ANALEPTICS IN HEMORRHAGIC SHOCK

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Vattakkalvalasu M. Ramaswamy

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This is to certify that the

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ANALEPTICS IN HEMORRHAGIC SHOCK

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Vattakkalvalasu M. Ramaswamy

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Department of Physiology and Pharmacology

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Major Professor

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ANALEPTICS IN HEMORRHAGIC SHOCK

By

Vattakkalvalasu M. Ramaswamy

AN ABSTRACT

Submitted to the College of Veterinary Medicine
Michigan State University of Agriculture and
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ABSTRACT

This study was undertaken to find out the comparative effects of a few analeptic drugs in artificially induced hemorrhagic shock in dogs over-anesthetized with sodium pentobarbital.

Mongrel dogs were anesthetized with sodium pentobarbital. The initial dose was 30 mg./Kg. body weight, followed by 10 mg./Kg. body weight after about 10 minutes. Hemorrhagic shock was produced by rapidly withdrawing blood from the femoral artery until the blood pressure reached 70 mm. Hg. This pressure was maintained for about an hour by occasional bleeding if necessary.

The amount of bleeding required to reach 70 mm. Hg. varied from 25 ml./Kg. body weight to 70 ml./Kg. The average bleeding required was 37 ml./Kg. body weight.

After maintaining the blood pressure at 70 mm. Hg. or slightly lower than that for an hour, the following drugs were administered through the femoral vein. Each drug was used in at least 4 dogs.

1)	Methetharimide	40 mg./Kg. body weight
2)	Amphetamine	4 mg./Kg. body weight
3)	Pentylenetetrazol	10 mg./Kg. body weight
4)	Methetharimide and Amphetamine	20 mg./Kg. + 2 mg./Kg body wt.
5)	Methetharimide and Pentylenetetrazol	20 mg./Kg. + 5 mg./Kg body wt.
6)	Pentylenetetrazol and Amphetamine	5 mg./Kg. + 2 mg./Kg body wt.
7)	Amphetamine and Metaraminol	2 mg./Kg. + 0.1 mg./Kg body weight

The following effects were observed after the injection of each drug:

1) Blood pressure

2) Ventilation

3) Respiratory rate

Seven dogs were used as controls. The effect of bleeding was observed for about two hours. This is to find out whether there is any considerable increase in blood pressure, especially during the second hour after the initial bleeding, when no bleeding is done.

The following results were obtained:

1. Methetharimide alone (40 mg./Kg. body weight) proved to be the best of all other single drugs and combinations because it produced the maximum increase of blood pressure (From 44 mm. Hg. to 87 mm. Hg.) and ventilation (From 4.05 liters per minute to 4.73 liters per minute) and these effects were maintained till the end of 60 minutes after the administration of the drug.

2. The next powerful drug was the combination of methetharimide and pentylenetetrazol, because this combination produced a significant increase of blood pressure (From 40.7 mm. Hg. to 65.5 mm. Hg.) and ventilation (From 4.3 liters per minute to 4.7 liters per minute), and these increases were steady and remained throughout the period of the experiment.

3. The third best was the combination of amphetamine and methetharimide. This combination produced an overall improvement on blood pressure (From 40 mm. Hg. to 68 mm. Hg.), ventilation (From 5.7 liters per minute to 6.3 liters per minute) and respiratory rate (From 28 per minute to 35.3 per minute). Even though there was a slight fall after the initial rise, the blood pressure began to improve gradually.

4. The rest of the combinations and single drugs either produced no significant effect or produced a negative effect. Amphetamine decreased the blood pressure, minute volume of ventilation and respiratory rate.

Therefore, the drugs of choice in hemorrhagic shock appear to be methetharimide alone, methetharimide and pentylenetrazol combination and methetharimide and amphetamine combination.

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DEDICATED TO

My Wife - Rukmani

and

My Son - Sekhar

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I wish to express my sincere gratitude and deep sense of appreciation to Dr. C. F. Cairy, Professor, Department of Physiology and Pharmacology for his interest and assistance, without which the work could never have been done.

I will be failing in my duty if I do not express my gratitude to Dr. B. V. Alfredson, Professor and Head of the Department of Physiology and Pharmacology for providing facilities and necessary help.

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CHAPTER I

INTRODUCTION

Even though several workers have attempted to produce a shock-like condition in experimental animals and tried to treat it, it is still an unsolved problem in the field of physiology, pharmacology and medicine.

Advanced shock constitutes a state of progressive deterioration which is not amenable to the types of therapy now available, probably because of fundamental biochemical changes that have developed as a result of prolonged deficiency of capillary flow. These changes may result from injury predominantly involving vital organs, such as the liver, or from cellular damage (Frank et al., 1953).

According to Frank et al., 1945, vasoconstriction is a normal response to a fall in blood volume, and excessive vasoconstriction caused by pressor drugs, even though it raises the blood pressure, is harmful to the system because it decreases flow through the capillaries. Pressor drugs are, therefore, said to be harmful to the system in shock in which there is a diminished blood volume, but the same worker reports that physicians still regard them as beneficial in shock. Several workers have tried different kinds of treatments in shock. Many regard fluid therapy, like blood transfusion, saline transfusion, etc., as beneficial in irreversible shock (Weil and Spink, 1955).

Frank et al., (1953) tried the therapeutic value of a variety of agents for the treatment of hemorrhagic shock which is not responsive to the replacement of all shed blood. He reports

that neither saline infusion nor drugs like Pitressin, Predrine and Coramine have any value in irreversible shock.

According to Goodman and Gilman and others, adrenergic blockade with dibenzyline provides protection against shock. The protection is probably largely due to the elimination of reflex compensatory vasoconstriction which ordinarily sustains blood pressure at the expense of blood flow to the vital centers during the early stage of development of shock. Therefore, Goodman and Gilman suggested a cautious therapeutic trial (Goodman and Gilman, 1950; Frank et al., 1953; Remington et al., 1950).

John et al., (1954) reports that replacement of blood volume is superior to vasopressor agents for improving cardiac output in shock.

Still others express that some of the vasoconstrictor drugs have proven to be a great help in shock. According to Sarnoff, the increased left auricular pressure is relieved and the left coronary flow is increased by pressor drugs, especially Metaraminol (Weil et al., 1956 and Sarnoff et al., 1954).

A large volume of literature is available for and against the use of vasoconstrictor drugs in shock (Frank et al., 1953; Goodman and Gilman, 1950; Remington et al., 1950; Weil, 1955).

The object of this project was to find out the effect of some of the analeptic drugs, singly and in pairs, in artificially induced shock in overanesthetized dogs.

CHAPTER II

REVIEW OF LITERATURE

A. Shock.

During the early part of the 19th century when the field of physiology was not well developed, considerable speculation occurred as to the cause of shock. The sudden collapse of vital processes attributable to no apparent pathological condition remained a mystery. Meanwhile, rapid progress was being made in the field of physiology. During 1825 the Weber brothers demonstrated that the pulse travels as a wave and in 1845 they discovered that the vagus nerves are not motor but inhibitory to the heart. The kymograph was invented by Ludwig in 1847 and the arterial pressure was recorded for the first time. During 1876 considerable interest was aroused in the subject of shock in France by Blum who summarized the current evidence favoring cardiac default from reflex vagal action. In the latter half of the nineteenth century, accumulation of physiological knowledge as to the control of the circulation served to focus attention on circulatory failure and the important features of shock (Wiggers, 1950).

There are various definitions of shock and the most important ones are as follows (White et al., 1947):

Moon: (1938) A circulatory deficiency, not cardiac nor vasomotor in origin, characterized by a decreased volume of blood, reduced cardiac output and by hemoconcentration.

Wiggers: (1950) Shock can be defined as a clinical syndrome or as an abnormal physiological condition in which deterioration of cellular functions occur until an irreversible state is reached.

Minot & Black: (1940) Peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume

of intravascular fluid.

Freeman: (1940) The clinical condition characterized by progressive loss of circulating blood volume, brought about by the tissue anoxia which results from inadequate circulation.

Harkins: (1940) A progressive vasoconstrictive oligemia initiated by traumatic local fluid loss, either whole blood or plasma or both, accompanied by decreased cardiac output, diminished volume flow, lowered venous pressure, decreased oxygen consumption, arteriolar vasoconstrictiom, acapnia and secondary blood pressure fall; and perpetuated by a summation of these factors and possible hyperpotassemia, increased generalized capillary permeability anoxia, action of tissue metabolites and deficiency of adrenal cortex hormone.

Shock may be defined as a state of circulation where there is disparity between the volume of the vascular bed and the circulating blood volume. It may also be defined as a condition where, due to either cardiac failure or peripheral vascular failure, there is a marked fall of blood pressure. This may occur (1) when the circulating blood volume is rapidly reduced by hemorrhage, loss of plasma or excessive loss of body fluid or any combination of these, leading to depletion of blood volume, (2) when the volume of the vascular bed is rapidly increased, without comparable increase in blood volume. This may occur rapidly as a result of extensive loss of tonus of the small arterioles, veins and capillaries (David et al., 1951), or (3) when deterioration of myocardial expulsive power contributes to the circulatory failure (Wiggers, 1950).

Kinds of Shock

It may be classified as primary and secondary shock. Primary shock is neurogenic in origin and occurs immediately due to intense pain, trauma, extensive burns, etc. Secondary shock is due to loss of circulating fluid, blood or plasma, resulting in decreased blood volume or gradual fall of blood pressure. In secondary shock there will be hemoconcentration and in primary shock there is no hemoconcentration (David et al., 1954).

Experimental Hemorrhagic Shock

Various methods were adopted by different workers to produce shock experimentally. Wiggers (1950) produced shock in etherized dogs by exposing and manipulating the intestines for a period of 1-3½ hours. He adopted no aseptic precautions and the dogs were allowed to recover from the anesthesia. After an hour or two the effects of anesthesia had passed off, the dogs showed many of the accepted clinical signs of shock, such as apathy, muscular weakness, reduced sensibility to surface stimuli, rapid breathing, and rapid heart rate. Out of 10 dogs used by Wiggers in this experiment only in four animals was the blood pressure reduced to 50 - 60 mm. Hg., which is the indication of shock (Wiggers, 1950).

The same author, in 1918, produced shock in 16 animals out of 21 animals by periodic testicular traumatization plus stimulation of the sciatic nerves under anesthesia.

Edward and Wiggers (1918) produced shock in dogs that were anesthetized with ether, by gastric massage. This was considered to be superior to intestinal manipulation. The

technique consisted of introducing the clenched hand into the abdomen through a small incision and bringing the knuckles down 50 to 60 times per minute upon the duodenal end of the stomach. This procedure produces shock, not by traumatization of the stomach, but by hyperventilation and acapnia, which result from pushing the diaphragm upward with each punch (Wiggers, 1950).

Green and his associates (1944) produced ischemia and compression of both hind legs for 5 to 6 hours under anesthesia. They observed progressive circulatory failure after release of compression and recovery from anesthesia.

Gregerson and Root (1947) produced shock by muscle contusion in temporarily etherized dogs. They observed that, like human beings, dogs in shock did not shiver when body temperature was reduced several degrees.

Hemorrhagic shock is the only one that can be produced experimentally without giving any anesthesia. According to Swingle and his associates (1934), unanesthetized dogs react very differently to withdrawal of a large quantity of blood. One dog may display "symptomatic shock after loss of only 25 cc./Kg. while another appears quite normal shortly after withdrawal of 35 cc./Kg. or more".

In recent years standardized hemorrhagic shock is produced by various workers. A single rapid bleeding which reduces the mean arterial pressure to 50 or 40 mm. Hg. may cause irreversible shock but only if the animal's compensatory ability is low (Wiggers, 1950).

Standardized Experimental Shock

The technique used for the production of standardized shock is very important to the study of the shock problem. The most

important ones are:

1. Skeletal muscle trauma
2. Ischemia produced by compression tourniquets or other means
3. General contusions
4. Burns and scalds
5. Hemorrhage
6. Bacterial toxins
7. Drugs - Histamine, peptone, etc.

Skeletal Trauma

Infliction of skeletal trauma by hammer blows is an old procedure adopted to produce experimental shock. The amount and degree of muscular trauma inflicted and the degree of swelling which results depend on the force as well as frequency, number and distribution of the blows. It also depends upon the size of the animal and susceptibility of the skin and muscles (Best et al., 1940); Blalock et al,, 1942). Research workers in the University of Chicago are able to produce shock consistently by applying blows with an 800 Gm. padded hammer to all faces of the thigh and upper leg of etherized dogs. In this, bones were not fractured and large vessels were not ruptured (Phemister et al., 1945).

Another group of workers in the University of Toronto (Best and Solandt, 1940; Solandt et al., 1941) produced shock by applying 1000 to 5000 light blows with a rubber mallet to the flexor muscles of each hind limb of anesthetized animals. In this, the muscle bundles were red and swollen but rarely severed transversely and never comminuted.

The Columbia University group also produced shock by applying 700 to 1000 blows with a 182 Gm. rawhide mallet (Gregorson et al., 1947).

In these experimental shock there will be local loss of fluid from injured capillaries. The volume of transudate which accumulates varies with capillary pressure and degree of injury. The edema is, therefore, variable. Opinions differ as to whether this mitigates the course of subsequent shock.

The degree of muscular injury is a second important factor in the production of shock, but some workers do not agree that crushing or maceration is indispensable (Wiggers, 1950).

A third factor in skeletal trauma is the passage of nociceptive impulses from traumatized regions. Some workers think that this factor is important but subsidiary to reduction in blood volume and others believe that the nociceptive impulses are not important.

Ischemic and Compression Injuries

This procedure eliminates pulping of muscles, but adds the factors of prolonged ischemia and greater stimulation of afferent nerves. Duncan and Blalock (1942) devised a press which they applied at a pressure of 500 lbs. for 5 hours to the hind limb of an anesthetized dog, and the animal developed shock after the pressure was released. Swingle and his associates (1942) adopted the same method and produced shock regularly in dogs by applying a pressure of 750 lbs. for 7 hours.

Tourniquet Shock

By this method, standardized shock can be produced. This method is adopted by many workers and it is very simple. The ischemia is produced by the use of rubber bands or clamps (Green et al., 1944; Haist et al., 1944). Such ischemia is produced in four legs (Rosenthal

et al., 1942; Chambers et al., 1944). Intervals of ischemia ranging from 2½ to 15 hours have been used but as a rule compression of both hind legs for 3 to 4 hours is regarded as adequate to produce nearly 100 percent mortality within 24 hours after removal of tourniquet (Rosenthal et al., 1942; Chambers et al., 1944; Zweitach et al., 1945). This procedure is suitable for small animals and particularly valuable in shock problems requiring large number of animals.

The shock procedure by this method is not due to fluid loss alone but is the resultant of a complicated series of reactions involving many variables. Hemorrhage and infection may also contribute. Many workers tried to apply this method on dogs, cats and rabbits (Hechter et al., 1945).

Generalized Contusions

Noble and Collip (1942) devised an apparatus so as to produce graded reproducible types of generalized trauma in rats. The rats can be caused to fall any number of times at regular intervals through a constant distance. This technique eliminates the complicating effects of anesthesia, hemorrhage and infection. They found that different strains of rats had different degrees of resistance.

Burns and Scalds

This shock depends upon the type and degree of heat applied, the duration of exposure and the surface area involved. This consists in producing required thermal injury. Scalding by immersion in hot water for measured short intervals of time has proven to be the most satisfactory procedure. Such methods have been standardized by many workers for use on mice, rats, rabbits, cats and dogs. The barbiturate is the best anesthesia in this case (Wiggers, 1950).

Hartman (1945) found that scalding 50 to 60 percent of the body surface of dogs with steam is not fatal. According to Netsky and Leiter (1943) dogs consistantly developed fatal shock in 4 to 19 hours when immersed to the axilla for 60 seconds in water at a temperature of 72 c., but immersion for only 5 seconds in water at 80 c. is required. It is said that shock produced by this method is characterized by progressive circulatory failure and marked hemoconcentration.

Hemorrhagic Shock

According to Wiggers (1950) reduction in blood volume is one of the important factors in the production of various types of traumatic shock. So withdrawal of a specific volume of blood will be an advantageous method to produce standardized shock. Some workers believe that loss of blood is not the only factor in the production of shock. According to Blum (1876) shock is hemorrhage and hemorrhage is shock. According to Moon (1938) shock involves damage to capillary endothelelium generally and represents a state in which fluid leaves the blood stream, whereas hemorrhage causes no such damage to the capillaries and, therefore, represents a state in which tissue fluid enters the blood stream. Moon furnishes details regarding the similarities and dissimilarities between hemorrhage and shock. They are as follows:

Similarities

1. Increased respiratory rate
2. Reduction in cardiac output
3. Declining arterial pressure
4. Cardiac acceleration

5. Peripheral vasoconstriction

6. Discharge of reservoir blood into the general circulation

7. Low basal metabolism

8. Decreased alkali reserve

9. Decreased serum protein

10. Increased blood sugar

11. Death due to inadequate circulatory function

Dissimilarities

Blood	Shock	Hemorrhage
Hemoglobin and Erythrocytes	Increased	Decreased
Specific gravity	Increased	Decreased
Non-protein nitrogen	Increased	Decreased
Potassium	Increased	No change
Coagulation time	Lengthened	Shortened
Blood Transfusion	Often ineffective	Effective
Necropsy findings		
Petechial hemorrhage Edems, congestion	Present	Absent
Visceral ischemia	Present	Absent

Many workers believe that loss of blood does not cause all the signs of shock immediately but it may cause shock if the arterial hypotension following hemorrhage persists for a considerable length of time (Blalock et al., 1942; Penfield, 1914). Both duration and bleeding are important in producing shock. The volume required to be bled to produce shock is in between the lethal bleeding volume and the sublethal bleeding volume. This volume, according to Wiggers, is called the critical bleeding volume. This volume

ranges from 3.7 to 8.86 percent of body weight (Taylor et al., 1943). Wiggers reports that he was able to produce shock by bleeding about 30-55 cc./Kg. of body weight in an anesthetized dog. H. C. Wiggers (1945) used unanesthetized dogs and he also found the same result.

The development of shock or demise is determined by the residual volume that remains in the body after bleeding and hence bleeding volume depends on the initial volume of blood that the animal possesses. Many workers (Gibson et al., 1938) have estimated the quantity of blood in the normal dog. According to them the volume ranges from 73 cc. to 130 cc./Kg. body weight of the dog. (McQuarrie and Davis - 73 - 114 cc./Kg. Walcott - 81 - 122 cc./Kg.). Another factor that has to be considered is the ability of the animal to replace the circulating blood lost by hemorrhage with tissue fluid and corpuscles. The ability of the compensatory cardiovascular mechanism which keeps the residual volume in circulation effectively enough to maintain a minimal flow through vital organs is also an important factor.

Standardized Hemorrhagic Shock.

According to Wiggers, the residual volume and the blood flow through tissues must be just enough for a sufficient period to produce shock. There are two methods by which hemorrhagic shock can be produced.

1. By bleeding a definite volume of blood according to body weight.
2. Bleeding to a particular pressure.

Weston and his associates (1943) removed 20-30 percent of

the blood volume within a period of 30 minutes. After 30 minutes, when compensation was thought to be complete, a second bleeding equal to 10-15 percent of the estimated blood volume was removed. If this did not reduce the mean arterial pressure to 45 to 50 mm. Hg., the bleeding was repeated. Shock was considered to have been produced if any two of the following factors were satisfied:

1. Hypotension below 70 mm. Hg.
2. Blood CO_2 less than 26 volume percent.
3. An increase in circulation time beyond 20 seconds.

Cleghorn and his associates (1943) anesthetized the dog with Pentothal sodium and bled them rapidly from the femoral artery until pressure was reduced to 70 mm. Hg. They maintained pressure below 70 mm. Hg. for another 75 minutes by additional bleeding if necessary. About 55 percent of the dogs died with the changes in the gastrointestinal mucosa which was characteristic of shock.

Werb, Cosby and Wiggers (1942) think that it is difficult to distinguish between simple hypotension and hemorrhagic shock especially in anesthetized animals. The most important factor is that the shock cannot be reversed by infusions of blood. These workers bled the animal through a femoral artery at a rate of 50 cc. per minute until the mean arterial pressure was reduced to 50 mm. Hg. This pressure was maintained for 90 minutes and additional blood was removed if necessary. At the end of 90 minutes the blood pressure was further reduced to 30 mm. Hg. by further bleeding and this pressure was maintained for another 45 minutes. If the pressure fell very rapidly, all the withdrawn blood (heparinized) was reinfused in a femoral vein. Wiggers reports about 82 percent

mortality within 6 hours after reinfusion.

Classification of Hemorrhagic Shock

According to Wiggers, hemorrhagic shock can be divided into

1) Oligemic Shock - that develops during preinfusion period. According to severity, it is further divided into
   a. Simple hypotension
   b. Impending shock
   c. Critical irreversible shock
2) Normovolemic shock - develops after the infusion of the withdrawn heparinized blood and is mainly due to the rapid decline of arterial pressure again.

B. Analeptics

Analeptic may be defined as a drug capable of stimulating the normal central nervous system and which is used for the purpose of overcoming a depression of that system (Eckenhoff et al., 1945). According to them, analeptics may be classified into four groups.

1) Those which have primary stimulant action on the nervous system and the value of which depends on that action. Picrotoxin, pentylenetetrazol, caffeine, strychnine and atropine belong to this class.

2) The analeptic effect of this group of drugs is due to reflexes from one source or another. The most powerful of those reflexes are those from carotid and aortic bodies - cyanide, sulfides and nicotine belong to this group, but are not used due to their toxic properties. Irritants of the nose, mouth and

stomach, smelling salt, apiritus Ammonia Aromaticus, whisky, brandy, etc., also belong to this group.

3) Drugs which stimulate both the C.N.S. and the cardiovascular system and which in sufficient dosage produce not only convulsions but also hypertension and tachycardia. The analeptic effects of this group presumably depend not only on the direct stimulation of nerve cells (like group one substance), but also an increase in the blood supply. This group includes particularly all of the aromatic sympathomimetic amines. Amphetamine, epinephrine, ephedrine, etc., belong to this group.

4) Substances which exert a specific stimulant effect on the nervous tissue by entering into biochemical reactions. These include intermediate products of carbohydrate metabolism, such as pyruvate, succinate and fumarate as well as the components of vitamine B Complex.

Mechanism of Analeptic Action

Depression caused by narcotic drugs is the most amenable to analeptic drugs. According to Eckenhoff and his associates (1945), other depressions are less likely to be helped and may be intensified by analeptic therapy. The suggested mechanisms of action of these drugs are (Goodman and Gilman, 1955; Beckman, 1952):

1) Direct chemical inactivation or neutralization of the narcotics by the analeptics.

2) Diminution in the effective concentration of the narcotic drugs within the nerve cell.

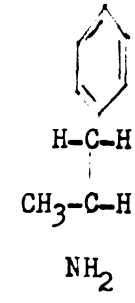
3) Physiologic antagonism, i.e., increased excitability of nerve cell overshadowing a continuing depressant effect.

According to Dripps and Larable, the analeptics facilitate the synaptic transmission and barbiturates depress this process (Eckenhoff et al., 1945).

Even though several explanations are given, the exact mechanism of action of analeptics is not clear.

Amphetamine

Amphetamine was first prepared by Edeleanu (Burger, 1951). It has the following chemical structure and occurs in d, l and racemic forms (Beyer, 1946). The sulphate is a stable salt, soluble in water. The important clinical uses of amphetamine were recognized by Alles and the drug was marketed under the brand name of Benzedrine. The d - form is from two to four times more active as a central stimulant than the racemic mixture (Burger, 1951). This drug resembles ephedrine in a number of aspects but differs from it chiefly in possessing greater ability to stimulate the higher nervous centers, particularly the cortex. It enjoys a wide range of therapeutic uses, some of which are not shared by other sympathomimetic drugs. This drug possesses about 1/100 to 1/200 the pressor potency of epinephrine, but the cardiovascular effect is longer in duration (Goodman and Gilman, 1955), and much less toxic when compared to epinephrine (Burger, 1951).



The peripheral sympathomimetic effects of amphetamine are the result of direct action of the drug on receptors of muscles and glands innervated by adrenergic nerves, as is true for epinephrine. Amphetamine differs from epinephrine in that it exhibits tachyphylaxis (decreasing response to repeated administration) and does not manifest

enhanced activity after cocaine or denervation (Goodman and Gilman, 1955). Amphetamine markedly potentiates the pressor response to epinephrine. It is a stronger inhibitor of aminoxidase than ephedrine.

The blood pressure is raised, the peripheral vessels are constricted, and the heart muscle is stimulated. It also stimulates the cerebrospinal exis, especially the brain stem and cortex. Attempts have been made to quantitate its potency as a central stimulant in comparison with other analeptics like picrotoxin, Metrazol, etc. It has been proven a potent drug for stimulating the medullary respiratory center depressed by anesthetic, narcotic and hypnotic drugs (Goodman and Gilman, 1955; Beckman, 1952). It affects respiration in two ways, by stimulating the respiratory center and by dilating the bonchioles (Goodman and Gilman, 1955).

Adequate doses usually cause a rise in both systolic and diastolic pressures and an increase in cardiac output. The effects are apparently accompanied by a direct myocardial action and by peripheral constriction of arterioles.

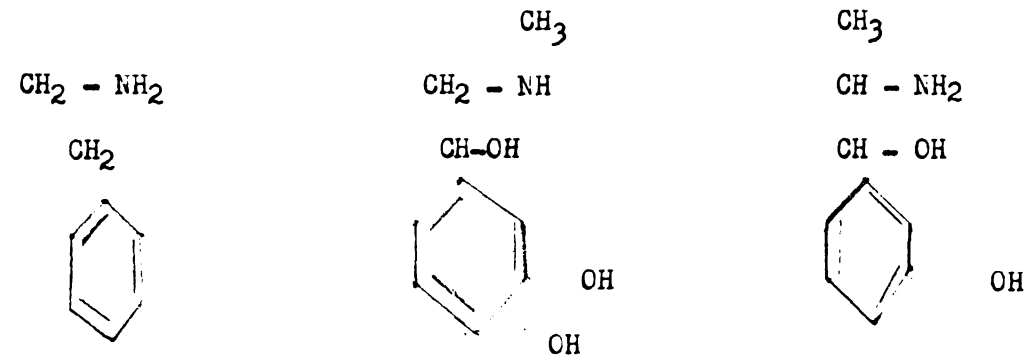
The most undesirable side action is promotion of wakefulness in patients in whom the prevention of normal sleep is not intended as a therapeutic measure (Burger, 1951).

Amphetamine is no doubt an effective barbiturate antagonist, but its use in shock is limited. Most of the available literature speaks against the use of the sympathomimetic drugs in shock (Goodman and Gilman, 1955; Frank et al., 1945; Remington et al., 1950).

Metaramiol

(Aramine)

This is a sympathomimetic drug like amphetamine. Beta-phenylethylamine is the structural nucleus of the group which includes epinephrine as its prototype, and the closely related compounds, ephedrine, phenylephrine and amphetamine. Minor modification of structure permits a wide selection of related pharmacological action (Weil, 1955).



Beta-phenylethylamine Epinephrine Metaraminol

Aramine is the tradename for metaraminol. Aramine has been studied extensively and the results indicate the value of this drug in shock.

According to Bayer (Merck, Sharp and Dohme Laboratory Report), the vasopressor properties of Aramine are similar to, but much more potent than, those of ephedrine. The augmented left auricular pressure and decreased coronary flow that occur during oligemic shock in dogs can be reversed by the administration of Aramine (Sarnoff et al., March, 1954). Sarnoff reports (Sarnoff, et al., Sept. 1954) that in an experiment designed to determine the effect of Aramine on the survival of dogs with severe hypotension

due to hemorrhage, 50 of the animals survived, in contrast to 10.5 percent survival in the control group.

According to Bayer, its pressor effect is decreased, but not reversed by adrenolytic drugs that reverse the vascular response to epinephrine (Merck, Sharp and Dohme Laboratory Report). The same worker reports that there is no tachyphylactic response to repeated injections of Aramine. Sarnoff et al., (1954) reports that intravenous dose of Aramine in vagotomized dog causes an increase in cardiac output, left main coronary artery flow, and aortic and pulmonary arterial pressure. He says that Aramine has a bivalent activity in that it increases myocardial vascular resistance and tone. Following the administration of Aramine the myocardium does not require a great coronary flow per unit of work.

Moyer et al (1954) reports that when Aramine is administered to correct severe hypotension, the blood pressure is elevated and renal blood flow and glomerular filtration rate are increased.

According to Beyer (Laboratory Report), Aramine either produces no effect or a moderate slowing of respiratory rate in the normal or anesthetized dog. Where the rate is decreased there is usually an increase in tidal volume.

Moyer (July, 1955) et al., reports that the elevation of blood pressure following the administration of Aramine in patients in shock is accompanied by increased glomerular filtration rate, renal blood flow and urinary output. The duration of action of Aramine is 2½ to 3 times more than epinephrine with regard to their pressor activity. According to Madonia et al., (May, 1954) the only electrocardiographic change following the use of Aramine was a

a decrease in heart rate. According to Livesay et al., (May, 1954) Aramine is a potent synthetic vasopressor agent which has the advantage of prolonged duration of action, minimal evidence of renal vasoconstriction, no detrimental alteration in cardiac output. He says that this drug may be of practical application in the treatment of shock.

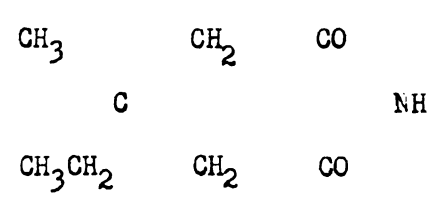
The indication for the use of a vasopressor agent is most likely to occur with hypotension due to a nonsurgical cause (Moyer, Oct., 1954). Even when the hypotension is due to hemorrhage and other surgical etiologies, vasopressor agents may prove to be a temporary expedient for maintaining blood pressure in patients who do not obtain a prompt and adequate response to blood and fluid administration.

According to a laboratory report of Merck, Sharp and Dohme, both the systolic and diastolic blood pressure are raised following intravenous infusion or intramuscular or subcutaneous injection. The onset of the pressor effect occurs within 1 to 2 minutes after intravenous infusion, in approximately 10 minutes after intramuscular injection and from 5 to 20 minutes following subcutaneous injection. The duration of action varies from 20 minutes to one hour. The cautious use of a properly selected pressor drug, which has a moderate positive inotropic effect on the heart without having a tendency to produce arrythmias, and which also produces a moderate peripheral vasoconstriction, may be life saving in certain cases (Merck, Sharp and Dohme Laboratory Report).

Methetharimide

(Mikedimide)

Methetharimide is chemically 3, 3-methylethyl glutarimide, having the following structural formula. It is related to barbiturates by the similarity of the ring system. Mikedimide possesses a poor solubility in water. According to the Technical Bulletin Parlam Corporation, Mikedimide appears to assert a direct antagonism on barbiturate on a milligram for milligram basis and also the antagonism in reversal of barbiturate anesthesia by Mikedimide in directly proportionate to the plane of anesthesia induced by barbiturate, and an overdose of the drug can induce mild convulsion which can easily be reversed by a small dose of barbiturate.



Shaw et al., (1954) reports that cats were aroused to a state of reflex activity and semiconsciousness from the narcosis of pentobarbital (60 mg./Kg.). He also observed that it stimulated the respiratory center markedly by action on the barbiturate depressed respiration, and the rate was as much as double for a period of 5 - 10 minutes after injection of Mikedimide.

Shulman et al., (1955) reports that if there is regression after the patient has been brought to the safe state, a further small dose may be given as required and according to him, regression is more likely to occur when coma has lasted for a long time before treatment is started or if the barbiturate is a long acting one.

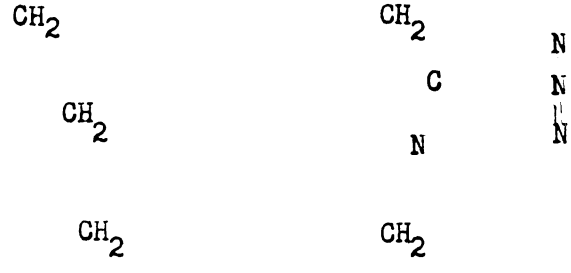
Harris (Jan., 1955) reports that Mikedimide is a barbiturate antagonist of real clinical worth and to omit to use it in treatment of barbiturate poisoning is to run the risk of bronchopneumonia that is so often fatal in such cases.

Several reports are available regarding the antagonistic action of this drug, (Shulman, 1955; McElligot, 1955; Shaw, 1955; Harris, 1955; Montudio, 1955), but there is not much of evidence to show that this drug is useful in shock.

Pentylenetetrazol

(Metrazol)

Metrazol, previously called cardiazol in Europe, is the name of 4, 5 - pentamethylenetetrazol whose structure contains the unusual combination of two condensed heterocyclic rings, one five membered and one seven membered.



Metrazol is one of the most rapidly acting although not the most effective analeptic. Its ability to arouse individuals from barbiturate induced sleep has been found useful in terminating mild hypnotic intoxication since only small doses of metrazol are needed for this purpose. Large doses of the drug produces convulsions. It is quickly metabolized and destroyed in the liver and its action is, therefore, of brief duration (Burger, 1951).

According to a laboratory monograph of Knoll Pharmaceutical Company, metrazol exerts its action mainly on the respiratory and vasomotor centers. Metrazol also improves synaptic transmission. Like Mikedimide, it is a good barbiturate antagonist but according to Werner, it ranks next to picrotoxin (Werner, 1938). Metrazol has no important effect on coronary flow, blood pressure or heart rate in intact animals (Stoland, 1937).

Respiratory, vasomotor and vagal centers are stimulated and the reflex activity of the spinal cord is markedly increased. The analeptic action is prominent when directed against the depression caused by barbiturates. Not only is motor activity restored, but failing respiration and circulation are stimulated through the medullary action of the drug (Goodman and Gilman, 1955).

Beckman (1952), reports that pentylenetetrazol has an awakening effect and in addition it maintains adequate respiration, circulation, metabolism and body temperature through direct stimulating actions on the medulla.

Woodbury et al., (1941) reports that arterial pressure effects are different in man and in dogs. In man, convulsant doses of metrazol increase the arterial pressure by an average maximum of 100 mm. Hg. Vasoconstriction plays only a minor role. The main rise of blood pressure is limited to the duration of, and is produced by, the contraction of the skeletal muscles. In man, these contractions increase markedly the extravascular pressure in most areas of the body, squeezing the blood vessels and elevating the blood pressure, but do not increase the effective pressure to the vital areas. But in unanesthetized dogs, subconvulsant and convulsant doses produce

large prolonged elevation of blood pressure which is due to vaso-constriction.

Metrazol is accepted and used as an effective analeptic, especially in barbiturate poisoning (Eckenhoff, 1945; Burger, 1951; Burn, 1939; Loewe, 1955). Not much literature is available regarding its use in shock. According to Stoland et al., (1937), Metrazol has practically no important effect on the coronary flow of dog. Hence, its use in shock is doubtful.

CHAPTER III

MATERIALS AND METHOD

Thirty six dogs of various breeds and different sizes, varying from 7 kgs. to 23 kgs., were used. Apparently healthy dogs were selected and they were carefully weighed and deeply anesthetized with 3% sodium pentobarbital solution, containing 10% ethyl alcohol, (11 cc. of 95% ethyl alcohol in 100 cc. of the prepared solution) at the rate of 40 mg./kg. body weight, administered intravenously. (First 30 mg./kg. body weight followed by 10 mg./kg. after about 10 minutes).

A linear incision was made on the ventral aspect of the neck of the animal, the skin was reflected, the trachea was exposed and a tracheal cannula was introduced. The tracheal cannula was connected to the flow meter through a pair of valves causing inspiration from room air and exhalation through the flow meter.

The flow meter is nothing but a gas meter or wet test gas meter (Cat. No. S. 39445. E. H. Sargent and Co., Detroit). This instrument is used for the measurement of gas volume transfer in connection with colorimetric determinations and for a wide variety of other gas tests. It employs a rotor sealed by water, maintained at a constant level. Accurate measurements are possible in transfers under very low pressure differentials. This instrument is modified in this laboratory to suit our requirements. An electrical dial contact, which is closed as 250 cc. of air passes into it, is built and it is used with a signal magnet. The principle indicator needle makes one complete revolution for each 3 liters of air.

The volume of the expired air was recorded on a kymograph by an ink-writing lever attached to the signal magnet which is connected to the flow meter through batteries. The signal magnet marks on the kymograph for every 250 cc. of air exhaled by the animal. A tambour was connected to a side arm of the flow meter for recording the rate of respiration. Instead of a paper belt, a continuous recording device was attached for recording continuously for 2 to 3 hours or even more if necessary.

One of the carotid arteries was exposed from the carotid sheath and a bulldog forceps was applied to the cardiac end of the artery and the cephalic end was tied with fine thread. Then the artery was cannulated with a three-way cannula which was connected to the mercury manometer through rubber tube and pressure bottle, containing 6% sodium citrate solution, for recording blood pressure on the kymograph by an ink-writing lever.

The femoral artery was cannulated with a three-way cannula, connected to a pressure bottle containing 6% sodium citrate solution, to prevent clotting in the cannula after bleeding. Bleeding was done through the side tube of the cannula.

One of the femoral veins was cannulated and connected to a burette, containing physiological saline. This preparation is necessary for injection of drugs.

All the writing levers, tambours, etc., were so arranged that all the points were in the same vertical line. Time was also recorded with a signal magnet. The time magnet was always adjusted in this experiment to register the zero pressure.

After preparing the dog and making necessary connections, the normal recording was taken for a few minutes. Then the dog was rapidly bled through the cannula, connected to the femoral artery, to reduce the blood pressure to 70 mm. Hg. and the blood collected in a graduated jar. The quantity of blood to be removed to bring down the blood pressure to 70 mm. Hg. was noted. After the first bleeding, about 10 minutes time was allowed and if there was rise of blood pressure above 70 mm. Hg., the animal was bled again. Thus, the blood pressure was kept below 70 mm. Hg. or slightly lower than that for at least an hour. After an hour, if there was no further significant rise of blood pressure, the following drugs were administered either alone or in combination of two.

(1) Amphetamine

(2) Methetharimide

(3) Pentylenetetrazol

(4) Methetharimide and Amphetamine

(5) Methetharimide and Pentylenetetrazol

(6) Pentylenetetrazol and Amphetamine

(7) Amphetamine and Metaraminol

The commercial products of these drugs are marketed under different tradenames. The tradenames, the strength of the solution used and the doses are as follows:

Official Name	Tradenames	Strength of the Solution	Dose in mg./ kg. body wt. if used alone	Dose in mg./ kg. body wt. if used with other drug
Amphetamine	Amphetamine *	5%	4	2
Methetharimide	Mikedimide **	3%	40	20
Pentylenetetrazol	Metrazol ***	10%	10	5
Metaraminol	Aramine ****	1%	-	0.1

The dose was calculated according to the body weight as noted above and injected through the cannula, connected to the femoral vein. After the injection of the drug a few ml. of saline was run in, in order to make the drug circulate in the blood stream. The result was recorded on the kymograph for about an hour or even more if necessary, At the end of the experiment, if the animal was alive, saturated magnesium sulphate is injected through the femoral vein to destroy the dog.

At least four dogs were used for each drug. The effect of these drugs on the rate of respiration, ventilation and blood pressure were recorded.

Seven dogs were used as controls. These dogs were anesthetized in the same way and connections were made for bleeding and recording changes in blood pressure, respiratory rate and ventilatory volume. After bringing down the blood pressure to 70 mm. Hg., the pressure was maintained at that level or slightly lower than that for about two hours or even more. After two hours if the animal was alive, it was destroyed with saturated magnesium sulphate.

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* Haver Glover Laboratories, Kansas City, Mo.

** Parlam Corporation, Englewood, N. J.

*** Knoll Pharmaceutical Co., Grange, N.J.

**** Merck Sharp and Dohme, Philadelphia.

CHAPTER IV.

RESULTS

The quantity of blood removed to reduce the blood pressure to 70 mm. Hg. varied tremendously from 25 cc./Kg. body weight to 70 cc./Kg. body weight. 25 cc. of blood per Kg. body weight was removed in 8% of the animals and 70 cc./Kg. body weight was removed in 2.8% of the animals. In 61% of the animals, 35 cc. to 40 cc. of blood per Kg. body weight was removed. The average quantity of blood removed to reduce the blood pressure to 70 mm. Hg. was 37 cc./Kg. body weight. The speed with which the blood was removed had no effect on the final blood pressure, provided the blood pressure was not reduced to below the critical level. Usually the blood pressure went up again after the first bleeding and hence more than one bleeding was necessary to keep the blood pressure under 70 mm. Hg., but after about 30 to 45 minutes there was no appreciable rise. Therefore, there was no need to bleed further after keeping the blood pressure below 70 mm. Hg. for about an hour.

As the blood pressure was reduced to 70 mm. Hg., the respiratory rate and ventilatory volume were found to increase rapidly. There was an increase of 52% of respiratory rate and 70% of ventilatory volume up to the time of administration of the drugs.

Controls Fig. 1 (Dog Nos. 8 to 14)

Seven dogs were used as controls. In all the seven dogs, blood pressure was reduced to 70 mm. Hg. and maintained at that level or slightly lower than that for about two hours, by subsequent bleedings if necessary, but no animal was bled after an hour of first bleeding. Out of seven dogs, five died and two were destroyed

at the end with magnesium sulphate after about 2½ hours. Out of those five dogs which died, two died between 70 and 110 minutes and the remaining three died after two hours. No increase of blood pressure above 70 mm. Hg. was noticed during the second hour when no blood was removed.

Amphetamine Fig. 2 (Dog Nos. 15, 17, 18 and 19)

This drug was used alone in four dogs, weighing from 12 Kgs. to 18 Kgs. All the dogs were kept under low blood pressure as described before and the drug injected slowly through the femoral vein. Except one animal (Dog No. 17) which showed slight increase of blood pressure, no other animal showed any increase of blood pressure, but all of them remained alive and were destroyed finally.

The average blood pressure response of these four dogs showed a decrease. Within ten minutes after the administration of the drug the blood pressure dropped from 58 mm. Hg. to 43 mm. Hg. and there was no further fall of blood pressure but a slight increase (47.5 mm. Hg.) was noticed at 60 minutes. The ventilation volume was reduced from 5.8 to 5.3 liters per minute. This slight decrease was maintained for about an hour. The initial respiratory rate of 35 per minute was maintained throughout, showing no change till the end of the experiment.

Pentylenetetrazol Fig. 3 (Dog. Nos. 20 to 23)

This drug was used in four dogs weighing from 9 Kgs. to 20 Kgs. In one of these four dogs, the blood pressure dropped below the critical level and the animal died an hour after the first bleeding and the other dogs were destroyed an hour after the administration of the drug.

Slight improvement in blood pressure was noticed in those three dogs. The average increase of blood pressure was from 46 mm. Hg. to 55 mm. Hg. within ten minutes after the administration of the drug and this improvement was maintained without any change for about an hour. There was no significant change in the respiratory rate and the initial rate of 25 per minute was more or less maintained till the end of the experiment. The minute volume increased from 5.3 liters per minute to 5.56 liters within ten minutes and to 5.9 liters within 20 minutes after the administration of the drug. The minute volume dropped to 5.6 liters per minute at 30 minutes and remained till the end of the experiment.

Methetharimide Fig 4 (Dog Nos. 4 to 7)

This drug was used alone in four dogs weighing from 9 Kgs. to 13 Kg. Dog No. 6 died about 30 minutes after the administration of the drug and the rest of the animals were destroyed an hour after.

There was a remarkable improvement in blood pressure in all the four dogs after the administration of the drug and the increase was from 44 mm. Hg. to 65 mm. Hg. at 10 minutes, to 84 mm. Hg. at 20 minutes and to 87 mm. Hg. at 40 minutes after injection of the drug. This increase began to decline to 76.6 mm. Hg. at 60 minutes. There was no significant improvement in the respiratory rate. The initial rate of 33 per minute was increased to 33.8, 33.1 at ten minutes and twenty minutes respectively. This slight increase in rate was followed by a slight decrease. The rate was reduced from 33.1 per minute to 31.6 within ten minutes and this reduced rate was maintained till the end of 60 minutes. Slight improvement in ventilation was also

observed. The ventilation increased from 4.05 liters per minute to 4.5 liters per minute at ten minutes and to 4.73 liters at 60 minutes.

Pentylenetetrazol and Amphetamine Fig. 5 (Dog Nos. 32 to 35)

Four dogs, weighing from 15 Kgs. to 20 Kgs. were used for this combination of drugs. The dose was calculated according to the body weight as already mentioned and each drug was drawn in a separate syringe and injected one after the other, using the same needle. All the four dogs remained alive until the end of the experiment and were destroyed at the end.

There was a sudden fall of blood pressure from 53.5 mm. Hg. to 49 mm. Hg. at ten minutes and this fall was followed by a steady rise of pressure up to 66 mm. Hg. at 60 minutes. Appreciable response was also noticed in the average respiratory rate and the increase was from 29 per minute to 36.8 at 20 minutes and to 35.7 at 30 minutes after the injection of the drugs. This increase of 35.7 was maintained for about 30 minutes and it dropped to 34.5 per minute at 60 minutes. There was a slight increase in ventilation in all the four dogs. The average volume increase was from 5.8 liters per minute to 6.2 liters per minute at ten minutes and again it dropped to 6 liters. This rate was maintained till the end of 60 minutes.

Methetharimide and Amphetamine Fig. 6 (Dog Nos. 24 to 27)

This combination of drugs was tried in four dogs. The drugs were injected one after another with two separate syringes. Out of four dogs, dog no. 25 died 55 minutes after the administration of the drugs and the rest were destroyed as usual at the end of the experiment.

All the four dogs showed significant increase of blood pressure. The average increase of pressure was from 49 mm. Hg. to 68 mm. Hg. within ten mimutes and this was followed by a gradual decrease up to 57 mm. Hg. at 40 minutes. This was again followed by an increase up to 69.6 mm. Hg. at 60 minutes. This combination produced a significant and steady increase of respiration. The average increase was from 28 per minute to 35.3 per minute at 40 minutes which dropped to 30.3 within ten minutes and this fall was again followed by an increase up to 36 per minute at 60 minutes. There was also a slight improvement in ventilation and the average increase was from 5.7 liters per minute to 6.3 liters per minute at ten minutes and this was followed by a steady decrease to 4.8 liters per minute at 50 minutes and this was again followed by an increase up to 6 liters per minute at 60 minutes after the administration of the drug.

Methetharimide and Pentylenetetrazol Fig. 7 (Dog Nos. 28 to 31)

This combination of drug was used in four dogs weighing from 7 Kgs. to 17 Kgs. The drugs were injected separately as usual. All the four animals remained alive until the end of the experiment and they were destroyed at the end.

All the 4 dogs showed a significant improvement in blood pressure and average increase of pressure was from 40.7 mm. Hg. to 61.7 mm. Hg. at 20 minutes and this increase was not only maintained but also showed a further steady increase up to 65.5 mm. Hg. at 40 minutes. This was followed by a steady decline to 64 mm. Hg. at 60 minutes after the injection of the drug. Slight improvement was also noticed in the respiratory rate and ventilation. The average

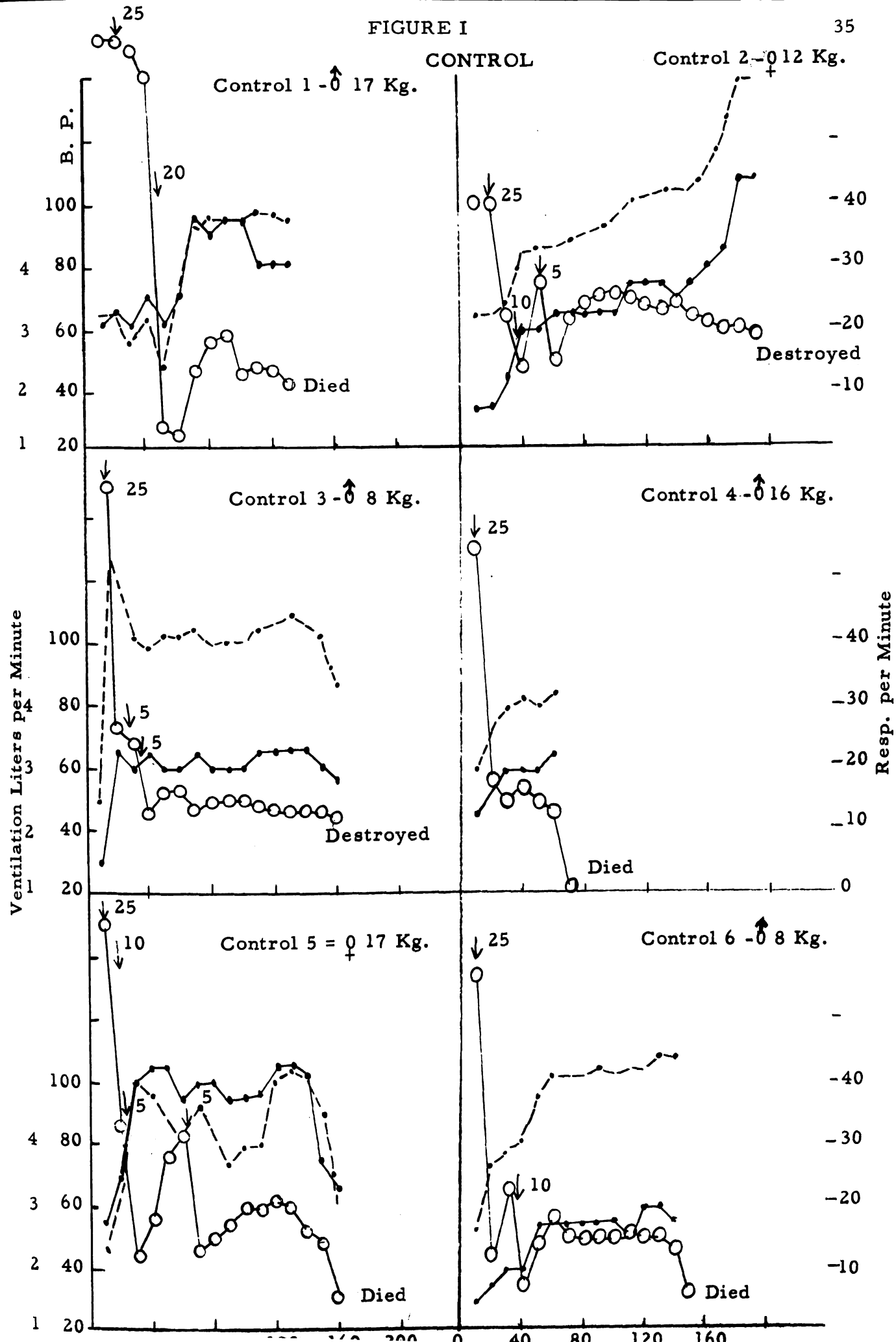
increase of respiratory rate was from 28.8 per minute to 30.7 in 30 minutes and this increase dropped to 29.8 at 60 minutes after the administration of the drugs. The increase of ventilation was from 4.3 liters per minute to 4.7 liters per minute and this increase was maintained throughout with very little change.

Amphetamine and Metaraminol Fig. 8 (Dog Nos. 36 to 39)

This combination was tried in four dogs weighing from 13 Kgs. to 20 Kgs. As usual, separate syringes were used for the injection of drugs. Excepting dog no. 36, which died about 40 minutes after the injection of drugs, the three dogs remained alive until the end of the experiment and were destroyed at the end.

All the four dogs showed a marked rise of blood pressure, but the pressure began to fall very rapidly within 10 minutes after the administration of the drugs. The blood pressure increased from 58 mm. Hg. to 78 mm. Hg. within ten minutes, but it began to fall rapidly to 48 mm. Hg. at 60 minutes. This combination had an immediate negative effect on the respiratory rate and this condition improved slowly. The rate dropped from 25.7 per minute to 23.7 per minute and this drop was followed by an increase up to 27 per minute at 40 minutes and again this rise was followed by a drop to 24 per minute at 60 minutes. A slight increase of ventilation was also observed. The increase was from 4.7 liters per minute to 5.1 liters per minute and this increase was maintained up to 50 minutes after the administration of the drug. This increase again dropped to 4.5 liters per minute at 60 minutes.

FIGURE I


CONTROL
Control 1 - ♂ 17 Kg.
Control 2 - ♀ 12 Kg.
Control 3 - ♂ 8 Kg.
Control 4 - ♂ 16 Kg.
Control 5 = ♀ 17 Kg.
Control 6 - ♂ 8 Kg.
B. P.
Ventilation Liters per Minute
Resp. per Minute
Died
Destroyed
25
20
10
5

Ventilation Liters per Minute

FIGURE 1 - Continued

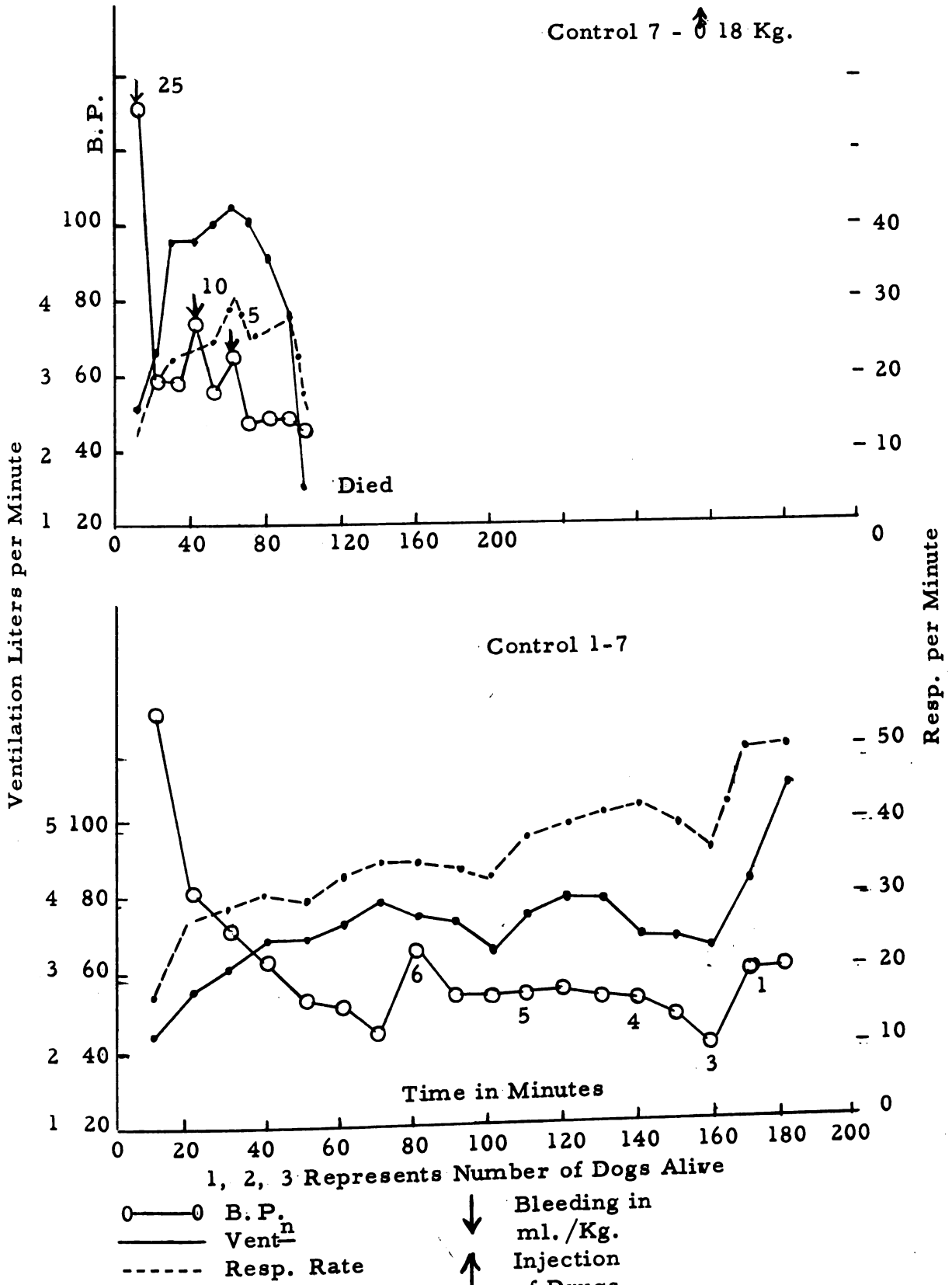


FIGURE II

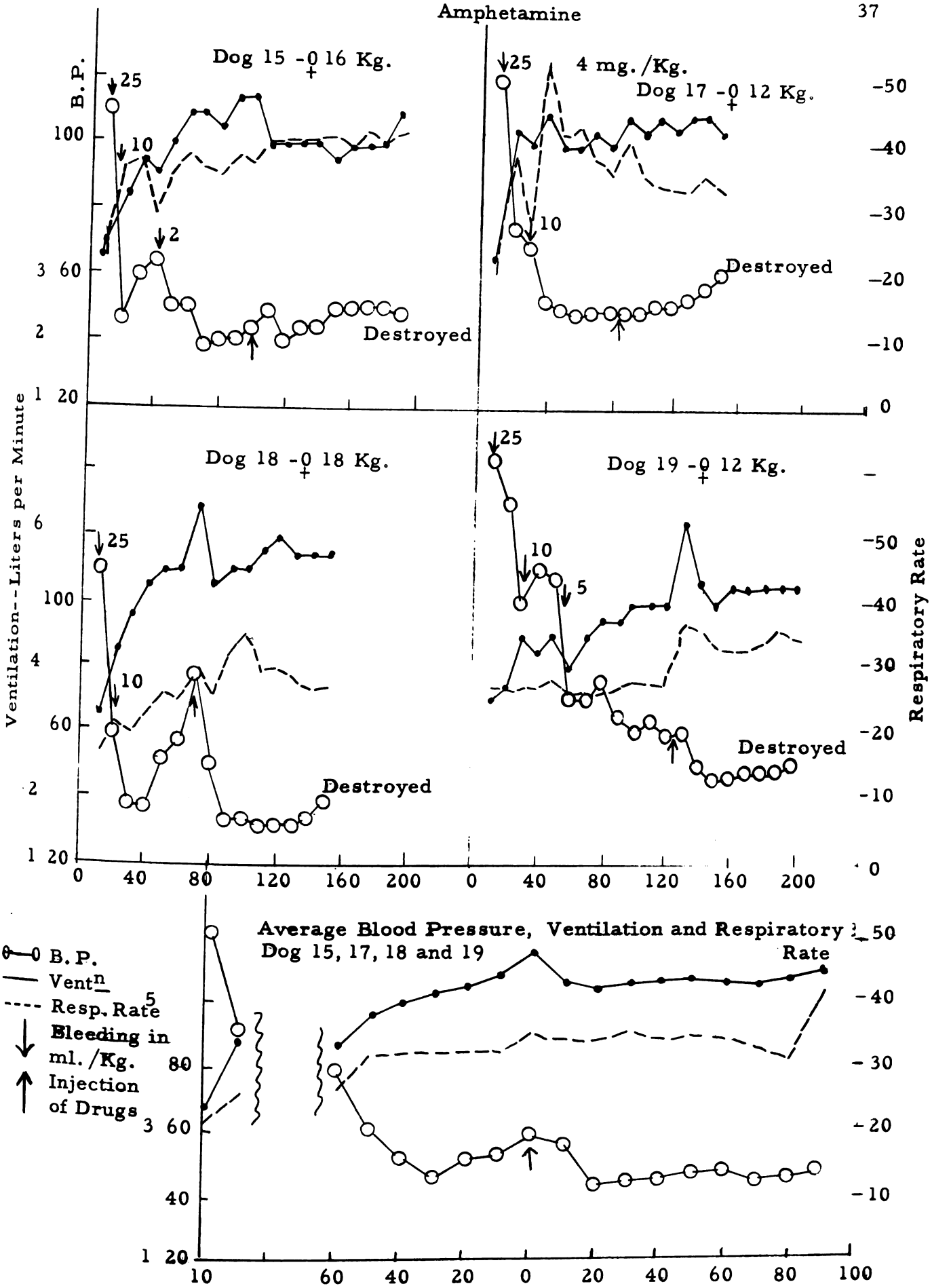
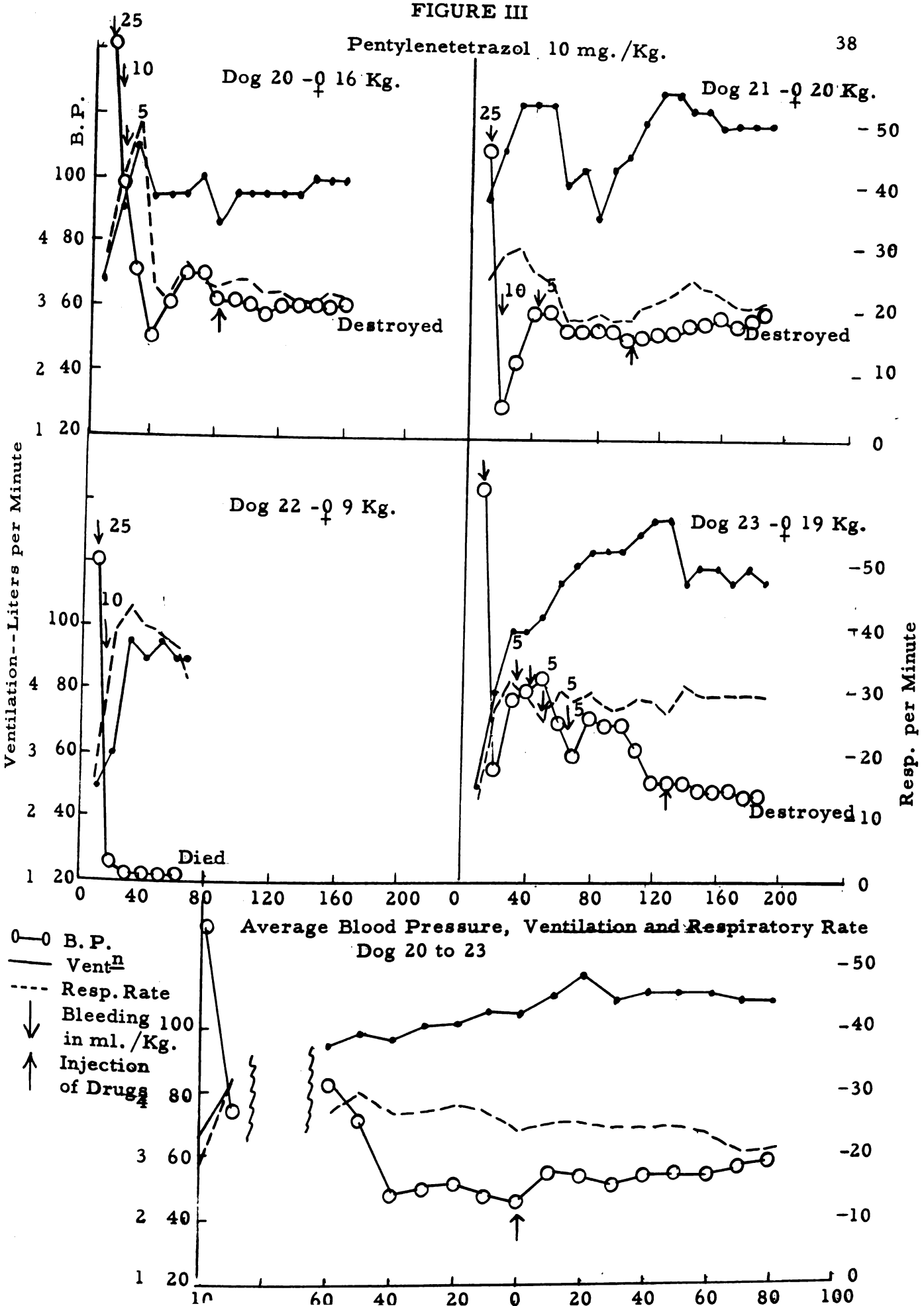

Amphetamine
37
Dog 15 -0 16 Kg.
4 mg./Kg.
Dog 17 -0 12 Kg.
Dog 18 -0 18 Kg.
Dog 19 -0 12 Kg.
B.P.
Ventilation--Liters per Minute
Respiratory Rate
Destroyed
Average Blood Pressure, Ventilation and Respiratory Rate
Dog 15, 17, 18 and 19
0—0 B. P.
Vent^n
Resp. Rate
Bleeding in ml./Kg.
Injection of Drugs

FIGURE III


Pentylenetetrazol 10 mg./Kg.
Dog 20 -♀ 16 Kg.
Dog 21 -♀ 20 Kg.
Dog 22 -♀ 9 Kg.
Dog 23 -♀ 19 Kg.
Destroyed
Destroyed
Destroyed
Died
B.P.
Ventilation--Liters per Minute
Resp. per Minute
Average Blood Pressure, Ventilation and Respiratory Rate
Dog 20 to 23
B. P.
Vent^n
Resp. Rate
Bleeding in ml./Kg.
Injection of Drugs

12

4 6

3

2 4

1 20

120

60

40

20

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of

FIGURE IV

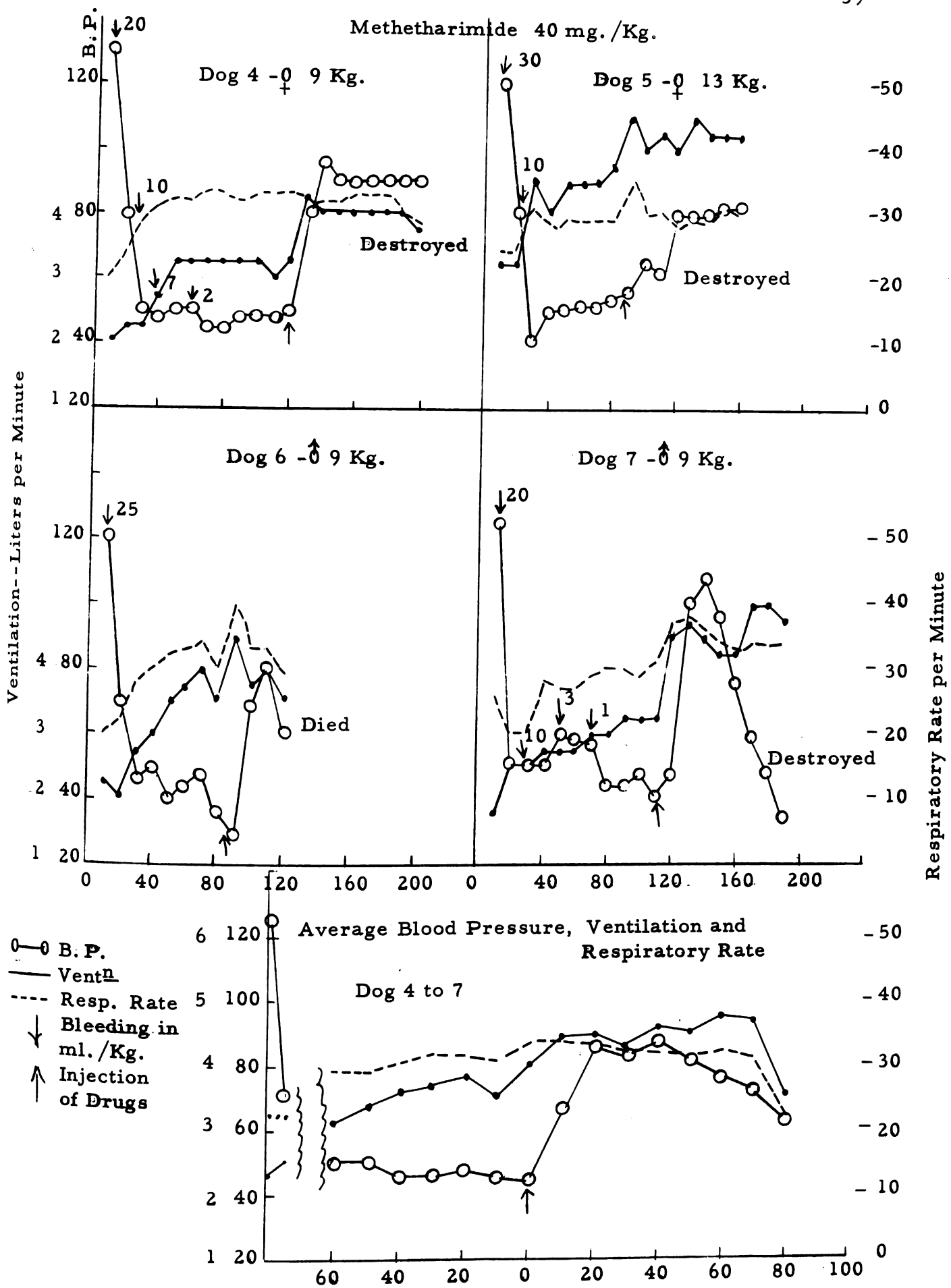

Methetharimide 40 mg./Kg.
Dog 4 -♀ 9 Kg.
Dog 5 -♀ 13 Kg.
Dog 6 -♂ 9 Kg.
Dog 7 -♂ 9 Kg.
B. P.
Ventilation--Liters per Minute
Respiratory Rate per Minute
Destroyed
Destroyed
Died
Destroyed
Average Blood Pressure, Ventilation and Respiratory Rate
Dog 4 to 7
B. P.
Vent^n
Resp. Rate
Bleeding in ml./Kg.
Injection of Drugs
Time in Minutes

FIGURE V Pentylenetetrazol and Amphetamine 5 mg./Kg. and 2 mg./Kg.

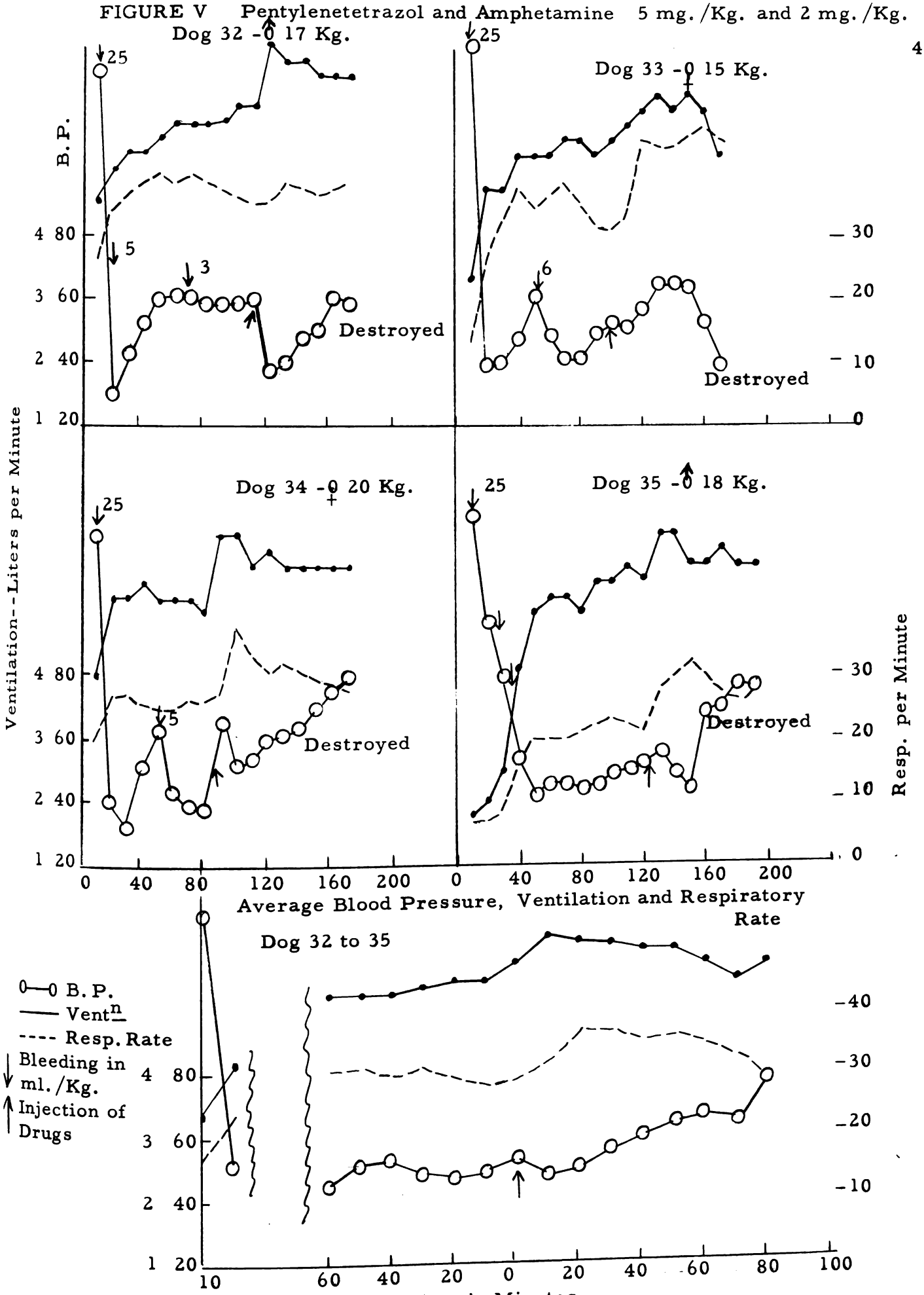


FIGURE VI

Methetharimide and Amphetamine 20 mg./Kg. and 2 mg./Kg.

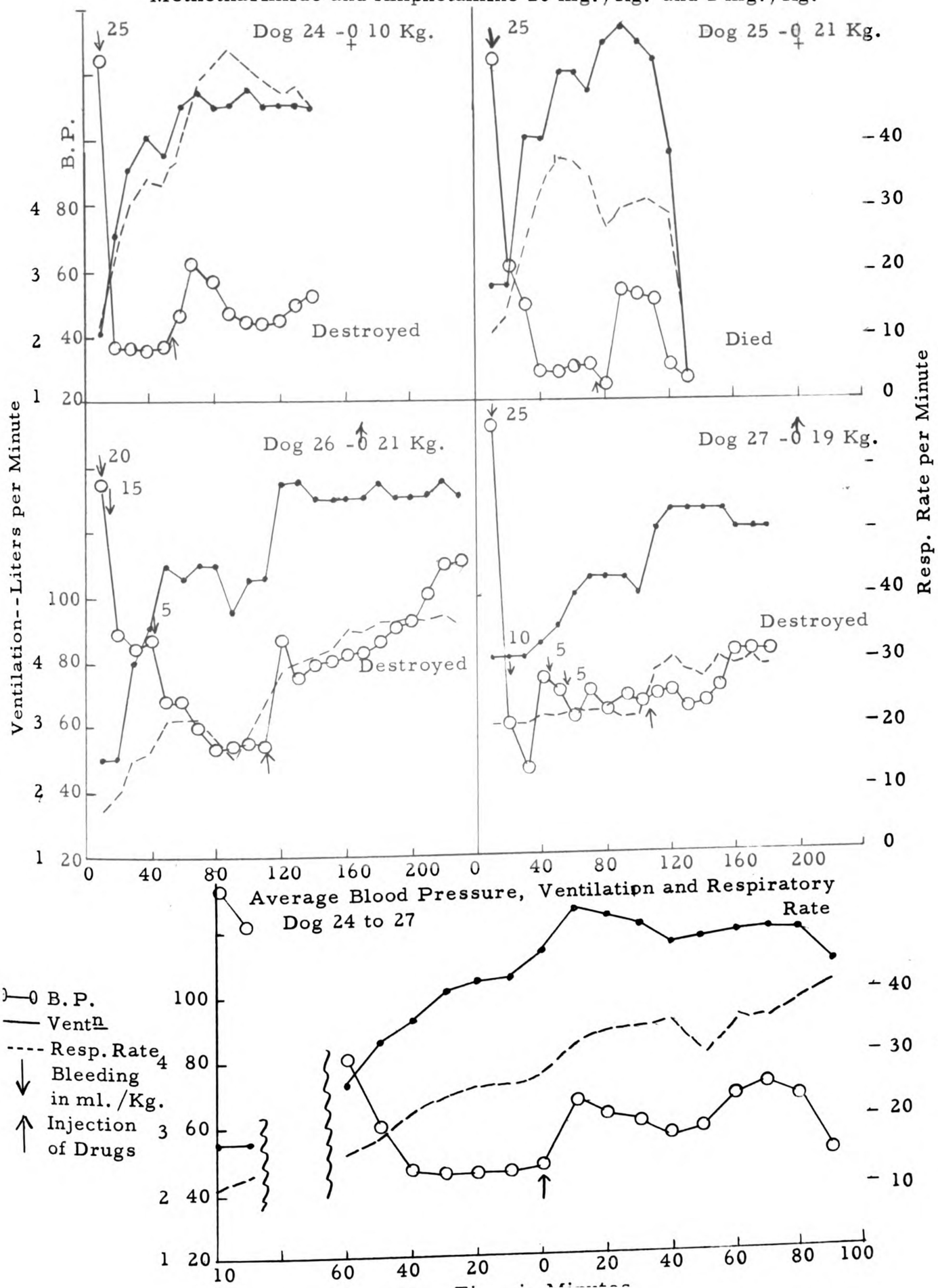


FIGURE VII. Methetharimide and Pentylenetetrazol 20 mg./Kg. and 5 mg./Kg.

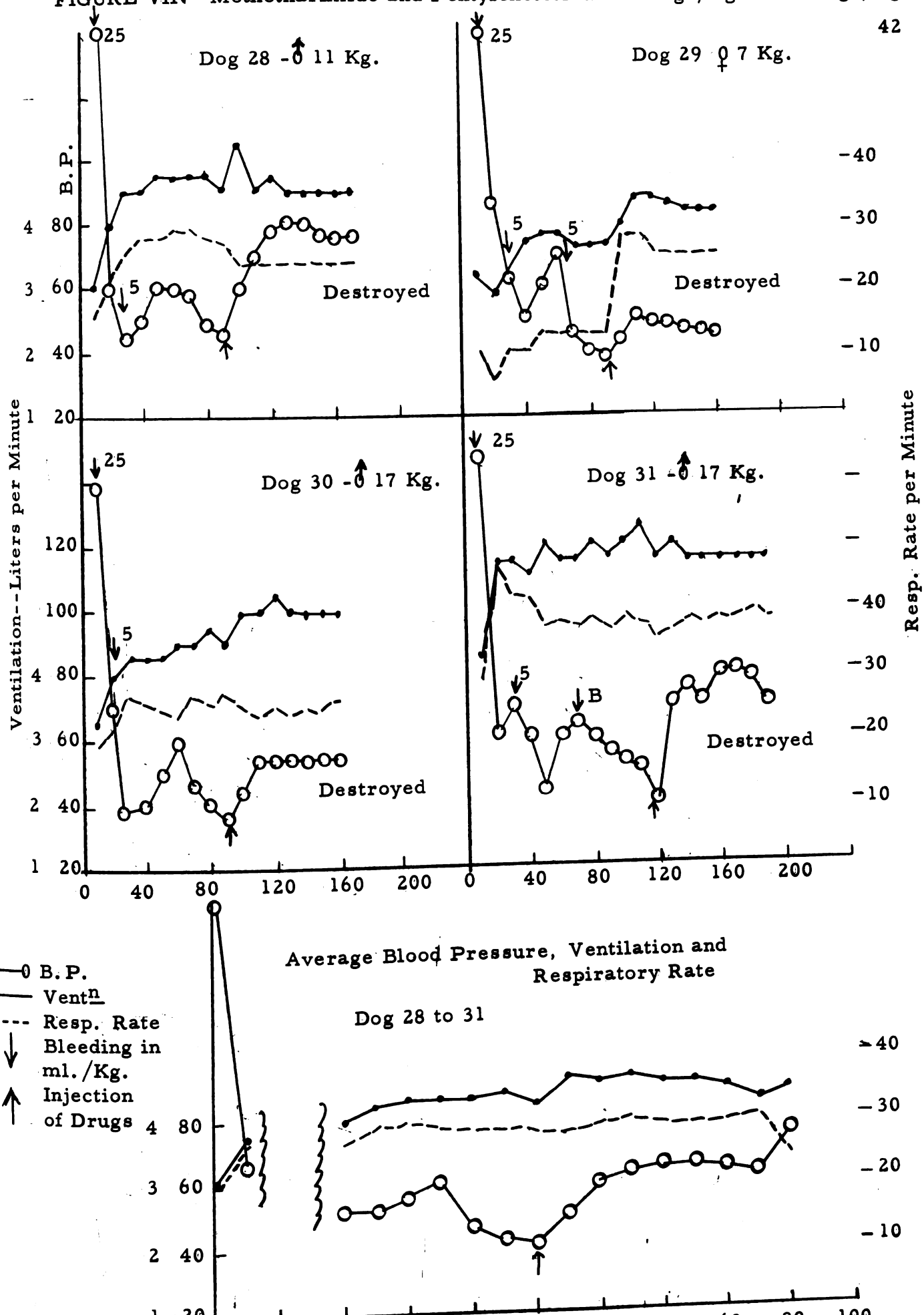


FIGURE VIII

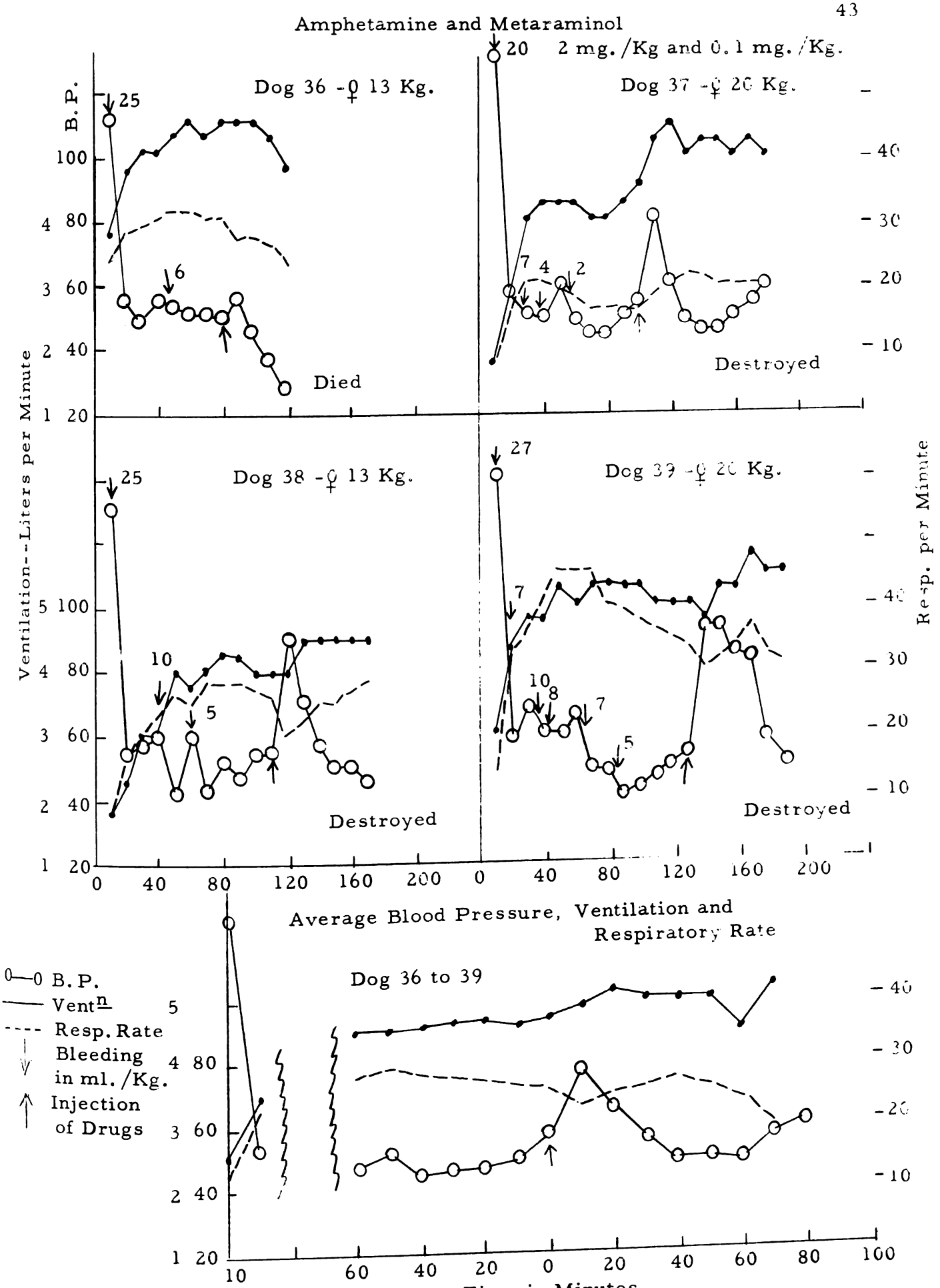

Amphetamine and Metaraminol
20 2 mg./Kg and 0.1 mg./Kg.
Dog 36 -♀ 13 Kg.
Dog 37 -♀ 20 Kg.
Dog 38 -♀ 13 Kg.
Dog 39 -♀ 20 Kg.
B.P.
Ventilation--Liters per Minute
Resp. per Minute
Died
Destroyed
Destroyed
Destroyed
Average Blood Pressure, Ventilation and Respiratory Rate
Dog 36 to 39
0—0 B.P.
Ventn
Resp. Rate
Bleeding in ml./Kg.
Injection of Drugs
Time in Minutes

FIGURE IX

COMBINATION GRAPH OF PERCENT INCREASE OF RESP. RATE--POSTINJECTION OF DRUGS

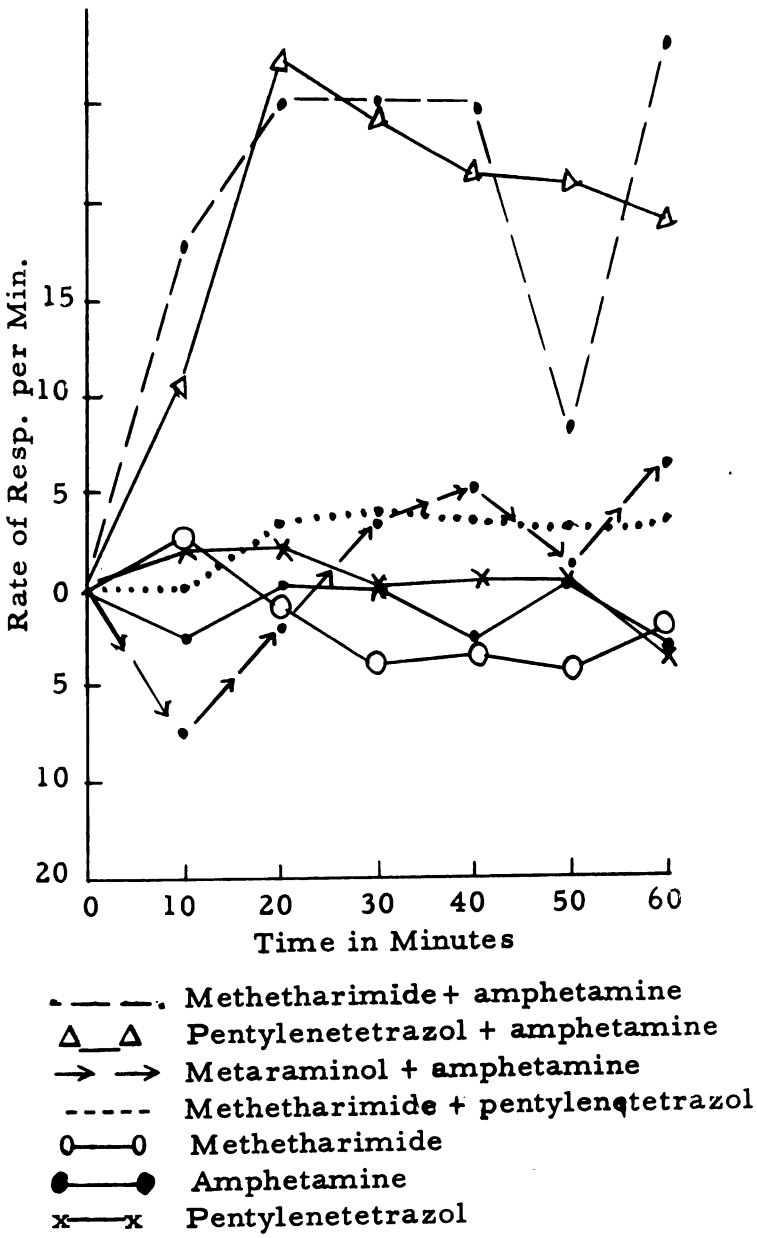


FIGURE X

COMBINATION GRAPH OF PERCENT INCREASE OF VENTILATION--POSTINJECTION OF DRUGS

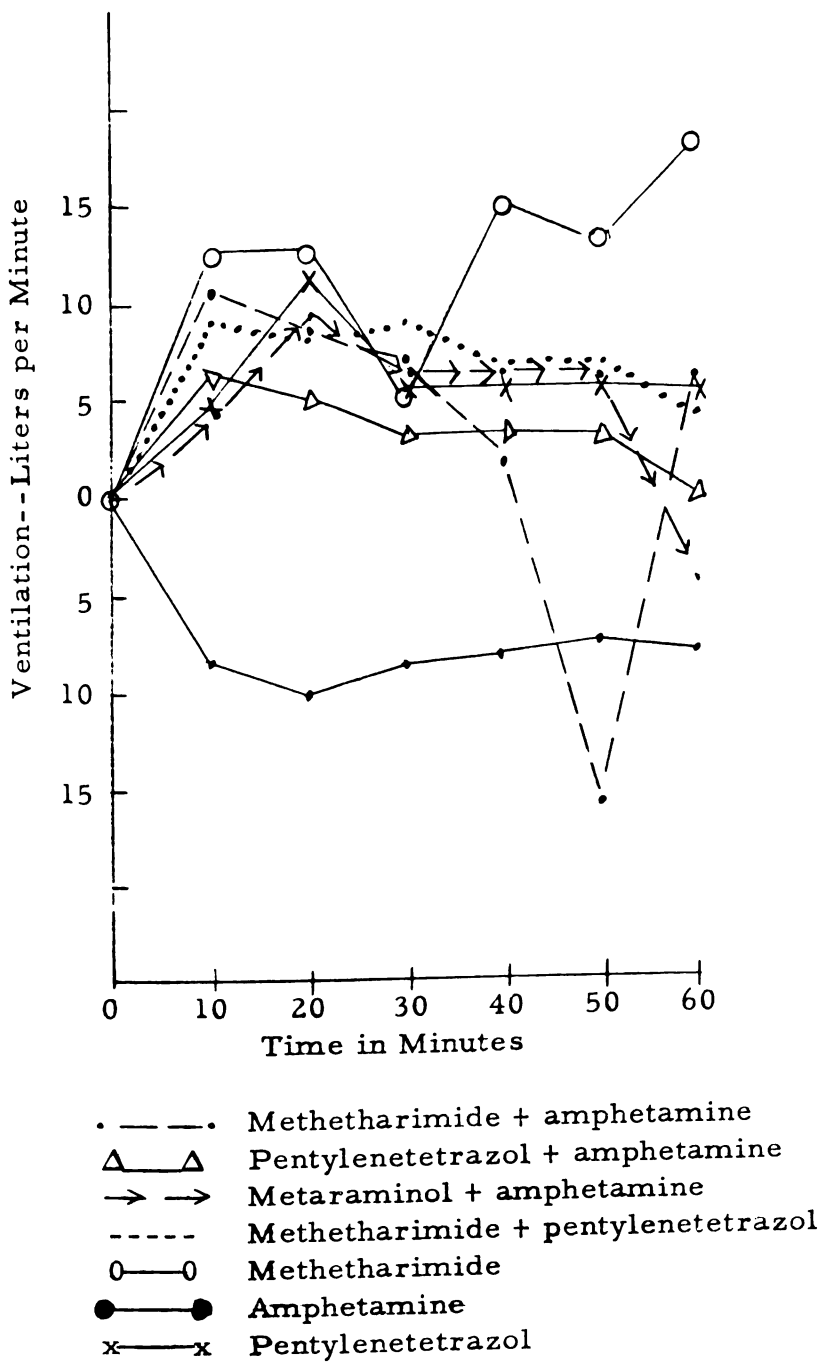


FIGURE XI

COMBINATION GRAPH OF PERCENT INCREASE OF B. P. --POSTINJECTION OF DRUGS

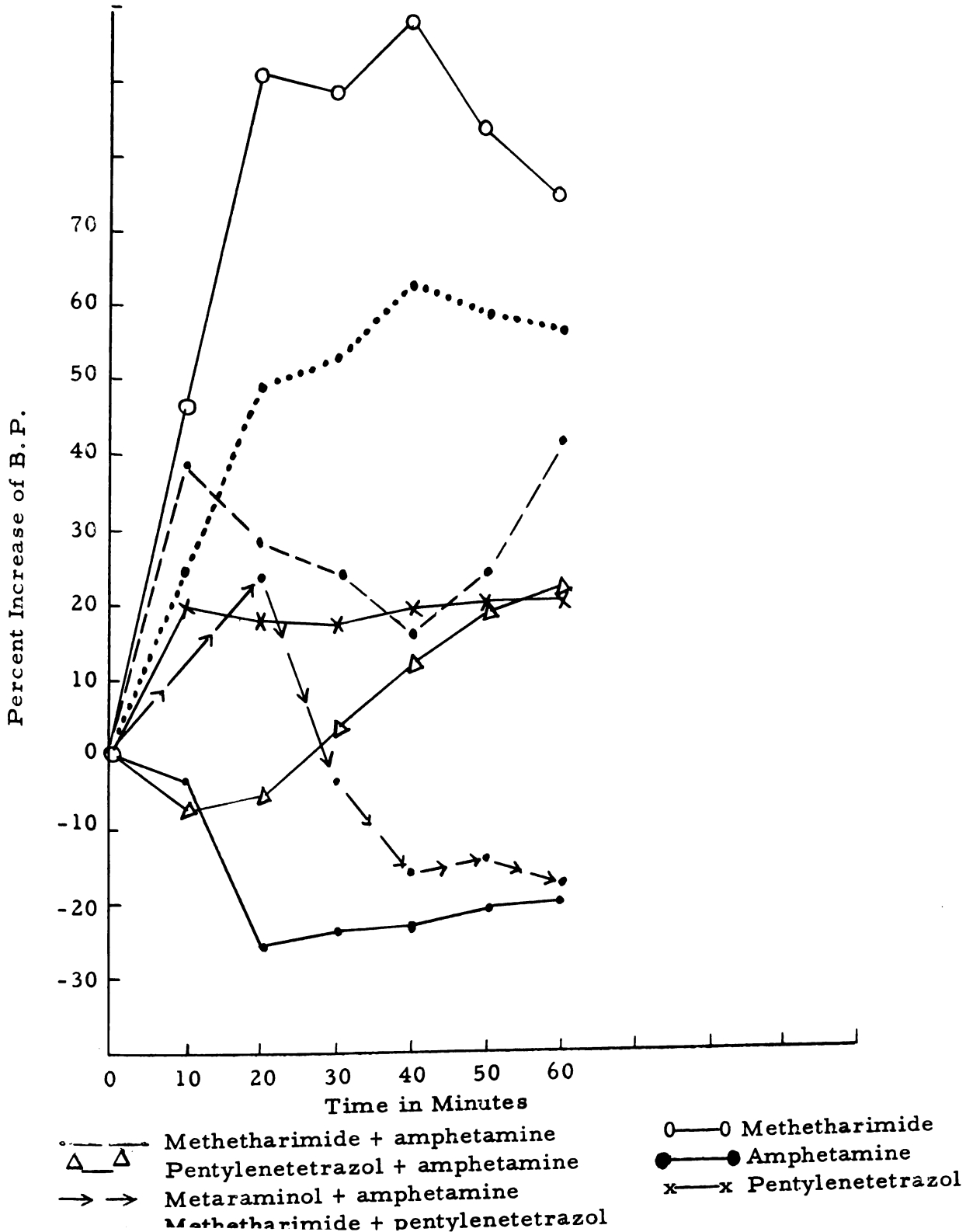
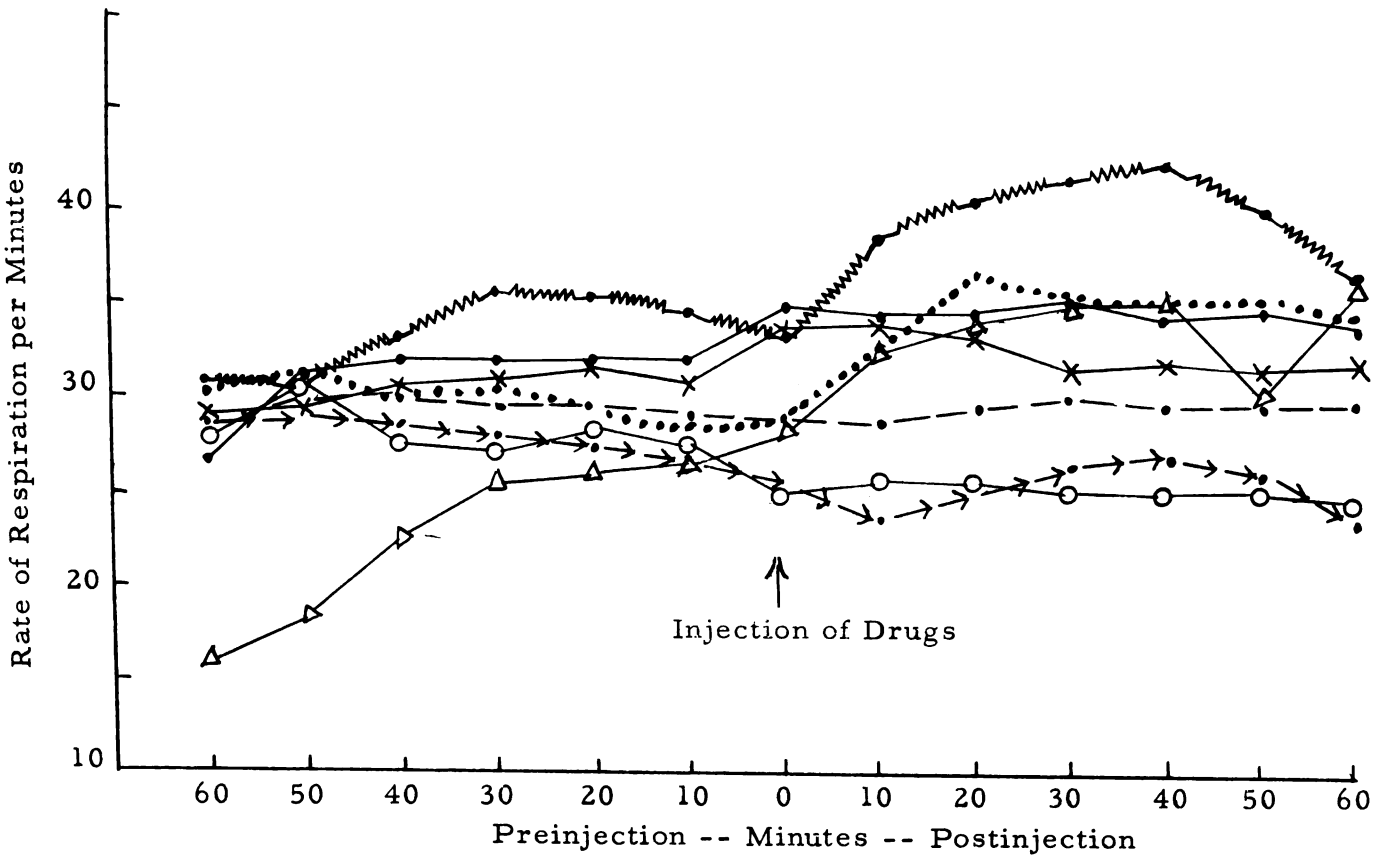


FIGURE XII

COMBINATION GRAPH OF AVERAGES AND CONTROLS
RESPIRATORY RATE




Methetharimide + amphetamine

FIGURE XIII

COMBINATION GRAPH OF AVERAGES AND CONTROLS--VENTILATION

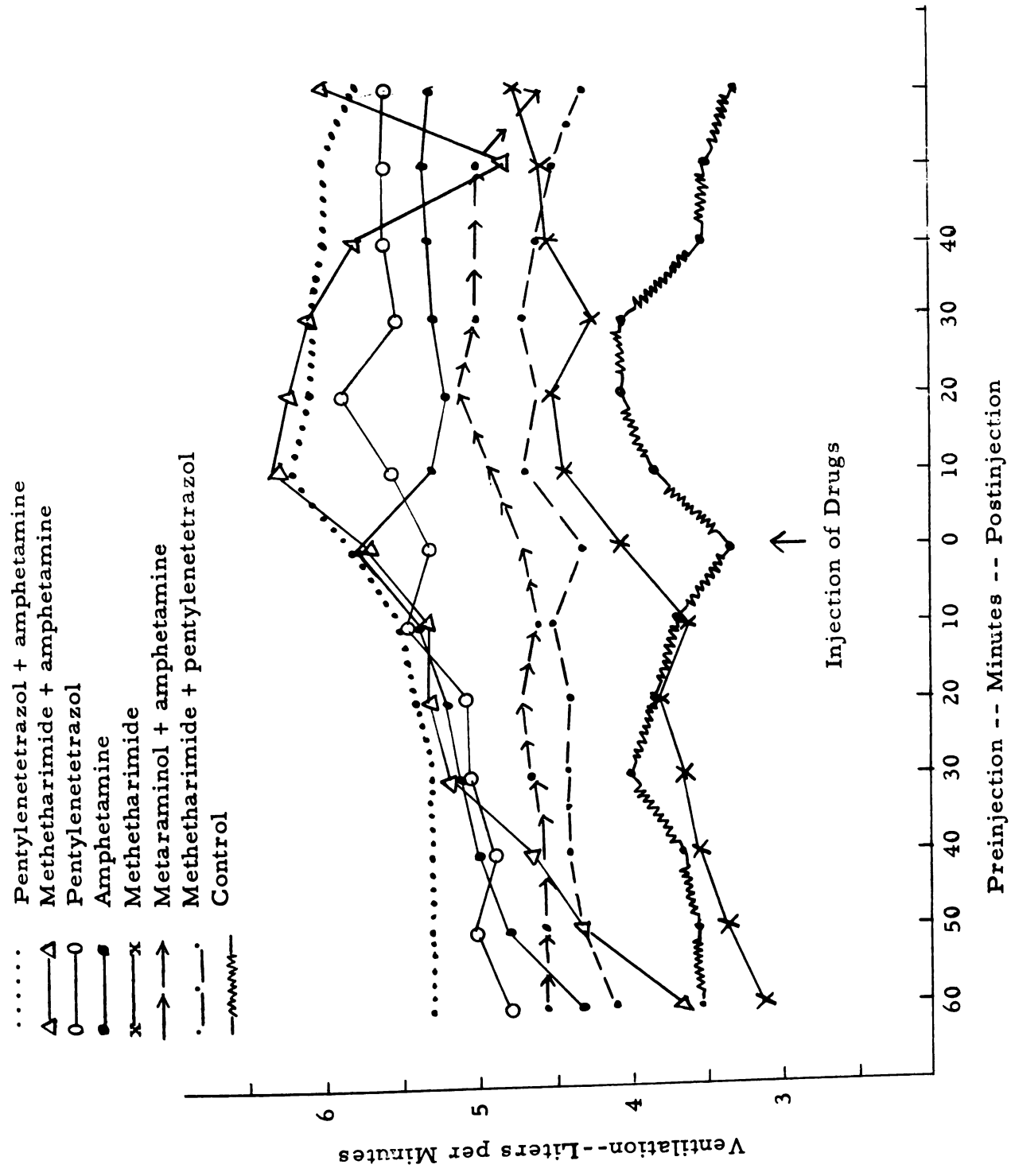
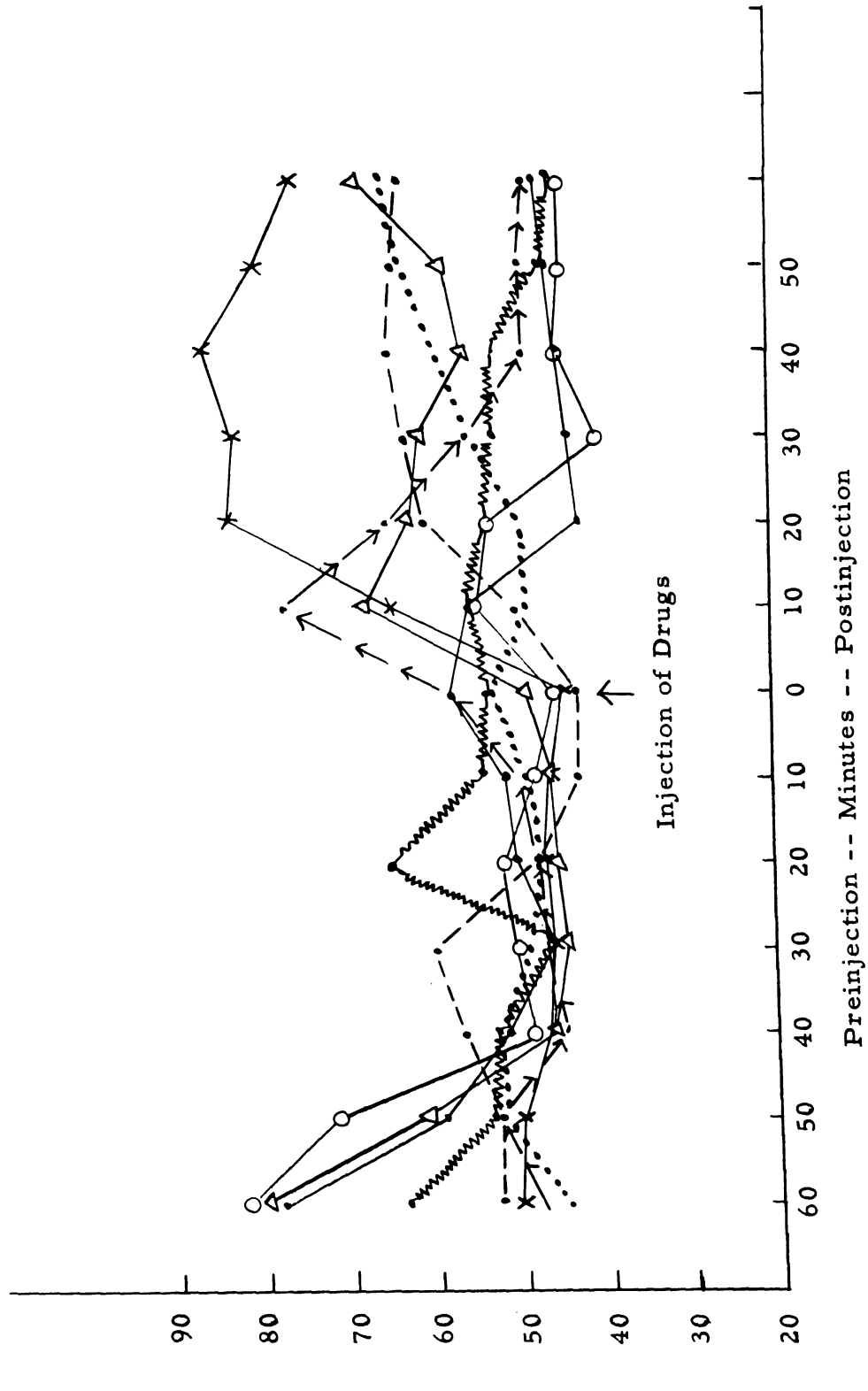


FIGURE XIV

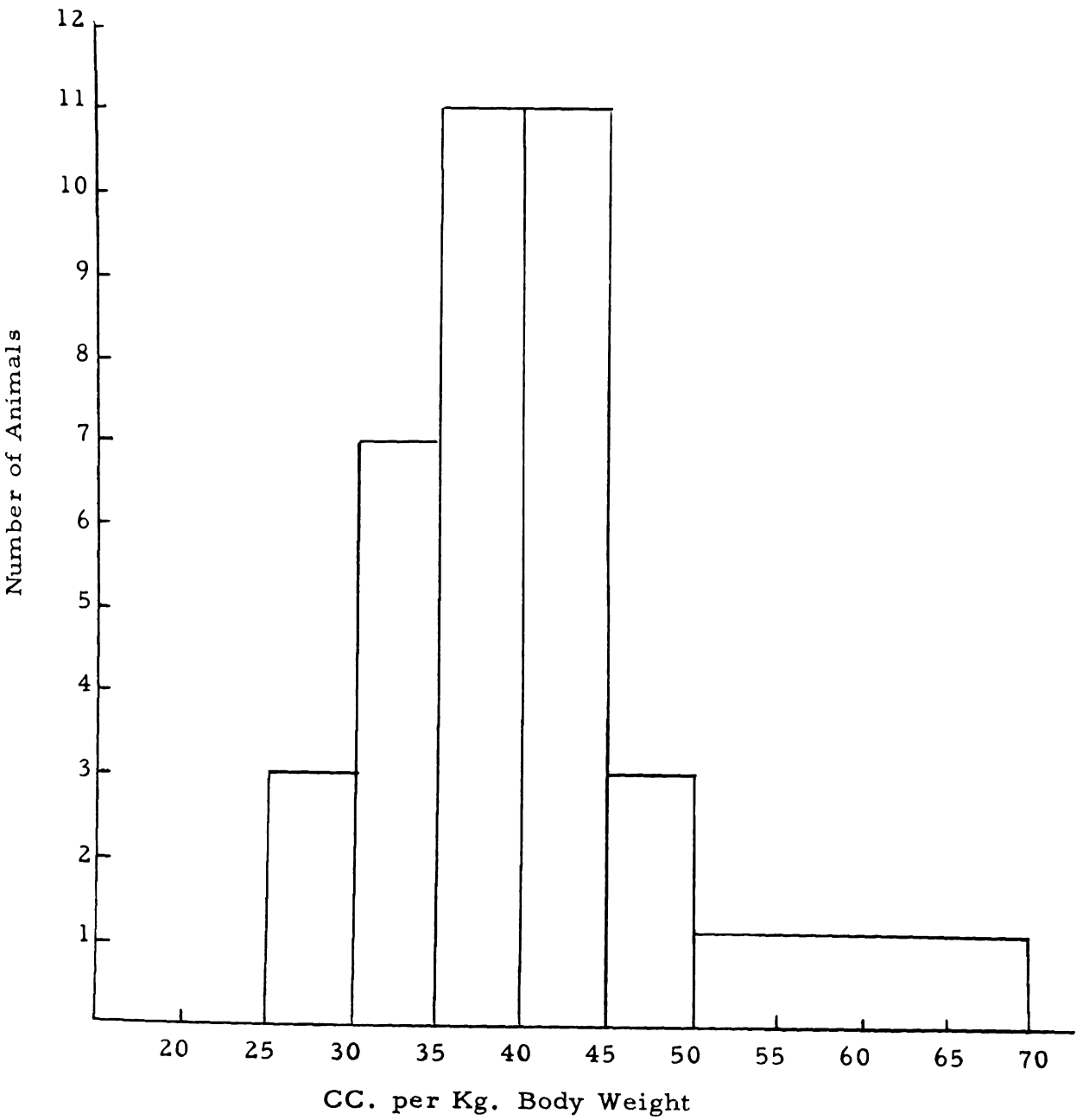
COMBINATION GRAPH OF AVERAGES AND CONTROLS--BLOOD PRESSURE



Number of Animals

FIGURE XV

PLOT SHOWING BLEEDING VOLUMES REQUIRED TO PRODUCE HEMORRHAGIC SHOCK



CHAPTER V

DISCUSSION

This investigation was undertaken to compare the effects of a few analeptic drugs in artificially induced hemorrhagic shock in dogs which were over-anesthetized with sodium pentobarbital.

The method adopted to produce oligemic shock can be compared well with standard procedures advocated by several workers. There are two major methods described by Wiggers (1950). One is removing a definite quantity of blood according to the body weight and the second is bleeding to a definite blood pressure and keeping under that reduced pressure for a certain period. The latter method was followed in this project because it was found to be better and safer. In the beginning a few animals were sacrificed when the former method was tried. If blood is to be removed according to the body weight irrespective of the condition of the animal, many fatty dogs may die due to acute hypotension before they develop shock. In this project the bleeding volume varied from 25 ml./Kg. body weight to 70 ml./Kg. body weight to bring down the blood pressure to 70 mm. Hg. This tremendous variation in bleeding volume may be due to the variation in condition, age, breed and sex, etc. According to Fine et al., (1943), the quantity of blood removed is not the important factor, but the pressure level maintained is the main factor. They reduced the mean arterial pressure in dogs to 70 mm. Hg. by an initial hemorrhage ranging from 1 to 2% of the body weight. They followed this by smaller withdrawals at intervals of 20 minutes. Many of their dogs apparently never developed hypotension of less than 70 mm. Hg. which many workers (T. Porter, 1925; Green, 1942) agree is above the critical value necessary to induce shock. So severe hypotension is not the main factor which

determines shock. According to Wiggers, the only evidence that shock exists in an animal is the production of a state so severe that it cannot be reversed. In this project, out of seven control dogs in which the blood pressure was maintained under 70 mm. Hg., five died, showing the irreversible condition existed in them. According to Weston and his associates (1943), shock was considered to have been produced if hypotension below 70 mm. Hg. existed along with an increase in circulation time beyond 20 seconds. Cleghorn and his associates (1943) anesthetized the dogs with pentothal sodium and bled them rapidly from femoral artery until arterial pressure was reduced to 70 mm. Hg. They maintained this pressure for another 75 minutes by additional bleeding if necessary. In their experiments about 55% of the dogs died with changes in the gastrointestinal mucosa which are characteristic of shock. All these facts show that the method adopted in this project is in agreement with the method adopted by several well known workers in this field.

The next question is whether analeptics can be of any use in such an irreversible state. There is no single answer to this question.

Available literature speaks for and against the use of analeptics in shock. Frank et al., (1953), is of the opinion that shock constitutes a state of progressive deterioration which is not amenable to the type of therapy now available because of fundamental biochemical changes that have developed as a result of prolonged deficiency of capillary flow. According to him the changes are due to injury predominantly involving vital organs. Even though the pressor drugs raise the blood pressure, it is harmful because they reduce the blood supply to the vital organs

by constricting the vessels further, Goodman and Gilman (1955) say that blocking of adrenergic nerves may be beneficial because their influence on the vessels are reduced and blood flows freely to the vital organs.

Whatever may be the laboratory findings in experimental animals, the physicians consider that these drugs are beneficial in shock (Frank et al., 1944). Indeed, it is difficult to differentiate between a case of acute hypotension and shock. Harkins (1941) says, "after all, it matters little what colour fluid is lost from the blood stream, red or yellow."

According to Sarnoff et al., (1954), the increased left auricular pressure is relieved and the left coronary flow is increased by pressor drugs.

The aim of this project was to find an answer to this controversial question. The experiments with these drugs in shock show a wide variation of results. Some are remarkably effective and some, instead of improving the condition, are deleterious and shorten the life of the animal.

The results of amphetamine injection show a negative effect on the blood pressure, respiratory rate and ventilation. This may be explained by the fact that amphetamine, being a pressor drug, further constricts the vessels that are already constricted due to the bleeding and further reduces the blood flow to vital centers in the medulla and worsens the condition (Frank et al., 1953).

Methetharimide produced a remarkable effect on blood pressure and ventilation and seems to be the best of all drugs used in this project. It increased blood pressure from 44 mm. Hg. to 87 mm. Hg.

and ventilation from 4.05 liters per minute to 4.73 liters per minute. The increased pressure and ventilation were maintained throughout the period of the experiment with little change. Its effect on respiratory rate is negligible. It is seen from the results that the rate of respiration is not proportional to the minute volume of ventilation. The minute volume can increase without apparent change in the rate. Therefore, the rate of respiration is not important for the life of the animal provided there is adequate ventilation. The awakening effect is most marked with this drug and remains for a few minutes. As far as I know, there is no literature available to support its beneficial effects in hemorrhagic shock. All available literature speaks about its use in barbiturate depression (Harris, 1955). It is worth trying this promising drug in clinical cases.

The effect of pentylenetetrazol (Metrazol) on blood pressure was from 46 mm. Hg. to 55 mm. Hg. This increase is negligible when compared to methetharimide. The effect on ventilation and respiratory rate was unsatisfactory even though it is said to stimulate the respiratory, vasomotor and vagal centers. It is mentioned that the arterial pressure effects are different in man and in dogs, (Woodbury, et al., 1941). According to them, the vasoconstriction plays a minor role and the main rise of blood pressure is due to the contraction of the skeletal muscles, but in dogs the rise of blood pressure is due to vasoconstriction.

The combination of methetharimide and amphetamine produced a moderate effect on blood pressure, respiratory rate and ventilation.

The average increase of blood pressure was from 49 mm. Hg. to 68 mm. Hg. within ten minutes and this was followed by a gradual decrease down to 57 mm. Hg. at 40 minutes and again followed by an increase up to 69.6 mm. Hg. at 60 minutes. A significant and steady increase of respiratory rate from 28 per minute to 35.3 per minute at 40 minutes was observed and this increase was maintained with a little decrease at 60 minutes. The effect on ventilation was from 5.7 liters per minute at 10 minutes and this began to decline mainly due to the fact that one of the animals died at 50 minutes after the administration of the drug. The uniform improvement on blood pressure, ventilation and respiratory rate may be due to the effect of powerful pressor action of amphetamine and medullary action of methetharimide. This combination, though not the best of all, is better than amphetamine alone and amphetamine and metaraminol combination, because it produces uniform increase of blood pressure, ventilation and respiratory rate.

The combination of methetharimide and pentylenetetrazol has also produced a very good result on blood pressure and the average increase was from 40.7 mm. Hg. to 61.7 mm. Hg. and this increase was maintained with a slight increase at 60 minutes. The respiratory rate was not much affected excepting a slight increase which was maintained till the end of the experiment. It has produced a steady increase of ventilation which was maintained throughout the experiment. The combination seems to be the second best of all the drugs used because of its steady effect on blood pressure, ventilation and to some extent on respiratory rate. It is to be mentioned that both the drugs of this combination are powerful medullary stimulants.

The combination of pentylenetetrazol and amphetamine produced a sudden fall of blood pressure from 53.5 mm. Hg. to 49 mm. Hg. at ten minutes and this was followed by a steady rise of pressure up to 66 mm. Hg. at 60 minutes after the administration of the drugs. The effect on respiratory rate was most marked when compared to other drugs. This combination does not seem to be promising because of its negligible effect on blood pressure and ventilation which are more important than rate of respiration.

The combination of metaraminol and amphetamine increased the blood pressure from 58 mm. Hg. to 78 mm. Hg. at 10 minutes but the pressure dropped to below the initial level within a few minutes. Its effect on blood pressure for a very short period, the negative effect on the respiratory rate and the negligible effect on ventilation go against the use of this combination in hemorrhagic shock. The failure may be due to the fact that both are mainly vasopressor drugs which prevent the blood flow to the vital organs in shock.

Out of all the drugs used singly and in pairs, the methetharimide alone (40 mg./Kg. body weight) produced the maximum effect on blood pressure (from 44 mm. Hg. to 87 mm. Hg.) and ventilation (from 4.05 liters per minute to 4.73 liters per minute). The improvement on respiratory rate was not much and at the same time it is not an important factor. Hence, methetharimide alone seems to be the best of all the drugs used in this project. The next best may be the pentylenetetrazol and methetharimide combination, because it produced a significant improvement in blood pressure and ventilation.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Hemorrhagic shock was produced artificially in dogs over-anesthetized with sodium pentobarbital at the rate of 40 mg./Kg. body weight. They were bled rapidly through the femoral artery to a definite blood pressure of 70 mm. Hg. and this pressure was maintained for about an hour by occasional bleeding if necessary. At the end of an hour the following drugs were administered singly and in pairs:

1) Amphetamine
2) Methetharimide
3) Pentylenetetrazol
4) Amphetamine and Methetharimide
5) Methetharimide and Pentylenetetrazol
6) Pentylenetetrazol and Amphetamine
7) Amphetamine and Metaraminol

The dose was calculated according to their body weight and administered through the femoral vein and their effects on the following were observed:

1) Blood pressure
2) Respiratory rate
3) Ventilation

The result of this experiment indicates the following:

1. Methetharimide alone proved to be the best of all other single drugs and combinations. This combination not only increased the blood pressure to an appreciable level (From 44 mm. Hg. to 87 mm. Hg.) but also maintained the pressure for a long time. Its effect on ventilation was also remarkable (From 4.05 liters per minute to 4.73 liters per minute)

and this effect was maintained till the end of the experiment.

2. The next powerful drug was the combination of methetharimide and pentylenetetrazol, because this combination produced a significant effect on blood pressure (From 40.7 mm. Hg. to 65.5 mm. Hg.), and ventilation (From 4.3 liters per minute to 4.7 liters per minute). This increase was steady and remained throughout the experiment with very little variation.

3. The third best was the combination of amphetamine and methetharimide. This combination produced a moderate overall improvement on blood pressure (From 49 mm. Hg. to 68 mm. Hg.), ventilation (From 5.7 liters per minute to 6.3 liters per minute) and respiratory rate (From 28 per minute to 35.3 per minute). Even though there was a slight fall after the initial rise, the blood pressure began to improve gradually.

4. The rest of the combinations and single drugs either produced no significant effect or produced a negative effect on blood pressure, ventilation and respiratory rate.

CHAPTER VII

BIBLIOGRAPHY

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Effect of Methetharimide in Hemorrhagic Shock

Particulars of Dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 4 Sex: F. Wt.: 9 Kgs.						
	10	2	20	130	20	
	20	2.25	24	80		
	30	2.25	29	50	10	Bled at 26th Min.
	40	2.75	31	48	7	At 37th Minute
	50	3.25	32	50		
	60	3.25	32	50		
	70	3.25	33	45	2	61st Minute
	80	3.25	33	44		
	90	3.25	32	48		
	100	3.25	33	48		
	110	3.00	33	48		
	120	3.25	33	50		Drug injected
	130	4.25	32	80		
	140	4.00	32	96		
	150	4.00	32	90		
	160	4.00	33	90		
	170	4.00	33	90		
	180	4.00	33	90		
	190	4.00	30	90		
	200	3.75	29	90		
	210	3.75	29	90		
	220	3.75	28	94		Destroyed
Dog No. 5 Sex: F Wt.: 13 Kgs.						
	10	3.25	24	120	30	
	20	3.25	24	80		
	30	4.50	31	40	10	At 21st. Minute
	40	4.0	28	50		
	50	4.50	29	50		
	60	4.50	29	52		
	70	4.50	29	52		
	80	4.75	29	54		
	90	5.50	35	56		Drug at 87th.Min.
	100	5.00	30	66		
	110	5.25	30	62		
	120	5.00	28	80		
	130	5.50	29	80		
	140	5.25	29	80		
	150	5.25	31	82		
	160	5.25	30	82		Destroyed

Dog No. 6
Sex: M
Wt.: 9 Kg.

10	2.25	20	120	25	
20	2.00	22	70	12	
30	2.75	28	46		
40	3.00	30	50		
50	3.50	32	40		
60	3.75	33	44		
70	4.00	34	48		
80	3.50	30	36		
90	4.50	40	28	1	Drug at 88th. Min.
100	3.75	33	68		
110	4.00	33	80		
120	3.50	29	60		Died

Dog No. 7
Sex: M.
Wt.: 9 Kg.

10	1.75	26	124	20	
20	2.50	20	50		
30	2.50	20	50	10	27th Min.
40	2.75	28	50		
50	2.75	27	60	3	
60	2.75	27	58		
70	3.00	29	56	1	
80	3.00	30	44		
90	3.25	30	44		
100	3.25	29	48		
110	3.25	31	40		
120	4.50	37	48		
130	4.75	38	100		
140	4.50	3o	108		
150	4.25	34	96		
160	4.25	33	76		
170	5.00	34	58		
180	5.00	34	48		
190	4.75	34	34		Destroyed

Effect of Amphetamine in Hemorrhage Shock

Particulars of dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 15 Sex: F Wt.: 16 Kg.						
	10	3.5	23	110	25	
	20	4.25	36	46	10	
	30	4.75	38	60		
	40	4.50	29	64		
	50	5.00	35	50	2	43rd. Min.
	60	5.50	38	50		
	70	5.50	36	38		
	80	5.25	35	40		
	90	5.75	38	40		
	100	5.75	37	44		Drug injected
	110	5.00	40	50		
	120	5.00	40	40		
	130	5.00	40	44		
	140	5.00	41	44		
	150	4.75	41	50		
	160	5.00	40	50		
	170	5.00	42	50		
	180	5.00	41	50		
	190	5.50	42	48		Destroyed
Dog No. 17 Sex: F Wt.: 12 Kg.						
	10	3.25	20	120	25	
	20	5.25	38	74		
	30	5.00	28	68	10	29th. Min.
	40	5.50	54	52		
	50	5.00	42	50		
	60	5.00	43	48		
	70	5.25	38	50		
	80	5.50	36	50		
	90	5.50	41	50		Drug injected at 87th. Min.
	100	5.25	35	50		
	110	5.50	34	52		
	120	5.25	34	52		
	130	5.50	34	54		
	140	5.50	35	58		
	150	5.25	34	62		Destroyed

Dog No. 18
Sex: F
Wt.: 18 Kg.

10	3.25	17	110	25	
20	4.25	21	60	10	
30	4.75	20	38		
40	5.25	23	38		
50	5.50	26	52		
60	5.50	25	58		
70	6.50	30	78		Drug injected at 69th. Min.
80	5.25	25	50		
90	5.50	32	34		
100	5.50	35	34		
110	5.75	30	32		
120	6.00	30	32		
130	5.75	28	32		
140	5.75	27	34		
150	5.75	27	40		Destroyed

Dog No. 19
Sex: F
Wt.: 12 Kg.

10	3.50	27	144	25	
20	3.75	27	130		
30	4.50	27	100	10	
40	4.25	27	110		
50	4.50	28	108		
60	4.00	26	70	5	At 56th. Min.
70	4.50	26	70		
80	4.75	26	76		
90	4.75	27	64		
100	5.00	28	60		
110	5.00	28	64		
120	5.00	28	60		
130	6.25	37	60		Drug injected at 127th. Min.
140	5.25	36	50		
150	5.00	33	46		
160	5.25	33	46		
170	5.25	33	48		
180	5.25	34	48		
190	5.25	36	48		
200	5.25	35	52		
210	5.50	34	56		
220	5.25	35	68		
230	5.25	34	68		Destroyed

Effect of Pentylenetetrazol in Hemorrhagic Shock

Particulars of dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 20 Sex: F Wt.: 16 Kgs.						
	10	3.75	24	160	25	
	20	4.50	40	98	10	At 14th. Min.
	30	5.50	48	70	5	At 24th. Min.
	40	4.75	23	50		
	50	4.75	20	60		
	60	4.75	27	70		
	70	5.00	24	70		
	80	4.25	23	62		Drug injected
	90	4.25	24	62		
	100	4.75	24	60		
	110	4.75	22	58		
	120	4.75	22	60		
	130	4.75	21	60		
	140	5.00	21	60		
	150	5.00	22	60		
	160	5.00	22	60		Destroyed
Dog No. 21 Sex: F Wt.: 20 Kgs.						
	10	4.75	25	110	25	
	20	5.50	29	30	10	At 19th. Min.
	30	6.25	30	44		
	40	6.25	26	60		
	50	6.25	25	60	5	At 42nd. Min.
	60	5.00	19	54		
	70	5.25	19	54		
	80	4.50	20	54		
	90	5.25	19	54		
	100	5.50	19	52		
	110	6.00	21	52		Drug injected at 104th. Min.
	120	6.50	22	54		
	130	6.50	23	54		
	140	6.25	25	56		
	150	6.25	24	56		
	160	6.00	23	58		
	170	6.00	21	56		
	180	6.00	21	56		
	190	6.00	22	60		Destroyed

Dog No. 22
Sex: F
Wt.: 9 Kgs.

10	2.50	16	120	25	
20	3.00	39	25	10	At 16th Min.
30	4.75	43	22		
40	4.50	40	22		
50	4.75	39	22		
60	4.50	37	18		Drug at 63rd.Min.
65	4.50	27	12		Died

Dog No. 23
Sex: F
Wt.: 19 Kg.

10	2.50	13	144	25	
20	4.00	28	56		
30	5.00	32	78		
40	5.00	30	80	5	At 32nd. Min.
50	5.25	26	84		
60	5.75	30	70	5	At 42nd. Min.
				5	At 50th. Min.
70	6.00	29	60		
80	6.25	30	72	5	At 65th. Min.
90	6.25	28	70		
100	6.25	28	70		
110	6.50	29	62		
120	6.75	29	52		
130	6.75	27	52		Drug injected
140	5.75	31	52		
150	6.00	30	50		
160	6.00	30	50		
170	5.75	30	50		
180	6.00	30	48		
190	5.75	30	48		Destroyed

Effect of Methetharimide and Amphetamine in Hemorrhagic Shock

Particulars in dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 24 Sex: F Wt.: 10 Kgs.						
	10	2.0	10	124	25	
	20	3.50	23	36		
	30	4.50	30	36		
	40	5.00	34	36		
	50	4.75	33	36		
	60	5.50	38	46		Drug injected at 56th. Min.
	70	5.75	49	62		
	80	5.50	51	56		
	90	5.50	53	46		
	100	5.75	51	44		
	110	5.50	49	44		
	120	5.50	47	44		
	130	5.50	48	48		
	140	5.50	45	52		
	150	5.50	45	50		Destroyed
Dog No. 25 Sex: F Wt.: 21						
	10	2.75	10	122	25	
	20	2.75	13	60		
	30	5.00	23	48		
	40	5.00	34	28		
	50	6.00	37	28		
	60	6.00	36	30		
	70	5.75	34	30		
	80	6.50	26	24		Drug injected at 79th. Min.
	90	6.75	29	54		
	100	6.50	30	52		
	110	6.25	30	50		
	120	4.75	28	30		
	130	1.25	6	26		Died
Dog No. 26 Sex: M Wt.: 21 Kgs.						
	10	2.50	7	134	20	
	20	2.50	10	90	10	At 15th Min.
	30	4.00	15	84		
	40	4.50	16	86		

50	5.50	21	68	5	42nd. Min.
60	5.25	21	68		
70	5.50	21	60		
80	5.50	18	54		
90	4.75	15	54		
100	4.75	19	56		
110	4.25	17	54		
120	6.75	29	86		Drug injected at 112th. Minute
130	6.25	30	74		
140	6.50	31	80		
150	6.50	32	80		
160	6.50	35	82		
170	6.50	35	82		
180	6.75	3o	86		
190	6.50	36	90		
200	6.50	36	94		
210	6.50	36	100		
220	6.75	37	110		
230	6.50	35	110		Destroyed

Dog No. 27
Sex: M
Wt.: 19 Kgs.

10	4.00	20	152	25	
20	4.00	20	60	10	
30	4.00	20	46		
40	4.25	21	74		
50	4.50	21	70	5	At 42nd. Min.
60	5.00	22	62	3	At 52nd. Min.
70	5.00	22	70		
80	5.25	22	64		
90	5.25	21	68		
100	5.00	21	66		
110	6.00	28	110		Drug at 107th.Min.
120	6.50	30	70		
130	6.50	28	64		
140	6.25	27	66		
150	6.25	30	70		
160	6.00	29	82		
170	6.00	30	82		
180	6.00	29	82		Destroyed

Effect of Methetharimide and Pentylenetetrazol in Hemorrhagic Shock

Particulars in dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 28 Sex: M. Wt.: 11 Kgs.						
	10	3.00	16	150	25	
	20	4.00	22	60		
	30	4.50	26	44	5	At 28th. Min.
	40	4.50	28	50		
	50	4.75	28	60		
	60	4.75	29	60		
	70	4.75	29	58		
	80	4.75	28	48		
	90	4.50	27	45		
	100	5.25	24	60		Drug at 91st.Min.
	110	4.50	24	70		
	120	4.75	24	78		
	130	4.50	24	80		
	140	4.50	24	80		
	150	4.50	24	76		
	160	4.50	24	76		
	170	4.50	24	76		Destroyed
Dog No. 29 Sex: F Wt.: 7 Kgs.						
	10	2.00	22	150	25	
	20	1.50	19	86		
	30	2.00	21	60	5	At 29th. Min.
	40	2.00	27	50		
	50	2.25	28	60		
	60	2.25	28	70		
	70	2.50	26	44	5	At 62nd Min.
	80	2.50	26	40		
	90	2.50	26	38		Drugs injected at 91st. Min.
	100	3.75	30	42		
	110	3.75	34	50		
	120	3.50	34	48		
	130	3.50	33	48		
	140	3.50	32	45		
	150	3.50	32	45		
	160	3.50	32	32		Destroyed
Dog No. 30 Sex: M Wt.: 17 Kgs.						
	10	3.25	19	140	25	
	20	4.00	22	70	5	

30	4.25	27	38		
40	4.25	26	40		
50	4.25	25	50		
60	4.50	24	60		
70	4.50	27	46		
80	4.75	26	40		
90	4.50	27	36		Drugs at 90th. Min
100	5.00	25	44		
110	5.00	24	54		
120	5.25	25	54		
130	5.00	24	54		
140	5.00	25	54		
150	5.00	25	54		
160	5.00	26	54		

Dog No. 31
Sex: M
Wt.: 17 Kgs.

10	4.25	29	180	25	
20	5.75	46	60		
30	5.75	42	70	5	At 31st Minute
40	5.50	41	60		
50	6.00	37	42		
60	5.75	38	60		
70	5.75	37	64	8	
80	6.00	38	60		
90	5.75	36	54		
100	6.00	38	52		
110	6.25	37	50		
120	5.75	35	38		Drugs at 117th.Min.
130	6.00	36	70		
140	5.75	38	75		
150	5.75	37	70		
160	5.75	38	80		
170	5.75	38	80		
180	5.75	39	78		
190	5.75	38	70		Destroyed

Effect of Pentylenetetrazol and Amphetamine in Hemorrhagic Shock

Particulars of dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 32 Sex: M Wt.: 17 Kgs.						
	10	4.50	26	132	25	
	20	5.00	34	30	5	At 19th. Min.
	30	5.25	36	42		
	40	5.25	38	52		
	50	5.50	39	60		
	60	5.75	38	60		
	70	5.75	39	60	3	
	80	5.75	38	58		
	90	5.75	37	58		
	100	6.00	36	58		
	110	6.00	35	60		
	120	7.00	35	36		Drugs at 112th.Min.
	130	6.75	38	40		
	140	6.75	37	48		
	150	6.75	36	50		
	160	6.50	37	60		
	170	6.50	38	58		Destroyed
Dog No. 33 Sex: F Wt.: 15 Kgs.						
	10	3.25	13	140	25	
	20	4.75	27	38		
	30	4.75	32	38		
	40	5.25	37	46		
	50	5.25	34	60		
	60	5.25	36	48	6	At 53rd. Min.
	70	5.50	38	40		
	80	5.50	34	40		
	90	5.25	31	48		
	100	5.50	31	52		Drugs at 99th.Min.
	110	5.75	33	50		
	120	6.00	45	50		
	130	6.25	44	64		
	140	6.00	44	64		
	150	6.25	46	62		
	160	6.00	47	52		
	170	5.25	45	38		

Dog No. 34
Sex: F
Wt.: 20

10	4.00	20	124	25	
20	5.25	27	40		
30	5.25	27	32		
40	5.50	26	52		
50	5.25	25	64	5	At 51st. Min.
60	5.25	25	44		
70	5.25	26	40		
80	5.00	26	38		
90	6.25	28	66		Drugs at 86th.Min.
100	6.25	38	52		
110	5.75	33	54		
120	6.00	31	60		
130	5.75	32	62		
140	5.75	31	64		
150	5.75	30	70		
160	5.75	29	76		
170	5.75	29	80		Destroyed

Dog No. 35
Sex: M
Wt.: 18 Kgs.

10	1.75	7	130	25	
20	2.00	7	98		
30	2.50	9	80	10	At 26th. Min.
40	4.25	17	52	5	At 33rd. Min.
50	5.00	20	42		
60	5.25	20	46		
70	5.25	20	46		
80	5.00	21	44		
90	5.50	22	46		
100	5.50	23	50		
110	5.75	22	50		
120	5.50	21	52		
130	6.25	28	56		Drugs at 123rd.Min
140	6.25	30	48		
150	5.75	32	46		
160	5.75	29	62		
170	6.00	27	70		
180	5.75	26	78		
190	5.75	27	76		Destroyed

Effect of Amphetamine and Metaraminol in Hemorrhagic Shock

Particulars of dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 36 Sex: F Wt.: 13 Kgs.						
	10	3.75	23	110	25	
	20	4.75	28	54		
	30	5.00	29	48		
	40	5.00	30	54		
	50	5.25	31	52	6	At 46th. Min.
	60	5.50	31	50		
	70	5.25	30	50		
	80	5.50	30	48		Drug at 81st.Min.
	90	5.50	27	56		
	100	5.50	27	44		
	110	5.25	26	35		
	120	4.75	23	26		Died
Dog No. 37 Sex: F Wt.: 20 Kgs.						
	10	1.75	7	130	20	
	20	3.00	15	56		
	30	4.00	20	50	7	At 29th. Min.
	40	4.25	20	50	4	At 39th. Min.
	50	4.25	19	60		
	60	4.25	18	48	2	At 56th Min.
	70	4.00	16	44		
	80	4.00	16	44		
	90	4.25	16	50		
	100	4.50	16	54		Drugs at 102nd.Min.
	110	5.25	18	80		
	120	5.50	20	60		
	130	5.00	21	48		
	140	5.25	21	45		
	150	5.25	20	45		
	160	5.00	20	50		
	170	5.25	20	54		
	180	5.00	20	60		Destroyed
Dog No. 38 Sex: F Wt.: 13 Kgs.						
	10	1.75	8	130	25	
	20	2.25	16	54		
	30	3.00	20	56		

40	3.00	23	62	10	
50	4.00	26	42		
60	3.75	25	60	5	At 61st. Min.
70	4.00	28	42		
80	4.25	28	52		
90	4.25	28	46		
100	4.00	27	54		
110	4.00	26	54		
120	4.00	20	90		Drugs at 111th.Min.
130	4.50	22	70		
140	4.50	25	56		
150	4.50	25	50		
160	4.50	27	50		
170	4.50	28	46		Destroyed

Dog No. 39
Sex: F
Wt.: 29 Kgs.

10	3.00	14	140	27	
20	4.25	32	58	7	At 19th. Min.
30	4.75	36	68		
40	4.75	41	60	10	37th. Min.
50	5.25	45	60	8	43rd. Min.
60	5.50	45	66	6	51st. Min.
70	5.25	45	48	7	61st. Min.
80	5.25	40	48		
90	5.25	39	40	5	87th. Min.
100	5.25	37	42		
110	5.00	36	46		
120	5.00	35	50		
130	5.00	33	52		
140	4.75	30	92		Drugs at 133rd.Min.
150	5.25	31	92		
160	5.25	34	84		
170	5.75	37	82		
180	5.50	32	58		
190	5.50	31	50		Destroyed

Effect of bleeding on blood pressure, ventilation and rate of respiration

Particulars of dog	Time in Minutes	Ventilation Liters per Minute	Resp. Rate Per Minute	Blood Pressure mm. Hg.	Bleeding ml./Kg. body wt.	Remarks
Dog No. 8						
Sex: M						
Wt.: 17 Kgs.						
	10	3.00	22	156	25	
	20	3.25	22	156		
	30	3.00	17	150		
	40	3.50	21	140		
	50	3.00	13	28	20	At 46th. Min.
	60	3.50	25	25		
	70	4.75	35	46		
	80	4.50	37	56		
	90	4.75	37	58		
	100	4.75	37	45		
	110	5.00	38	48		
	120	5.00	38	46		
	130	5.00	37	42		
Dog No. 9						
Sex: F						
Wt.: 12 Kgs.						
	10	1.75	22	100	25	
	20	1.80	22	100		
	30	2.25	24	64		
	40	3.00	32	48	10	At 38th. Min.
	50	3.00	33	74		
	60	3.25	33	50	5	At 51st. Min.
	70	3.25	34	62		
	80	3.25	35	68		
	90	3.25	36	70		
	100	3.25	37	72		
	110	3.75	40	70		
	120	3.75	41	68		
	130	3.75	42	66		
	140	3.50	42	68		
	150	3.75	42	64		
	160	4.00	45	62		
	170	4.25	50	60		
	180	5.50	60	60		
	190	5.50	60	58		Destroyed
Dog No. 10						
Sex: M						
Wt.: 8 Kgs.						
	10	1.5	46	150	25	
	20	3.25	54	72		

30	3.00	41	68	5	At 23rd. Min.
40	3.25	39	45	5	At 37th. Min.
50	3.00	41	52		
60	3.00	41	52		
70	3.25	42	46		
80	3.00	40	50		
90	3.00	40	50		
100	3.00	40	50		
110	3.25	42	48		
120	3.25	43	46		
130	3.25	44	46		
140	3.25	43	46		
150	3.00	41	46		
160	2.75	32	44		Destroyed

Dog No. 11
Sex: M
Wt.: 16 Kgs.

			130	25	
10	2.25	20	56		
20	2.75	27	50		
30	3.00	30	54		
40	3.00	31	50		
50	3.00	30	46		
60	3.25	32	12		Died

Dog No. 12
Sex: F
Wt.: 17 Kg.

10	2.75	13	150	25	
20	3.50	21	86	10	At 16th. Min.
30	5.00	40	44	5	At 21st. Min.
40	5.25	38	56		
50	5.25	34	76		
60	4.75	31	84		
70	5.00	36	45	5	At 64th. Min.
80	5.00	32	50		
90	4.75	27	54		
100	4.75	30	60		
110	4.75	30	60		
120	5.25	40	62		
130	5.25	42	60		
140	5.00	41	52		
150	3.75	35	48		
160	3.25	20	30		Died

Dog No. 13
Sex: M
Wt.: 8 Kgs.

10	1.50	1o	134	25	
20	1.75	27	45		

	30	2.00	29	66		
	40	2.00	31	34	10	At 37th. Min.
	50	2.75	38	48		
	60	2.75	41	56		
	70	2.75	41	50		
	80	2.75	41	50		
	90	2.75	42	50		
	100	2.75	41	50		
	110	2.50	42	52		
	120	3.00	42	50		
	130	3.00	44	50		
	140	2.75	44	46		Died
Dog No. 14						
Sex: M						
Wt.: 18 Kgs.						
	10	2.50	12	130	25	
	20	3.25	19	58		
	30	4.75	22	58		
	40	4.75	23	74		
	50	5.00	24	54	10	At 43rd. Min.
	60	5.25	30	64	5	
	70	5.00	25	46		
	80	4.50	27	48		
	90	3.75	27	48		
	100	1.50	15	44		Died