	24	1.6		400	132	24	1.6
130	84		152	24	1.5	80		140	26	1.8
150	82		152	22	1.6	76		124	22	0.5
170	80		156	22	1.4	78		132	22	0.9
190	88		160	20	1.4	90		140	20	0.8
210	90		160	20	2.0	86		140	20	1.5
230	112		108	14	7.0	120		100	20	8.5
260	130		140	24	4.9	120		116	16	8.9
290	132		128	20	4.4	116		120	18	7.0
320	124		120	16	4.2	108		132	20	6.0
350	128		120	14	4.0	100		148	28	5.4
Outcome	SURVIVAL 48 Hours.					DEATH - 6 Hours. '3'				
Spleen Weight	64 Grams.					70 Grams.				
Bleeding Volume	45.4 cc/kg.					43.9 cc/kg. #				
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.5	45%	6.5	3.0	3.5	13.7	41%	6.2	3.3	2.9
After Reinfus.	12.1	36%	5.1	2.6	2.5	11.7	34%	5.1	3.1	2.0

TABLE C - XII. EXPERIMENT XXXVII. SPLENECTOMIZED.

29 APR. 1960	TEST - HYDROCORTISONE n 46 M 11.4									
Minutes	B.P.	Res. Vol.	Pulse	Resp.	V.P.	B.P.	Res. Vol.	Pulse	Resp.	V.P.
-30	130		112	16	5.2					
-10	128		120	16	5.2					
0	40	290	104	16	8.5					
10		300	102	16	7.0					
20		320	100	16	6.0					
30		350	110	16	6.3					
40		380	120	16	6.5					
50		410	124	18	6.0					
60		420	132	20	5.6					
70		460	136	22	3.8					
80	70	330	132	24	4.9					
90		310	130	22	5.0					
100		350	128	20	5.2					
110		330	126	18	5.0					
120		300	124	16	4.7					
130	68		120	20	6.4					
150	76		128	20	7.1					
170	84		130	22	7.0					
190	86		140	24	6.8					
210	86		140	24	7.6					
230	110		124	22	9.5					
260	120		132	24	8.9					
290	124		128	20	8.6					
320	124		124	20	8.6					
350	124		120	18	8.6					
Outcome	SURVIVAL 48 Hours.									
Spleen Weight	51 Grams.									
Bleeding Volume	40.4 cc/kg.									
Chemistry	Hgb.	Hct.	Prot.	Alb.	Glob.	Hgb.	Hct.	Prot.	Alb.	Glob.
Before Haemorr.	14.5	44%	5.5	2.5	3.0					
After Reinfus.	14.3	43%	5.7	2.7	3.0					

BIBLIOGRAPHY

1. Allen, F.M. "Theory and Therapy of Shock: Reduced Temperatures in Shock Treatment," Am. J. Surg., LX (1943), 335.

2. Amberson, W.R. "Substitutes for Blood," Memphis M.J., XI (1936), 11.

3. Arimoto, F., Necheles, H., Levinson, S.O. and Janota, M. "Haemorrhagic Shock: Method for Its Production and Formula for Prognosis," Am. J. Physiol., CXLIII (1945), 198.

4. Aviado, D.M.Jr. "Cardiovascular Effects of Some Commonly Used Pressor Amines," Anaesthesiology, XX(1959), 71.

5. Aust, J.B., Johnson, J.A., and Visscher, M.B. "Plasma Sequestration in Endotoxin Shock," Surgical Forum Vol. VIII (1957), 8.

6. Barcroft, J., Harris, H.A. "Physiology of the Spleen," Lancet, I (1925), 319.

7. Blalock, A., and Hawson, T.R. "Effect of Anaemia and Haemorrhage on Cardiac Output of Dogs," Am. J. Physiol., LXXX (1927), 157.

8. Blalock, A., and Mason, M.F. "AComparison of the Effects of Heat and Those of Cold in the Prevention and Treatment of Shock," Arch. Surg., XLII (1941), 1054.

9. Bradley, S.E., Marks, P.A., Reynell, P.C., and Meltzer, C. "Circulating Splanchnic Blood Volume in Dog and Man," Tr.A.Am. Physicians, LXVI (1953), 294.

10. Burn, J.H., and Rand, M.J. Nor-adrenalin in Artery Walls, Lancet, CCLXXIV (1958), 673.

11. Cannon, W.B. "Acidosis in Shock," Med. Res. Comm.(G.B.) (Special Report Series) XXV-II (1919), 109.

12. Catchpole, B.N., Hackel, D.B., and Simeone, F.A. "Coronary and Peripheral Blood Flow in Experimental Haemorrhagic Hypotension Treated with L-norepinephrine," Ann. Surg., CXLII (1955), 372.

13. Chambers, R., and Zweifach, B. W. "Topography and Function of the Mesenteric Capillary Circulation," Am.J. Anat., LXXV (1944),173.

14. Clark, J.H., Nelson, W. et al. "Problem of Reduced Blood Volume in Chronically Ill Patient: Concept of Chronic Shock," Ann. Surg., CXXV (1947), 618.

15. Cleghorn, R.A., Armstrong, J.B., and McKelvey, A.D. "The Effect of Different Environmental Temperatures on the Survival of Dogs After Severe Bleeding," Canad. M.A.J., XLIX (1943), 363.

16. Cohn, R., and Parsons, H. "Relationship of Portal Hypertension and Irreversibility of Shock," Am. J. Physiol., CLX (1951), 437.

17. Connolly, J.E., Bruns, D.L., and Stofer, R.C. "The Use of Intravenous Hydrocortisone in Haemorrhagic Shock," Surgical Forum Vol., IX (1958),17.

18. Coonse, G.K., Foisio. P.S., Robertson, H.F., and Aufranc, O.E. "Trauma and Haemorrhagic Shock; Experimental and Clinical Study," N.Eng. J.Med., CCXII (1935),647.

19. Culbertson, W.R., Elston, W., and Altemeier, W.A. "Further Bacterial Studies in Haemorrhagic Shock," Surgical Forum Vol., X (1959), 392.

20. Delorme, E.J. "Arterial Perfusion of Liver in Shock" Experimental Study, Lancet,I (1951), 259.

21. Dworkin, R.M. "Effects of Pectin and Saline Solutions on Survival Time of Dogs in Haemorrhagic Hypotension," Proc. Soc. Exper. Biol. and Med., LVI (1944), 20.

22. Ebert, R.V., and Stead, E.A. Jr. "Demonstration That in Normal Man no Reserves of Blood Are Mobilized by Exercise, Epinephrine, and Haemorrhage," Am. J. Med. Science, CCL (1941),655.

23. Edwards, W.S., Tidwell, O.K., and Lombardo, C.R. "The Mechanism of Death from Thoracic Aortic Occlusion," Surgical Forum Vol., V, (1954), 90.

24. Elman, R., Lischer, C.E., and Davey, H.W. "Red Cell Volume, Plasma Albumin and Globulin in Fatal Surgical Shock Due to Repeated Haemorrhage," Am. J. Physiol., CXL (1944), 737.

25. Evans, R.D., Gibson, J.G., Seligman, A.M., Peacock, W.C., Aub, J.C., and Fine, J. "The Distribution of Red Cells and Plasma in Large and Minute Vessels of the Normal Dog, Determined by Radioactive Isotopes of Iron and Iodine," J.Clin.Investig., XXV (1946), 848.

26. Ferguson, A.T., Wilson, J.N., Jenkins, D., and Swan, H. "The Effect of Hypothermia Induced After Rapid Arterial Haemorrhage in the Dog," Surgical Forum Vol., VIII (1957), 1.

27. Fine, J., and Seligman, A.M. "Traumatic Shock; Study of Problem of 'Lost Plasma' in Haemorrhagic Shock by Use of Radioactive Plasma Protein," Ann. Surg., CXVIII (1943), 238.
J. Clin. Investig., XXII (1943), 285.

28. Fine, J., Frank, H.A., Schweinburg, F., Jacob, S., and Gordon, T. "The Bacterial Factor in Traumatic Shock," Ann. N.Y. Acad. Science, LV (1952), 429.

29. Fine, J. "Relation of Bacteria to Failure of Blood Volume Therapy in Traumatic Shock," Internat. J. Anaes., II (1954), 29.
N. Eng. J. of Med., CCL (1954), 889.

30. Fine, J., Frank, E.D., Ravin, H.A., Rutenburg, S.H., and Schweinburg, F.B. "The Bacterial Factor in Traumatic Shock," N. Eng. J. of Med., CCLX (1959), 214.

31. Foster, J.H. Collins, H.A., and Scott, W.H.Jr. "The Effect of Levarterenol on Renal Blood Flow in Dogs Subjected to Haemorrhagic Shock," Surgical Forum Vol., V (1954), 781.

32. Fox, C.L. Jr. "Oral Sodium Lactate in Treatment of Burn Shock," J.A.M.A., CXXIV (1944), 207.

33. Fox, C.L.Jr. "Mechanism of Shock from Burns and Trauma Traced with Radiosodium," Surg., Gynec., and Obst., LXXX (1945), 561.

34. Fozzard, H.A. and Gilmore, J.P. "Levarterenol in Irreversible Shock," Am. J. Physiol., CXCVI (1959), 1029.

35. Frank, H.A., and Fine, J. "Traumatic Shock; A Study of the Effect of Oxygen on Haemorrhagic Shock," J.Clin. Investig., XXII, (1943), 305.

36. Frank, H.A., Seligman, A.M., and Fine, J. " The Treatment of Haemorrhagic Shock Irreversible to the Replacement of Blood Volume Deficiency," J. Clin. Investig., XXIV (1945), 435.

37. Frank, H.A., Seligman, A.M., and Fine, J. "Traumatic Shock; Prevention of Irreversibility in Haemorrhagic Shock by Vivi-Perfusion of the Liver," J.Clin. Investig., XXV (1946), 22.

38. Frank, H.A., Fine, J., Friedman, E., Glotzer, P., Jacob, S., and Schwartz, A. "Adrenal Cortical Therapy and Hepatic Vascular Resistance: Two Aspects of an Inquiry into the Pathologic Physiology of Experimental Haemorrhagic Shock," Surgical Forum Vol., I (1950), 522.

39. Frank, H.A., Glotzer, P., Jacob, S., and Fine, J. "Traumatic Shock; Haemorrhagic Shock in Eck Fistula Dogs," Am. J. Physiol., CLXVII (1951), 508.

40. Frank, H.A., Physiological Principles of Surgery. Edited by Zimmerman, L.M., and Levine, R. Philadelphia: W.B. Saunders Co., 1957.

41. Frawley, J.P. "Plasma Retention and Urinary Excretion of Dextran and Modified Gelatin in Combat Casualties," Surgery, XXXVII (1955), 384.

42. Goodman, L.S., and Gilman, A. The Pharmacological Basis of Therapeutics. 2nd Edit. New York: The MacMillan Company, 1955.

43. Griffin, J.C., Webb, W.R., et al. "The Effect of Nor-epinephrine (Levophed) on Survival in Standard Oligaemic Shock," Surgical Forum Vol., IX (1958), 4.

44. Gropper, A.L., Cockrell, E.W., Rarsz, L.G. and Pulaski, E.J. "A Comparison of Dextran and Oxypolygelatin in the Treatment of Haemorrhagic Hypotension," Am. J. Physiol., LXIX (1952), 749.

45. Gurd, F.N. "Current Trends in the Treatment of Shock," Canad.M.A.J., LXXIII (1955), 977.

46. Hampson, L.G., Scott, H.J., and Gurd, F.N. "Studies in Therapy of Haemorrhagic Shock with Associated Myocardial Damage," Master's thesis, Department of Experimental Surgery, McGill University, 1953.

47. Harkins, H.N. "Recent Advances in Study and Management of Traumatic Shock," Surgery, IX (1941), 231, 447, 607.

48. Harper, W.H., and Blain, A.B. "Penicillin in Experimental Intestinal Obstruction," Bull. Johns Hopkins Hosp., LXXVI (1945), 221.

49. Hay, E.B., Webb, J.K. "Effect of Increased Arterial Blood Flow to Liver on Mortality Rate Following Haemorrhagic Shock," Surgery, XXIX (1951), 826.

50. Haynes, B.W. Jr., and DeBakey, M.E. "Evaluation of Plasma Substitutes in Clinical Shock; Dextran." Surgical Forum Vol., II (1951), 631.

51. Hull, E. "Emergency Use of Corticoids and Corticotropins," Kansas City Med. J., XXXIII (1957), 19.

52. Hume, D. "Secretion of Epinephrine, Nor-epinephrine, and Corticosteroids," Surgical Forum Vol., VIII (1957), 111.

53. Inglis, F.G., Hampson, L.G., and Gurd, F.N. "Effect of Chlorpromazine on Survival Time and Mesenteric Blood Flow in Experimental Shock," Ann. Surg., CXLIX (1959), 43.

54. Ingraham, R.C., and Wiggers, H.C. "Alkalinizing Agents and Fluid Priming in Haemorrhagic Shock," Am. J. Physiol., CXLIV (1945), 505.

55. Jamieson, R.A., and Kay, A.W. A Textbook of Surgical Physiology. Edinburgh and London: E. & S. Livingstone Ltd., 1959.

56. Karlson, K.E., and Senn, LaV.Y. "The Simultaneous Determination of Plasma Volume and Red Cell Mass with a Pulse Height Analyzer," Surgical Forum Vol., X(1959), 411.

57. Kendrick, D.B. Jr., and Uihlein, A. "Shock in Control and Splenectomized Animals Under Ether and Pentobarbital Sodium Anaesthesia," Surgery, XII (1942), 76.

58. Kovach, A.G.B., Foldi, M., Menyhart, J., Erdelyi, A., and Koltay, E. "Effect of Dibenamine on Renal Function in Dogs with Ischaemic Shock," Acta Physiologica, Academiae Scientiarum Hungaricae, XIV -3(1958), 239.

59. Kovach, A.G.B., Roheim, P.S., Irayni, M., Kiss, S., and Antal, J. "Effect of the Isolated Perfusion of the Head on the Development of Ischaemic and Haemorrhagic Shock," Acta Physiologica, Academiae Scientiarum Hungaricae, XIV - 3 (1958), 637.

60. Knutson, R.C., Bollman, J.L. and Lundy, J.S. "Comparative Effectiveness of Certain Volemic Substances in Maintaining Plasma Volume after Blood Loss," Surgical Forum Vol., II (1951), 637.

61. Laborit, H., et Huguenard, P. "L'hibernation Artificielle chez le Grand Choque," La Presse Medicale, LXI (1953), 1029.

62. LeFemine, A.A., Marks, L.J., Teter, J.G., Leftin, J.H., Leonard, M.P., and Baker, D.V. "The Adrenocortical Response in Surgical Patients," Ann. Surg., CXLVI (1957), 26.

63. Lamson, P.D., and DeTurk, W.E. "Studies on Shock Induced by Haemorrhage; Method for Accurate Control of Blood Pressure," J. Pharm. and Exper. Therapy, LXXXIII (1945), 250.

64. Lawson, H., and Rehm, W.S. "Effect of Haemorrhage and Replacement of Apparent Volume of Plasma and Cells," Am. J. Physiol, CXLIV (1945), 199.

65. Levine, R., Huddlestun, B., Persley, H., and Soskin, S. "Successful Treatment of So-called 'Irreversible' Shock by Whole Blood Supplemented with Sodium Bicarbonate and Glucose," Am. J. Physiol., CXLI (1944), 209.

66. Lillehei, R.C. "The Prevention of Irreversible Haemorrhagic Shock in Dogs by Controlled Cross Perfusion of the Superior Mesenteric Artery," Surgical Forum Vol., VII (1956), 6.

67. Lillehei, R.C. and MacLean, L.D. "The Intestinal Factor in Irreversible Endotoxin Shock," Surgery, XLII (1957), 1043.
Ann. Surg., CXLVIII (1958), 513.

68. Madsen, J., Done, A.K., E.Y, R.S. et al. "Evaluation of Water-soluble Hemisuccinate Esters of Hydrocortisone and Prednisolone; Plasma 17-Hydroxycorticosteroid Concentrations Following Intravenous Administration," J. Dis. Children, XCVII (1959), 66.

69. Markowitz, J., Archibald, J., and Downie, H.G. Textbook of Experimental Surgery, 4th Edit. Baltimore: The Williams and Wilkins Co., 1959.

70. Mazur, A., and Shorr, E. "Hepatorenal Factors in Circulatory Haemostasis; Identification of Hepatic Vasodepressor Substance, V.D.M., with Ferritin," J. Biol. Chem., CLXXVI (1948), 771.

71. Mazur, A., and Shorr, E. "Quantitative Immuno-chemical Study Of Ferritin and its Relation to Hepatic Vasodepressor Material," J.Biol. Chem., CLXXXII (1950), 607.

72. Moyer, J.H., Handley, C.A. "The Problem of Renal Vascular Shunts," Am. J. Physiol., CLXV (1951), 548.
J. Pharm. and Exper. Therapeutics, CIII (1951), 368.

73. Moyer, J.H., Skelton, J.M., and Mills, L.C. "Nor-epinephrine; Effect in Normal Subjects; Use in Treatment of Shock Unresponsive to Other Measures," Am. J. Med., XV (1953), 330.

74. Moyer, J.H., Morris, G., and Beazley, H.L. "Renal Haemodynamic Response to Vasopressor Agents in the Treatment of Shock," Circulation, XII (1955), 96.

75. Overton, R.C., and DeBakey, M.E. "Experimental Observations on the Influence of Hypothermia and Autonomic Blocking Agents on Haemorrhagic Shock," Ann. Surg., CXLIII (1956), 439.

76. Parkins, W.M., Ben, M., and Vars, H.M. "Tolerance of Temporary Occlusion of Thoracic Aorta in Normothermic and Hypothermic Dogs," Surgery, XXXVIII (1955), 38.

77. Perera, G.A., Knowlton, A.I., Lowell, A., and Loeb, R.F. "Effect of Desoxycorticosterone Acetate on Blood Pressure in Man," J.A.M.A., CXXV (1944), 1030.

78. Postel, A.H., Reid, L.C., and Hinton, J.W. "The Therapeutic Effect of Hypothermia in Experimental Haemorrhagic Shock," Ann. Surg., CXLV (1957), 311.

79. Price, P.B., Hanlon, C.R., Longmire, W.P., and Metcalf. W. "Experimental Shock; Effects of Acute Haemorrhage in Healthy Dogs," Bull. Johns Hopkins Hospital, LXIX (1941), 327.

80. Reece, M.W., Edwards, K.M., and Jepson, R.P. "The Adrenocortical Response to Surgery," Surgery, XLII (1957), 669.

81. Reinhard, J.J., Glasser, O., and Page, I.H. "Experimental Haemorrhagic Shock; Study of its Production and Treatment," Am. J. Physiol., CLV (1948), 106.

82. Remington, J.W. et al. "Some Circulatory Responses to Haemorrhage in the Dog," Am. J. Physiol., CLXI (1950), 106.

83. Remington, J.W. et al. "Role of Vasoconstriction in Response of Dog to Haemorrhagic Shock," Am. J. Physiol., CLXI (1950), 116.

84. Remington, J.W. et al. "Vasoconstriction as a Precipitating Factor in Traumatic Shock in Dogs," Am. J. Physiol., CLXI (1950), 125.

85. Reubi, F.C. "Renal Hyperemia Induced in Man by a New Phthalazine Derivitive," Proc. Soc. Exper. Biol. and Med., LXXIII (1950), 102.

86. Richards, T.A. "Studies in Therapy of Haemorrhagic Shock with Overtransfusion," Master's Thesis, Department of Experimental Surgery, McGill University, 1959.

87. Rosenthal, O., Shenkin, H., and Drabkin, D.L. "A Method of Haemorrhagic Shock; Oxidation of Pyruvate and Glucose in Brain Suspensions from Animals Subjected to Irreversible Haemorrhagic Shock, Carbon Monoxide Poisoning or Temporary Arrest of Circulation," Am. J. Physiol., CXLIV (1945), 334.

88. Rosenthal, S.M., and Tabor, H. "Experimental Chemotherapy of Burns and Shock; Effects of Potassium Administration, of Sodium Loss, and Fluid Loss in Tourniquet Shock," Pub. Health Rep., LX (1945), 373.

89. Seligman, A.M., Frank, H.A., and Fine, J. "Traumatic Shock; Successful Treatment of Haemorrhagic Shock by Vivi-perfusion of the Liver in Dogs Irreversible to Transfusion," J. Clin. Investig., XXVI (1947), 530.

90. Selkurt, E.E. "Comparison of Renal Clearances with Direct Renal Blood Flow under Control Conditions and Following Renal Ischaemia," Am. J. Physiol., CXLV (1945), 376.

91. Selkurt, E.E. "Renal Blood Flow and Clearance During Haemorrhagic Shock," Am. J. Physiol, CXLV (1945), 699.

92. Selkurt, E.E., Alexander, R.S., and Patterson, M.B. "The Role of the Mesenteric Circulation in the Irreversibility of Haemorrhagic Shock," Am. J. Physiol., CXLIX (1947), 732.

93. Shorr, E., Zweifach, B.W., et al. "Hepatorenal Factors in Circulatory Homeostasis; Tissue Origins of Vasotropic Principles, V.E.M., and V.D.M. which Appear during Evolution of Haemorrhagic and Tourniquet Shock," Circulation, III (1951), 42.

94. Simeone, F.A. "Shock and Blood Pressure," Surg. Gynec. and Obstet., CVIII (1959), 740.

95. Slaney, G. "Tolerance of Dogs Resuscitated with Dextran to Subsequent Surgical Stress," Surgical Forum Vol., VII (1956), 1.

96. Small, H.S., Weitzner, S.W., and Nahas, G.G., "Cardiovascular Effects of Levarterenol, Hydrocortisone Hemisuccinate, and Aldosterone in the Dog," Am. J. Physiol., CXCVI (1959), 1025.

97. Swan, H., Jenkins, D., and Helmreich, M.L. "The Adrenal Cortical Response to Surgery," Surgery, XLII (1957), 202.

98. Swingle W.W., and Kleinburg, W. "Plasma, Gelatin, and Saline Therapy in Experimental Wound Shock," Am. J. Physiol., CXLI (1944), 713.

99. Swingle, W.W., Brannick, L.J., and Parlow, A.F. "Effect of 2-methyl, 9-alpha, Fluorohydrocortisone on Internal Distribution of Fluid and Electrolytes of Fasted Adrenalectomized Dogs," Proc. Soc. Expt. Biol., XCIV (1957), 156.

100. Swingle, W.W., DaVanzo, J.P., Crossfield, H.C., Glenister, D., Osborne, M. and Wagle, G. "Effects of Various Adrenal Steroids on Internal Fluid and Electrolyte Shifts of Fasted Adrenalectomized Dogs," Proc. Soc. Expt. Biol., XCIX (1958), 75.

101. Walcott, W.W. "Blood Volume in Experimental Haemorrhagic Shock; Standardization of Experimental Haemorrhagic Shock," Am. J. Physiol., CXLIII (1945), 247.

102. Wang, S.C., Overman, R.R., Fertig, J.W., Root, W.S., and Gregersen, M.I. "Relation of Blood Volume Reduction to Mortality Rate in Haemorrhagic and Traumatic Shock in Dogs," Am. J. Physiol., CXLVIII (1947), 164.

103. Webb, W.R., Shahbazi, N., and Jackson, J. "Metabolic Effects of Vasopressors and Vasodilators in the Hypovolemia of Standard Haemorrhagic Shock," Surgical Forum Vol., X (1959), 378.

104. Weil, M.H. "Current Concepts on the Management of Shock," Circulation, XVI (1957), 1097.

105. Weil, P.G. Hypotension, Shock, and Circulatory Failure. Philadelphia, London and Montreal: J.B. Lippincott Co., 1955.

106. Wiggers, C.J. Physiology of Shock. New York: The Commonwealth Fund, 1950.

107. Wiggers, H.C., Ingraham, R.C., and Dille, J. "Haemorrhagic Hypotension and Shock in Locally Anaesthetized Dogs," Am. J. Physiol., CXLIII (1945), 126.

108. Wiggers, H.C., and Ingraham, R.C. "Value of Alkalinizing Agents in Preventing Transition from Impending to Irreversible Hæmorrhagic Shock," Am. J. Physiol., CXLVI (1946), 431.

109. Wilson, B.J., and Stirman, G. "The Value of Saline Infusions in Haemorrhagic Shock," Paper Read before the American College of Surgeons Congress; 1959.

110. Wilson, J.N., Marshall, S.B., Beresford, V., Montgomery, V., Jenkins, D., and Swan, H. "The Deleterious Effect of Hypothermia on Survival and a Comparative Evaluation of Plasma Volume Changes," Ann. Surg., CXLIV (1956), 696.

111. Winkler, A.W., and Hoff, H.E. "Potassium and Cause of Death in Traumatic Shock," Am. J. Physiol., CXXXIX (1943), 686.

112. Wood, G.O., Mason, M.F., and Blalock, A. "Arterio-venous Osygen Differences after Haemorrhage; Studies on Effects of Inhalation of High Concentrations of Oxygen in Experimental Shock," Surgery, VIII (1940), 247.

113. Zingg, W., Nickerson, M., and Carter, S.A. "Effect of Hydralazine on Survival of Dogs Subjected to Haemorrhagic Shock," Surgical Forum Vol., IX (1958).

114. Zweifach, B.W., Baez, S., and Shorr, E. "Effect of Dibenamine on Humoral and Vascular Changes in Dogs Subjected to Haemorrhagic Shock," Fed. Proc. Am. Soc. Expt. Biol., XI (1952), 177.