EFFECTS OF SOME ANALEPTIC DRUGS AGAINST DEEP PENTOBARBITAL ANESTHESIA IN DOGS

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Presented by

MOHAMMAD ANWARUL ISLAM KHAN

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Clyde F. Cairy
Major Professor

EFFECTS OF SOME ANALEPTIC DRUGS AGAINST DEEP PENTOBARBITAL ANESTHESIA IN DOGS

By

Mohammad Anwarul Islam Khan

A THESIS

Submitted to
Michigan State University
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Dedicated To:

My beloved parents Mr. and Mrs. Nurul Islam Khan for teaching me the moral and spiritual values throughout my life.

AND

Parveen Banu for her inspiration, encouragement and tolerance and who represented a great incentive to make my program a success in U.S.A.

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Finally, I owe to myself, to my sponsoring authority (AID), and to my country to make the most of the opportunity that circumstances or life has offered me and to equip myself for my coming role in the great future of my country--Pakistan.

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INTRODUCTION

The author was interested to do research on some analeptics in order to partly solve the problem of death due to overdose of barbiturates, particularly pentobarbital sodium which has become a quite common tool for self-destruction. Moreover the previous work on analeptics led the author to find still improved drugs, if any, for the treatment of deeply barbitalized patients.

The commitment of suicide by an overdose of barbiturate has been one of the greatest problems in the field of medical science. It is found that in 1954, 391 people committed suicide in England and Wales by taking an overdose of barbiturate--eight times as many as in 1945. There was no corresponding increase in the total number of suicides, so it is clear that barbiturates are increasingly preferred as a means of self-destruction and that the treatment of intoxication by these agents has consequently become an important medical problem. Acute barbiturate poisoning has become more and more common during recent years, and in Sweden during the last 15 years, both the number of poisoning and the number of deaths have increased roughly sixfold. The same sharp rise in the figures occurs in Denmark. In Sweden in 1947 the number of deaths from infantile paralysis and from acute barbiturate poisoning

stood at the same level. In Denmark in the same year there was one death from barbiturate poisoning for every two deaths from pulmonary tuberculosis.

The widespread use of certain barbiturates, particularly pentobarbital as hypnotics, narcotics and anesthetics has created a problem throughout the world to find a suitable antidote in cases of overdose with these agents. The more extensive use of barbiturates has led to more accidents by deliberate or accidental improper use and overdose. Over the past decade the amount of barbiturate used on both sides of the Atlantic has more than trebled while the incidence of barbiturate poisoning has increased fivefold (Nilsson, 1951; Locket & Angus, 1952; Clemmenson, 1954; Goldstein, 1947; Doppany, and Fezekas, 1950, 1952, 1954; Moller, 1954; Atwall & Lunderquist, 1951; 1953; Goodman & Gilman, 1947).

The greatly increased importance of barbiturate poisoning as a therapeutic problem is forcefully documented by recent statistics from England, Sweden and the United States. In the United States alone, the yearly number of reported deaths has risen from 266 in 1935 to a peak of 1,140 in 1949 and remained close to 1,000 through 1953. When one takes into account the discrepency between reported and the actual number of deaths, as well as the probable ratio of 13 to 1 of reported nonfatal cases to fatal cases some perspective is gained in assessing the magnitude of the problem. It is safe to estimate that considerably more than 15,000 patients will be seen each year in the United States for

accidental or intentional overdose of barbiturates. During the last 20 years the mortality, according to literature, has obstinately maintained itself at about 20% in severe cases, in spite of successes supposed to have been achieved by the appearance of central analeptics.

The ready availability of some drugs, notably the barbiturates, has given rise to the alarming increase in drug poisoning both accidental and suicidal. Statistics of 1931 show that out of a total of 5,147 suicides by all methods, 0.23% were due to barbiturates and another 0.23% due to "accidental" poisoning with the same drugs. The corresponding figures in 1951 were 4,469 suicide with 5.5% due to barbiturates and 2.6% due to "accidental" deaths from the same drugs. The figures for 1952 show that the rise continues; of 4,338 suicides, 10.9% were due to barbiturates and 3.2% due to accidental poisoning. No fewer than 98 different brands of various barbiturates are available on the open market. Sollmann stated that only carbon monoxide is more commonly used, as one-seventh of all cases of poisoning (excluding those due to carbon monoxide) treated in hospitals of the large cities of the United States in recent years were due to barbiturates. Goldstein placed these figures even higher, stating that one-fifth of drug poisoning cases in 14 hospitals having a total admission rate of 1,060,275 patients during 1940 to 1945 was due to barbiturates. The number of deaths in the United States for the 1943, 1944, and 1945 (454, 520 & 795 respectively) demonstrates the increasing

seriousness of this problem. In New York City in 1945 there were 197 deaths as contrasted to 42 deaths in 1939 according to Billow and data from the Medical Examiners. This is an increase of 400%. Addiction to barbiturates is a growing problem, and the mental changes accompanying barbiturate poisoning are a cause of concern.

Analeptics are known to be CNS stimulants employed to counteract CNS depressants, notably barbiturates, without remarkable side effects. The traditional use of pharmacological analeptics for the treatment of patients depressed to the point of coma has been more often employed to counteract the depressant effect. But in the absence of adequate information concerning the mode of action of central analeptics, some dangers are involved in their use (Nilsson, 1951; Locket and Angus, 1952; Clemmenson, 1954). Different views are expressed by different authors regarding the effective treatment of barbiturate poisoning. Some workers do not favour their use on the grounds that the convulsions they produce may cause irreparable damage to the brain through anoxia by increasing the cerebral oxygen demand in excess of the available oxygen supply. Others who recommend their use, condemn the objection by the fact that analeptics have a protective effect against anoxia and state that analeptics, by their awakening effects and respiratory and cardiovascular stimulation, potentially can save the patient from barbiturate poisoning (Miller and Miller, 1956). However the following advantages may make the analeptics more useful:

1. Prolonged endotracheal intubation is not needed.
2. The immediate or delayed risk to the patients' life is lessened.
3. Cost of treatment is lessened as prolonged and strict nursing can be avoided.
4. This provides differential diagnosis in cases of intoxication other than barbiturates for planning further therapy for the patient.
5. To help the patient to awaken earlier than he would normally do in less serious cases.

The author decided to use methylphenidate, methetharimide and amphetamine sulfate. In some cases two analeptics were combined with the idea that they would possibly show synergistic or additive effects, thus enhancing the therapeutic value over one drug alone. The author used methylphenidate alone as well. The individual action of methetharimide has been observed in deeply barbitalized dogs in this laboratory (Cairy, Leash and Sisodia, 1961). Methetharimide and amphetamine sulphate were selected because they were found to be effective in the previous study, in combination as well as individually (Cairy, Leash and Sisodia, 1961).

CHAPTER I

REVIEW OF LITERATURE

METHYLPHENIDATE

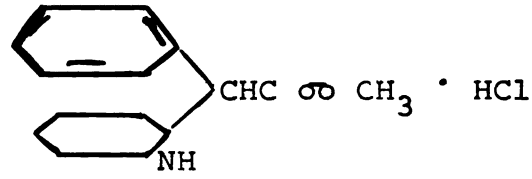
Trade Names: Ritalin, methyl phenidyl acetate, phenidylate.

Introduction:

Shortly after the advent of tranquilizing agents as a therapeutic weapon in the new chemotherapy of various severe mental states, particularly psychosis, it was noted that there was often an unpredictable aggravation of already existing and observable depression, or even production of depressions where no such reaction had been observed clinically. Because of this, the clinician turned to the apparently paradoxical, but well-established therapeutic device of limiting the effect of one drug by administering its physiologic opposite, either simultaneously or consecutively; amphetamine was given with apparent good effect. The rather excessive side reactions of amphetamine such as tachycardia, jitteryness and anxiety, appeared, however, in such a high percentage of cases that it was necessary to search for a drug with the approximate physiologic effectiveness of amphetamine without the distressing side effects. It could therefore be postulated that a drug on a physiological scale halfway between caffein at the lower end of the scale and amphetamine at the

upper end, would be a good drug. Methylphenidate appears to be the drug.

Methylphenidate hydrochloride occurs as fine, white, needle-like crystals which are freely soluble in water. Chemically methylphenidate is methyl-α-phenyl -2-piperidineacetate hydrochloride. The structural formula is:



Methylphenidate is a cerebral cortical stimulant which increases psychomotor activity without appreciable sympathomimetic effects. It arouses the apathetic, listless, moody, "tired," mild and moderately depressed individuals toward more normal levels of mental and physical activity, usually without producing an exaggerated sense of well-being or depressive rebound. Methylphenidate counteracts the drowsy sedative and other unwanted side effects of tranquilizers, antihistamines, barbiturates and rauwolfia derivative drugs.

It is the drug of choice in the treatment of narcolepsy and has found widespread application in the control of functional behaviour problems of children. Exogenous depressive states can be well-managed with methylphenidate, while deep, endogenous depressives can be aroused to cooperation with other psychiatric measures.

The favourable mood-elevating effect may not be immediately apparent during the treatment of some depressed

individuals, for it may take time to build up to an adequate therapeutic level. Therefore, therapy should be continued for a week or two before proper evaluation is made. Methylphenidate has the following advantages:

1. It acts quickly and smoothly.
2. It rarely causes excessive stimulations or jitteryness.
3. The stimulant effect disappears gradually, usually without depressive rebound.
4. It lacks the usual side effects of other stimulants and has no toxic or adverse effects on blood, urine, liver or kidney function.
5. It rarely affects appetite, blood pressure or pulse rate.

Pharmacological Action:

Pharmacological and clinical trials have shown that methylphenidate stimulates the central nervous system to a degree between that of caffein and amphetamine compounds (Meier, Gross, and Trippod, 1954; Drassdo and Schmidt, 1954) in the dog, rat, mouse and rabbit but with less sympathomimetic effect than either of the latter drugs. They observed coordinated motor movements in these animals. Their experiments (depending on the animal species and mode of administration) showed that the central stimulating effect appeared after doses of 0.5 mg/kg , lasted for several hours, and then subsided, leaving the treated animal with signs of fatigue. Larger doses produced an ataxic gait and clonic-tonic

convulsions. Pharmacological studies conducted by CIBA Research Laboratories showed that the administration of 1 mg/kg of methylphenidate subantaneously caused a definite increase in the spontaneous activity of mice for a period of 40 to 45 minutes as measured in a jiggle cage. Doses of 5 mg/kg caused more marked activity, lasting one hour. Recovery is complete and without any apparent sequelae.

When 1 mg/kg methylphenidate is administered intravenously to dogs, restlessness, hyperactivity, and jerking movements of the head are noted. This excitement reaches a maximum in about 30 minutes and then gradually subsides in 1 1/2 to 2 hours. Rats anesthetized by subcutaneous injection of 30 mg/kg pentothal showed a definite analeptic effect after a subcutaneous injection of 25 mg/kg methylphenidate. However, the analeptic effect of methylphenidate is not effective when tested against large doses of other long-lasting barbiturates such as phenobarbital.

Studies by Maxwell et al showed no change in blood pressure of normotensive dogs when methylphenidate was given in lighter than motor-stimulating doses. It blocked the pressure response elicited by bilateral carotid occlusion and produced a prompt reduction in blood pressure which has been elevated by amphetamine or ephedrine. On the other hand, methylphenidate potentiated the pressure responses to epinephrine, norepinephrine and naphazoline.

Methylphenidate had no adverse effects on the cardiovascular system with the exception of the few patients who

were hypersensitive to the drug. Repeated examinations of the pulse revealed no change in the cardiac rate or rhythm. Frequent blood pressure recordings did not disclose adverse effects on the blood pressure. This drug did not prevent or accentuate the hypertensive effect of rauwolfia or chlorpromazine. In those patients hypersensitive to methylphenidate, the cardiovascular changes (mild tachycardia, palpitation and mild elevation of blood pressure) were not due to the direct action of this drug on the heart but were secondary to its central effect.

Methylphenidate is a mild stimulant of the central nervous system which has been administered in oral form since its introduction in Europe by Dassdo and Schmidt in 1954. It has been effective in the treatment of depression of CNS resulting from the administration of reserpine and other tranquilizers. It has also been effective in the treatment of various depressive mental states and was deemed superior to other stimulants because of its relative freedom from circulatory side effects.

In 1956, Yoss and Daly reported favourably on the use of methylphenidate in the treatment of narcolepsy. This preliminary report described the results of therapy in 25 patients with narcolepsy who were treated from one to six months. Of these patients 84% reported good to excellent relief of their abnormal sleepiness. Encouraged by these results, they have continued to use the drugs. Narcolepsy in 60 patients was treated by methylphenidate for eight to

twenty-seven months. Good to excellent relief of abnormal sleepiness was reported by 49. They still believe that methylphenidate is the drug of choice in the treatment of narcolepsy. In their experience, an initially satisfactory result can be maintained after prolonged use of this agent.

Ayd in 1957 observed that methylphenidate (Ritalin) is a new psycomotor stimulant. Pharmacologic studies of this compound suggest that it is a safe analeptic that can be employed profitably in the treatment of certain psychic disorders. Methylphenidate was administered in varying doses from a minimum of 5 mg. twice a day to a maximum of 50 mg. three times a day. The individual response to methylphenidate hydrochrolide was variable. This was contingent upon two factors namely (1.) the individual patient, susceptibility to the drug and (2.) the clinical condition for which the patient was treated. Careful analysis of the various dosage levels tested indicates that the majority of patients responded satisfactorily to an average dose of 30 mg. daily. Larger doses are seldom necessary and may cause symptoms of central stimulation.

As to its effect on the gastrointestinal system, methylphenidate in therapeutic doses does not affect the appetite. Weight losses, which were usually minimal, occurred in those patients who were either hypersensitive to the drug or in whom methylphenidate had little or no therapeutic effect.

Methylphenidate had no effect on the genito-urinary system. It did not prevent the enuresis that occurs in some patients treated with rauwolfia.

In therapeutic doses methylphenidate had no effect on sleep. Many patients were able to take this drug in the late afternoon without any difficulty in falling asleep.

In contrast to other analeptics, methylphenidate did not produce euphoria in the doses tested. The majority of patients did not experience psychological effects except the sense of well-being that accompanied the relief obtained from rauwolfia or chlorpromazine oversedation.

Rauwolfia and chlorpromazine may cause anxiety in certain patients because the lethargy and fatigue induced by these drugs prevents the patient from measuring up to his self-imposed standards. Methylphenidate relieved this psychological complication by removing the drug-induced lethargy and fatigue. Hypersensitive patients complained of increased nervousness, irritability, excitability, overtalkativeness, motor-restlessness, and increased physical activity. No detectable fatigue or depression occurred following the use of methylphenidate.

Pennington has recently reported favourable mood elevating effects on a large group of patients in a mental hospital setting, all of whom were classified as chronic and as previously non-responsive to therapy, including electric shock treatment, ataraxics and psychotherapy. Many of these patients were in the schizophrenic category. With methylphenidate added to ataraxics, a significant improvement occurred, both in behavior and in their ability to communicate.

Carter found methylphenidate of use in overcoming reserpine-induced lethargy and depression, particularly in epileptic children. Young patients who could not be controlled by anti-convulsants, because of the sedative effects of the necessarily large doses, become more manageable with methylphenidate. Of the methylphenidate group of 27 patients (receiving psychotherapy for depression), 22 showed minimal to marked improvement. Five patients showed no improvement and required hospitalization and/or electric convulsive therapy. Methylphenidate appeared to increase the effectiveness of psychotheraphy with elderly depressed patients.

Lytton and Knobell (1959) stated that methylphenidate seems to be efficacious in the treatment of behavior disorders in children. The conclusion is drawn that methylphenidate acts on the cortex and produces coordinated behavior. Methylphenidate was found efficacious in 15 out of 20 behavior disturbed children. Side effects were minimal.

In a joint statement, Ferguson, Linn, Sheets and Nickels in 1956 agreed that because of its safe, fast action in overcoming most of the so-called side actions of tranquilizing drugs and because of the improvement they have witnessed in chronically underactive patients, the parenteral form of methylphenidate gives promise of opening new doors in our quest to eradicate mental illness.

Clinically, Ferguson (1955), Slier (1955), Geller (1955), Zahn (1955), Jacobson (1956), Natenshon (1956), Davidoff et al (1957) and Pennington (1957) have shown

methylphenidate to be of value in treating patients suffering from depression.

Animal studies demonstrated that this drug has the typical central stimulating effects of the phenylisopropylamine derivatives, with the addition of a stimulating caffein-like effect. However, methylphenidate differed from the psychomotor amines by being milder in peripheral sympathomimetic effect and in the quality of its psychomotor action. It lacked the marked euphorizing tendency of these drugs and, in therapeutic doses, was completely free of undesirable side reactions. Moreover, despite its caffein-like action, it did not produce the usual complex circulatory reactions associated with this drug (Ferguson, 1955).

Methylphenidate is a central stimulating drug with properties that lie somewhere between the amphetamines and caffeine, although chemically it is unrelated to either one of these preparations. Therapeutic doses produce an increase in alertness and coordinated psychomotor activity. Its effect on the cardiovascular and respiratory systems is marked by an increase in blood pressure, pulse rate, and respiration. To this date methylphenidate has been employed primarily to counteract psychomotor retardation in nonspecific patients with symptoms of depression and fatigue (Harlert and Brown-Mayers, 1958).

Addiction to methylphenidate:

Patients were kept on this drug as long as their conditions warranted usage of the drug. These periods varied

from a week to a year; however in no instances did any patient develop tolerance to the drug, or show any evidence of habituation when they were taken off the drug (Natenshon 1956).

No evidence of habituation was noted (Ayd 1957).

Barbiturate-methylphenidate antagonism:

Smith et al (1958) in treating 26 patients proved methylphenidate to be "more effective than older analeptics in mild and severe barbiturate intoxication."

Methlphenidate in doses of 30 to 1400 mg. was administered intravenously to 11 patients hospitalized because of self-administration of undetermined amounts of barbiturates with suicidal intent by Tickti et al (1958). Eight of the patients showed clinical awakening as a result of the treatment. Cann et al (1960) analyzed the therapy of 280 cases of overdosage of psychopharmacological agents and reported to the national clearing house for poison control centers. He noted that methylphenidate was frequently used in treating both mild depression and coma.

Gale (1958) stated that the intravenous median lethal doses (LD 50) were very high compared to the intravenous effective doses and were four to thirty times higher than the effective subcutaneous and oral doses. Five to ten milligrams of methylphenidate after the administration of 30 mg/kg of thiopental produced "a distinct analeptic effect" in rats, and doses of 25 mg/kg of methylphenidate subcutaneously were required to abolish the barbiturate effect completely. The

analeptic effect was less after the administration of chloral hydrate, urethane, barbital and phenobarbital. In dogs, respiratory acceleration was observed after doses of 1 mg/kg and was more marked after 2 mg/kg. Greater stimulation of respiration was noted in anesthetized animals than in unanesthetized ones. Its stimulating effect was "particularly distinct" following morphine-induced respiratory depression.

Rosenberg, Rape and Rumble (1959); Potyk (1959); Powell (1960) have used methylphenidate successfully in treating overdose emergencies for a variety of agents which include barbiturates, meprobamate, ethyl alcohol, propyl alcohol and chorpromazine. Powell considers methylphenidate to be "an invaluable drug in the armamentarium for the treatment of the patients suffering from an overdose of central depressants."

Plummer and Yorkman have summarized the effect of methylphenidate on the circulatory system of the dog. They have emphasized that this agent is free of the pressor action of amphetamine, that it antagonizes the hypertensive effect of amphetamine and suppresses the pressor effect of ephedrine, but in contrast, that it potentiates the pressor effect of levarterenol in dogs. Its value in reducing the recovery time of patients from anesthesia has been reported shortening recovery time after by a number of observers, Gale showed methylphenidate to be "useful in shortening recovery time after thiopental-nitrous oxide anesthesia" and suggested its value in counteracting "the respiratory and circulatory

effects of anesthetic adjuvants." Smith and Adriani wrote that this drug proved to be "more effective than the older analeptics in mild and severe barbiturate intoxication" and that it tends "to shorten the period of depression and reduce complications."

Curter and Maley emphasized the safety of methylphenidate in a report on its use in patients with profound chronic brain damage, it had the effect of stimulating respiration and alerting consciousness. Ferguson demonstrated the effectiveness of methylphenidate in relieving the feeling of depression and in counteracting the crippling aspects of the sedative effect of high doses of ataraxics in patients with no organic brain disturbance.

Ivey (1958) concluded that parenterally given methylphenidate, a central nervous system stimulant with a wide margin of safety, may provide an advantage in the treatment of patients who have taken an overdose of sedatives, barbiturate and non-barbiturate.

Marpurgo and others report the usefulness of methylphenidate administration in post anesthetic states. In view of the distinct stimulating effect of this substance in a number of clinical observations, it was noticed that a single intramuscular injection of 20-30 mg. of methylphenidate markedly hastened the wakening process of the patient from anesthesia, associated with a subjective feeling of well-being.

Workers with human volunteers (Heiss et al, 1956; Dassdo and Schmidt, 1954) showed that methylphenidate had a

stimulating action, and the latter investigations, as well as those of Rizze (1954) and Belluncci (1955) demonstrated that it antagonized and shortened the action of barbiturates. Clinically, Ferguson (1955); Stier (1955), Geller (1955). Zahn (1955), Jacobson (1956), Natenshon (1956), Darindoff et al (1957), and Pennington (1957) have shown methylphenidate has the apparently specific central stimulation of respiration and "alerting" of consciousness in case of overdosage by tranquilizing agents and barbiturates. Moreover it has a wide margin of safety, this appears to warrant more intensive clinical evaluation.

Fate and Excretion:

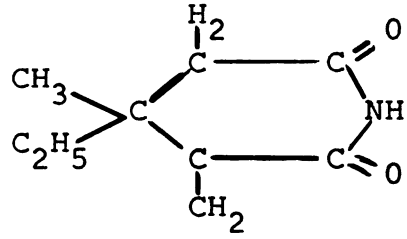
Methylphenidate was found to be distributed in the body in several chemical forms including the intact drug, its product of hydrolysis and a water soluble conjugate. Over a 24 hour collection period approximately 70% of the injected dose appeared in the urine while only 2% appeared in feces. Most of the drug in the excreta was composed of a degradation product similar in certain respects to those found in the tissues (Sheppard, Tsien, Rodegker and Plummer, 1960).

METHETHARIMIDE

Trade Names: Mikedimide, Megimide, Bemigride, NP13.

Introduction:

Methetharimide was first synthesized in 1911. Its antibarbiturate activity was first observed by Shaw and others in 1951. It was subsequently investigated in animals (Shaw et al 1954) and in man (Shulman et al 1955). Chemically it is . . . . β-β-methyl ethyl glutarimide or 3,3-methylethyl glutarimide.



Megimide and Mikedimide are preparations of methetharimide. They are chemically the same differing in their solvents and concentrations. Megimide is a 0.5% solution in water and Mikedimide is a 3% solution in propylene glycol of methetharimide.

Only Mikedimide was used by the author. The way of excretion of propylene glycol is the same as that of methetharimide and in large doses it has a CNS depressant action.

Methetharimide is of particular clinical interest because of attempted suicide and accidental overdose with barbiturates are common, and an effective antidote would help to reduce the morbidity and mortality which results. Such an

antidote must be free from dangerous side actions, e.g., convulsions, and effective because careful conservative care without the use of drugs has already brought the mortality down to 1.6% (Clemmensen 1954) in Scandinavian centers devoted to this problem. Some preliminary work was done previously by Shaw et al 1954, and their work is an extension of it.

Pharmacological Actions:

Methetharimide is related to barbiturates by the similarity of the ring system. It possesses a poor stability in water. According to the technical bulletin of Parlam Corporation, methetharimide appears to exert a direct antagonism to barbiturates on almost a milligram for milligram basis and is active against most barbiturates. The antagonism or reversal of barbiturate anesthesia by methetharimide is directly proportionate to the plane of anesthesia induced "to effect" by the barbiturate employed. The level of barbiturate antagonism by methetharimide is also "to effect" and the changes produced are notably demonstrated in reflex return, respiration rate, pulse rate, heart sounds and increase in blood pressure. An overdose of methetharimide can induce mild convulsions particularly when it is given too rapidly. A small dose of the barbiturate through the same needle readily reverses this effect. In laboratory animals, this effect has been demonstrated at will and the specificity of antagonism of these drugs for one another is clearly seen.

According to Cass (1956), it is concluded that methetharimide is a more effective barbiturate antagonist than the

commonly used analeptics. Its chief disadvantage is its convulsant action when given to patients who have not had barbiturates previously. The same difficulty accompanies the use of pirotoxin. An electroence-phalographic study of methetharimide has demonstrated the following:

1. It markedly reverses the pattern of deep depression due to all barbiturates and thiobarbiturates tested.
2. It does not reverse the pattern of deep depression due to some non-barbiturates, hypnotics and anesthetics.
3. It is capable of reversing the deep barbiturate pattern more than the commonly used analeptics and convulsants.

Banica and Wilson in 1950 and Shaw et al in 1954 are of the opinion that methetharimide is a CNS stimulant in both barbitalized and normal animals. The clinical impression remains that methetharimide provides the most effective means of reversing barbiturate anesthesia. Hahn and associates found methetharimide the most potent drug against barbital, while in studies by Richard in 1959 in mice picrotoxin and metrazol were observed to possess advantages over pentobarbital. In experiments in human beings, by Gershon and Shaw, Megimide was found more effective against phenobarbital than against amobarbital. According to Shulman, Shaw, Cass, Whyte (1955), the more active agent, methetharimide, unlike the central analeptics in current use, appears to exert in

therapeutic doses at best, a direct antagonism to the offending barbiturate, and will readily restore the patient from a deep coma to desired state of light anesthesia--"the safe state"--from which spontaneous recovery to full consciousness usually occurs within eight hours. This removes the need for strict and prolonged medical and nursing care (Nilsson, 1951; Locket and Angus,1952; Clemmensen, 1954; Mouer, 1954) and virtually eliminates the risk of complications. The chemical structure of methetharimide indicates a definite resemblance to the barbiturate ring system. However, methetharimide in high doses, and particularly if given rapidly, will cause convulsions in both barbitalized and normal animals (Benica and Wilson, 1950; Shaw et al, 1954) and some workers, (Shulman, Shaw, Cass, Whyte, 1955) often experiment without the loss of an animal.

However, full animal investigation (Shaw and Bently, 1952; Shaw et al, 1954) has indicated that these substances possess a high therapeutic index, and no signs of toxicity have been observed with the suggested method of treatment. The pharmacology of methetharimide has briefly been described and evidence presented to suggest that methetharimide which has a structural resemblance to the barbiturate ring system, may exert its effect by a direct antagonism to the offending barbiturate. It is suggested that these substances may provide an effective means of controlling anesthesia induced by barbiturates, both in enabling the rapid recovery to the conscious state where desired and in counteracting any emergency such as laryngeal spasm.

Although methetharimide, a glutarimide, has some structural resemblance to a barbiturate, it cannot be considered as an antimetabolite displacing the barbiturate from a receptor site. The antagonism is pharmacologic, a stimulant counteracting a depressant (Slater). In an isolated mitochondrial system methetharimide does not antagonize but rather enhances the decrease in oxygen uptake caused by amobarbital.

In 1954, Shaw et al showed that methetharimide was capable of reducing the narcotic effect of barbiturates in animals and man and suggested than in therapeutic dosages it exerts a direct antagonism to barbiturates. It has been known for a long time that barbiturates depress the respiratory system of the cells, and preliminary experiments seem to show that a certain correlation exists between the narcotic effect of barbiturates and their ability to depress the respiration in an isolated liver mitochondrial system. He observed no antagonistic effect of methetharimide on amytal in this system. On the contrary, in higher concentration, it intensified the depressing action of amytal on the mitochondrial respiration.

The pharmacological activity exhibited by methetharimide in animals and man generally depends upon the quantity and rate of its administration. Slow intravenous infusion usually produces a symptomatic awakening even from very deep barbiturate narcosis. This has been shown in dogs under EEG control (Shaw et al 1954) and has been confirmed in the mouse,

rat, rabbit, cat, phalanger, sheep and man. Rapid intravenous administration to such deeply narcotized dogs produces, both clinically and electroencephalo-graphically, a pattern of cerebral excitation followed by convulsion. Evidence is presented suggesting that the analeptic activity may be due to a selective specific site competition which may depend upon three receptor sites, one of which anchors the -CO-NH-CO grouping which is common to all these drugs. The others, producing pharmacologically opposite effects, are so disposed as to respond to the substituent groups on the carbon atoms α or β to the -CO-NH-CO groupings (Shulman 1956).

According to Wyke and Frayworth (1957), it is suggested that methetharimide is a direct reticular stimulant, facilitating transmission through counterbalancing the depression of this system that exists during barbiturate narcosis. The manifestations of narcosis are reversed for as long as enough methetharimide remains in the blood and in the tissue fluids of the central nervous system. These inferences receive further support from encephalographic studies of Cass (1956) and Wyke (1957) and from studies of narcotized and other subjects (Delany et al 1956 and Drossoponlo et al 1956, Crean and Fink 1957). They led to the conclusion that methetharimide is not a pharmacological antagonist to barbiturates in the literal sense. There is now much evidence (Wyke 1957) that the anesthetic action of barbiturates depends primarily on their interferring with activity in the reticulocortical activating system, which links the cerebral

cortex and the reticular nuclei in the brain-stem. This reticular depression underlies the patient's diminishing contact with his environment, the muscular relaxation and reduction in reflex responses to sensory stimulation, and the diminution in pulmonary ventilation, which are such characteristic features of anesthesia.

In therapeutic doses it appears to cause a slight rise in blood pressure, and a large dose given intravenously to a barbiturized patient has produced a large rise in blood pressure and sweating, suggesting a direct effect on the autonomic ganglia (Shulman et al 1955); Shaw et al (1954) reports that cats were aroused to a state of reflex activity and semi-consciousness from the narcosis of pentobarbital (60 mg/kg). He also observed that the patient was brought to a "safe state." The improvement was shown by the raised blood pressure, deeper respiration and the presence of some reflexes. 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.

Methetharimide--Barbiturate antagonism:

In 1955 Shaw reported that he had discovered a real antidote to the barbiturates, and the early publications on the subject were very encouraging. Methetharimide was supposed to lighten the coma of even deeply unconscious patients

and to bring them up into a "safe state" from which they could relatively quickly be aroused to wakefulness. Louw and Sonne in 1956 investigated methetharimide treatment on a series of poisoned patients, several of whom were apneic or becoming so. The first and striking experience was that methetharimide brought about a tangible stimulation of respiration and a simultaneous hyperreflexia. Clemmensen in 1956 considered this a noteworthy effect and one which he had never previously witnessed during his efforts to forestall or reverse apnea, a much dreaded complication. Further investigation failed to confirm Shaw's findings that methetharimide shortened the duration of coma, hastened the elimination of barbiturate, and caused the patient to awaken with higher blood barbiturate levels than was possible previously. In 1956 Pedersen established that the stabilizing effect of methetharimide was not such as to allow any relaxation of antishock measures and that barbiturate elimination followed the same course as in those patients who had received no methetharimide. Kjaer-Lessen was able to show in 1956 that a considerable number of methetharimide-treated patients exhibited psychosis during convalescence. The psychosis were characterized partly by visual halucinations and partly by delirium. They were admittedly of relatively slight degree, the incidence being about 30%, and spontaneous recovery usually occurred in 2-6 days. The early impressions remain and the effect on respiration, even in desperately grave cases, is beyond dispute. Its properties do not lie, however in a purely pharmacologic

antagonism to barbiturates, since the effects of the latter persist. As a central analeptic, which methetharimide must be regarded, it is superior to early preparations in that it does not cause hypertension and overtaxing of the already intoxicated myocardium, neither does it cause hyperpyrexia. The use of methetharimide in patients occasionally does not, however, justify neglecting the antishock regimen, which remains the most vital factor in bringing about as normal a physiologic condition as possible during the coma period.

In rats, mice and rabbits, methetharimide antagonized pentobarbitone, thiopentone and barbitone anesthesia, reducing the sleeping time by half and doubling the barbiturate-depressed respiration rate. In unanesthetized animals, methetharimide produced fasciculations and/or generalized convulsions with doses of 30 mg/kg; fatal convulsions occurred in these animals (Harris 1955).

Shaw et al (1955) and Shulman et al (1955) have shown that methetharimide is a valuable and effective barbiturate antagonist. Perinpanayagam et al (1955) reported the case of a child of 15 months who was successfully treated with methetharimide after taking 21 grains (1.5 Gm) of barbiturate. Clemmensen (1956) published his results on the treatment of over 70 cases of barbiturate poisoning, and this is the most extensive series treated with methetharimide so far reported. Two cases of barbiturate poisoning were recently reported in which methetharimide treatment led to a successful outcome after the injection of doses of barbiturate within the fatal

range. One had taken 16 Gm. of phenobarbitone and the other 23 Gm. of barbitone. The findings of Gerson and Shaw (1957) indicated that 10% or more methetharimide in combination with barbiturates affords protection against the central depressant effects of the latter. In the human methetharimide is a more effective antidote to the central depressant effects of phenobarbitone than to those of amylobarbitone and pentobarbitone.

In 1954 Shaw et al described their investigations of methetharimide and claimed it to be a barbiturate antagonist. They based their opinion on experiments in which they had found a reduction of sleeping time in animals of several species that had been narcotized with pentobarbitone, barbitone or phenobarbitone as well as on clinical experience.

In 1955 Shaw stated that the action of methetharimide was specific and that it did not affect the depressant actions of other anesthetic agents such as ether, chloroform and morphine.

Lately voices have been raised against the specificity of methetharimide, which is instead believed to act mainly as a central analeptic. Thus Hahn et al stated that it is "a functional and not a competitive antagonist." They found that methetharimide acts mainly as a central analeptic.

Louw & Sonne (1956) observed that in barbituric acid poisoning, narcosis is known to be due to inhibition of respiratory process which leads to the formation of adenosine triphosphoric acid, necessary for acetylcholine synthesis. It

would therefore seem reasonable to seek the answer to the question whether methetharimide is an antagonist in the strict sense of the word in studies on its effect on the formation of adenosine triphosphoric acid in the nerve cell. Possibly the drug has both effects: It may be an antidote as well as a cerebral stimulant. As a stimulant it has novel features. It does not raise the blood pressure or induce hyperpyrexia as do other analeptics, and it does not seem to provoke increased oxygen consumption by the cerebral tissue. Accordingly it can be regarded as a valuable supplement to other remedies for poisoning by narcotic drugs.

In the cat it was observed to have marked stimulating action on the barbiturate depressed respiration, the rate being as much as doubled for a period of 5-10 minutes after injection (Shaw, Simmon, Cass, Shulman, Austee, Nelson 1954).

Delay et al (1956) have published a complete review on the pharmacology of this drug concerning its clinical use as barbiturate antagonist. Trantner et al (1957) have observed that it makes prolonged sleep therapy with a barbiturate safer. Gershon and Shaw (1957) have reported that oral mixtures of barbiturates and methetharimide lead to hypnosis without secondary effects and avoid the danger of barbiturate overdosage. A number of papers have dealt with the clinical application of methetharimide in man. Methetharimide is not a specific barbiturate antagonist since it will antagonize other depressors unrelated in chemical structure to the barbiturates.

Fate and excretion:

Relatively little seems to be known about the absorption and the fate of this compound despite its considerable use in therapeutics. Anderson (1958) described a spectrophotometric procedure capable of detecting B-B disubstituted glutarimides in biological fluids, and showed that methetharimide disappeared rapidly from the blood stream after intravenous injections, 90% having gone within 20 minutes. This was attributed to a rapid and even distribution throughout the body and a slow rate of excretion in the urine. Much of methetharimide is excreted in the urine unchanged (Shulman et al, 1955). Mccallum (1955) showed that methetharimide was excreted by man partly unchanged and partly as P-(2-hydroxy ethyl) -β- methylglutarimide. A specimen (70 mg) of methetharimide labeled with 14C at the two α positions was used to determine the distribution and the fate of the drug. It had a specific activity of 8.5 Mc/mg. The PKa of 11.2 indicates that methetharimide exists in the blood largely in an unionized form. It has a low coefficient of distribution between arachis oil and phosphate buffer (PH 7.4 at $37_{\circ}$) of 3.2, and is very soluble in fat solvents such as ether and chloroform. The content of methetharimide in fat found after injection into the blood is consistently low and examination of residues has confirmed that this is a true state of affairs and not a misconception due to poor extraction from fat. Methetharimide must, therefore, penetrate cells by some other route than the lipophilic one if such exists. The work of

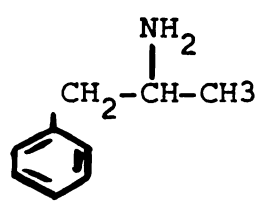
Kahn (1952) with picrotoxin and that of Achor, Gieling and Domek (1956) with methetharimide on the distribution of [355] thiopentone sodium implies that methetharimide decreases the concentration of barbiturate in the central nervous system, reduces its storage in fat and increases the rate of excretion in urine, while picrotoxin has no effect on distribution. If this effect (essentially one on membrane permeability) is indeed the basis of the mode of action it must be effective at low concentration of methetharimide, because antagonism to barbiturate can be demonstrated in mice or men for two hours or more after injection and at that time the concentration in the brain and cerebraspinal fluid is very low. Also this effect must modify the distribution of other sedative-hypnotics in a similar way. It seems unlikely. The retention of one-third of the initial dose after 24 hours suggests the possibility of a long persisting clinical activity and low toxicity.

AMPHETAMINE

Trade names: Benzedrine, Amfetasul.

Introduction:

Initial investigations on amphetamine were reported by Piness and co-workers (1930) who described the vasopressor responses to amphetamine in dog and man. Hartang and Munch (1931) also observed the pressure response to the drug in dogs and compared its potency with isomeric phenylpropylamines. Amphetamine was first prepared by Edeleane (Burger 1951). Chemically it is racemic B-phenyl isopropylamine or α-phenyl β-amino propane or 1-phenyl-2-amino propane.



Amphetamine exists in three isomeric forms--levo, dextro and dl or racemic form. It is a sympathomimetic amine. The racemic form is commonly referred to as amphetamine, the dextro form is called dextroamphetamine which is most potent, while the levo form is the least potent in all the isomers. The d-form is from two to four times more active a central stimulant as the racemic mixture (Burger 1951). The racemic mixture of d-and l-forms is the most commonly used. Amphetamine sulfate is the preferred salt. It is a white, odorless powder which is freely soluble in water.

Pharmacological Action:

Amphetamine is a synthetic sympathomimetic amine closely related to epinephrine and ephedrine and it differs from them in the following properties:

1. It is resistent to enzymatic destruction in the gastrointestinal tract and so can be given orally.
2. It shows no synergism with cocaine or reversal effect with ergotamine.
3. Cocaine synergises the action of epinephrine by inactivating the amine oxidase and phenol oxidase which destroy epinephrine.

Amphetamine enjoys a wide range of therapeutic uses. This drug possessed about 1/100 to 1/200 the pressor potency of epinephrine, but the cardiovascular effect is longer in duration (Alles, 1933) and much less toxic when compared to epinephrine (Burger, 1951). It has been suggested that amphetamine is a strong inhibitor of amine oxidase; it would act by preventing the oxidation of epinephrine by amine oxidase and by competing with epinephrine for the receptor substance in the effector cells (Goddum and Kwait-Kouski, 1938). It stimulates the cerebrospinal axis, especially the brain stem and the cortex. It compares well with all other drugs in analeptic effectiveness and finds considerable use in counteracting over-depression caused by anesthetics, narcotics, hypnotics, etc. Animals receiving sufficiently large amounts of amphetamine exhibit tremors, restlessness and increased motor activity. This is due to cortical stimulation

by the drug, but it may also result in part, from excitation of the brain stem. It does not produce seizures or subconvulsive dysrhythmia in a normal animal. Indeed, the drug can obtund the maximal electroshock seizure and prolong the recovery period after such seizures. These properties may be related to the usefulness of amphetamine in certain cases of epilepsy. 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 is reputed to be an anorexigenic agent, but how it decreases appetite is not completely known. There is some evidence that by adrenergic action it increases the emptying time of the stomach. Others believe that the appetite depression is the result of cortical stimulation. A recent pharmaceutical development is the combination of a barbiturate such as amobarbital or phenobarbital with amphetamine or d-amphetamine. These preparations are described as "elevating" or "ameliorating" the mood.

The blood pressure is raised, the peripheral vessels are constricted, and the heart muscle is stimulated. Bradycardia rather than tachycardia is the usual cardiac response. Amphetamine differs from epinephrine in that it exhibits tachyphylaxis and does not manifest enhanced activity after cocaine or denervation (Goodman and Gilman 1955). Amphetamine markedly potentiates the pressor response to epinephrine. Therapeutic doses of amphetamine in normal subjects do not increase cardia output, pulmonary circulation

time, vital capacity, B.M.R. (Altschule and Iglaner, 1940; Goodman and Gilman, 1955). Amphetamine causes a rise in mean blood pressure. This rise in blood pressure is accompanied by a decrease in cerebral blood flow and cerebral oxygen utilization. Amphetamine causes vasoconstriction centrally by stimulating the medullary vasoconstrictor centres and locally by stimulating the sympathetic receptive substance in the muscle cell of the blood vessels. Amphetamine applied locally to mucous membranes causes vasoconstriction and shrinkage of congested tissue by the same mechanism. Amphetamine sulfate has no marked effect on cardiac muscles. The electrocardiogram is not greatly altered in the vast majority of cases (Myerson 1940). In several instances a transistory reflex showing of the pulse occurred in man at the outset of the rise of arterial pressure. In some such cases a transitory slight increase in cardiac output was also detected (Altschule and Iglaner 1940). Rise in blood pressure in man is marked and lasts for 1-2 hours. The effects tend to lessen and disappear after the drug is used over an extended period (Myerson 1940). Detrick, Millikan, Modern and Thienes (1937) found an irregular effect of amphetamine on the blood pressure in dogs. They observed variation over a wide range from decrease to an increase in normal blood pressure. They also observed that ergotamine tartrate when used before could increase, decrease and even abolish the effects following amphetamine and that cocaine decreased the pressure effect of amphetamine. Its effects in raising the red cell and white cell counts are often

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

It has been proven a potent drug for stimulating the medullary respiratory center depressed by anesthetic, narcotic and hypnotic drugs (Goodman and Gillman, 1955; Beckman, 1952). It affects respiration in two ways--by stimulating the respiratory center and by dilating the bronchioles (Goodman and Gilman, 1955). The latter effect is weaker but much more prolonged than with epinephrine (Alles and Prinzmel et al, 1933).

The respiration is first depressed mostly in amplitude, probably reflexly with the rise in blood pressure. Then it soon comes to the preinjection level and then is further stimulated markedly in rate and amplitude both to increase ventilation rats considerably (Alles 1933). Detrick, Millikan, Modern and Thiens (1937) observed that with the first dose of amphetamine (0.25-4 mg/kg) in dogs and cats anesthetized with pentobarbital, there was a marked increase in rate and depth of respiration. Subsequently doses produced successively smaller increases and finally often a decrease in rate. The actual mechanism of respiratory stimulation was not determined. However, from the facts that the anesthetized animal showed obvious symptoms of CNS stimulation it may be inferred that the action was central. The stimulant effect of amphetamine is not yet clear and it is doubtful whether its

peripheral sympathomimetic action can be profitably correlated at present with its excitatory effect on the CNS. Repeated injections of amphetamine may cause depression of respiration. Hyperventilation is reported as another risk associated with the use of these amines. Small doses should be preferred since they are said to relax the bronchial muscle and slow and deepen the respiration.

Amphetamine produces an "arousal reaction" in animals under anesthesia and as an analeptic finds a wide use in shortening the duration or decreasing the intensity of anesthesia. It stimulates the respiratory centers to increase the rate and depth of respiration. In addition, it dilates the bronchioles through its sympathomimetic activity.

The psychic effects of amphetamine have been studied in great detail in man; the response elicited depends upon the mental state and dose administered. The main results seen are wakefulness, alertness, increased initiative and elevation of mood, enhanced confidence, euphoria, lessened sense of fatigue, increased vasomotor and speech activity and increased ability to diminish sense of fatigue is purely subjective and central in origin. Amphetamine does not enable subjects doing rapidly exhausting work to perform longer or to recover more quickly. It is said to inhibit production of fatigue, particularly in monotonous skilled tasks and somewhat to restore performance in a fatigued individual. The wakeful psychologic effects are related to some unknown control stimulation (Myerson 1940). The effect in counteracting

sleep has brought about the use of amphetamine sulphate as a specific in narcolepsy. This has been well established by a number of workers (Prinzmel and Bloomberg, Ulrich), Amphetamine sulphate does not cure narcolepsy, but it produces a sympathetic relief of such magnitude as to entitle it to be designated as symptometic specific. There has developed a general use of amphetamine sulfate to offset sleep and fatigue whenever something extraordinary has to be performed, during a period of which sleep or fatigue should be disastrous or undesirable. Amphetamine by its central action exerts a direct analgesic effect. It has been found to enhance and prolong the analgesic action of morphine in man while it decreases the drousiness, dizziness and weakness caused by morphine. However, amphetamine largely eliminates the analgesic action of nitrous oxide. After prolonged use or after large doses of the drug, fatigue and mental depression or other adverse effects may occur.

Addiction to amphetamine:

The drug is neither habit forming nor have any untoward symptoms yet been observed from its constant use (Myerson 1940). However, therapeutic indications for amphetamine are today becoming vanishingly slight. Diet and not pills should control obesity. Amphetamine has not shown itself to be of value in endogenous depression (Hare et al 1962). Yoss and Daly (1960) recommend methylphenidate (Ritalin) as superior to amphetamine in the treatment of narcolepsy. It has been established by, among others, Kiloh and Brandon (1962)

that amphetamine consumption leads to a tendency to increase the dose. Up to 10 times the "therapeutic" dose is common among amphetamine and phenmetrazine addicts. These preparations produce a detrimental effect on the individual and on the society. In the individual they produce an egocentricity of outlook and impairment of those skills necessary to the conduct of successful social relationships, sometimes physical harm and occasionally a frank psychosis (Connell, 1958; Beamish and Kiloh, 1960).

Connell (1958) states that addiction causes "delusions of persecutions and auditory and visual halucination indistinguishable from those occurring in paranoid schizophrenia." There appears to be very little danger of serious habituation with this drug. A characteristic abstinence syndrome does not develop when amphetamine is abruptly withdrawn but depression, tremors, weakness and gastrointestinal symptoms may have been observed in some individuals. Prolonged use of amphetamine in orthostatic hypotension to maintain blood pressure within normal limits leads to insomnia which is rather difficult to overcome even by full doses of barbiturate and lasts for 24-72 hours (Korus and Randall, 1938). These drugs (amphetamine and phenmetrazine) and drugs with comparable actions, such as diethylpropion (Clein and Benady, 1962) are dangerous drugs, in fact, if not yet in law. In a monograph on the ampetmines, C.D. Leake wrote: "Habituation to the use of amphetamine may occur, but addiction, in the sense defined by the World Health Organization, is extremely rare and not satisfactorily substantiated."

Barbiturate-Amphetamine antagonism:

Amphetamine is a powerful stimulant to the central nervous system and has seen considerable use in counteracting over-depression from barbiturates or morphine.

Amphetamine owes its stimulating effect on brain tissue respiration in the presence of R. CH_2 NH_2 to its inhibiting action on the formation of R-CHO. Owing to the competition between amphetamine and R_1 CH_2 NH_2 for amine oxidase, the greater the quantity of the inhibitory amine present, the greater is the quantity of amphetamine required to neutralize the inhibition of brain respiration. It has been known for some time that the presence of amine brings about a marked diminution in the respiration of brain examined in vitro. The molecule R. CHO, for example, isovaleric aldehyde, has been found to be highly toxic to respiratory processes in brain and this toxicity is not influenced by the presence of amphetamine. Its stimulating effect is only observable if an amine such as tyramine is also present. At relatively high concentration amphetamine itself exerts large inhibitive effects on brain respiration.

Amphetamine does not neutralize the inhibitive action on brain respiration of narcotics such as barbiturates, or of a drug such as bulbocapnine. Its effect appears to be confined to the amines capable of aldelyde formation in the CNS.

It is permissable to suggest, in view of these facts, that the clinical effects of amphetamine administration may

be related to respiratory changes in the brain. It would be of interest to discover whether there accumulates, in the condition of narcolepsy, toxic bodies (aldelydes), the formation of which is related to the administration of amphetamine.

A valuable evidence of antagonistic action of amphetamine sulfate to soluble amytal in man was produced by Rufenstein and Davidoff (1938) when they brought their ten volunteers out of deep narcosis produced by 7 1/2 grains of soluble amytal intravenously in each by 1, 2 or 3 intravenous injections of 10 mg of amphetamine sulfate within an hour of narcosis. Fourteen barbiturate-poisoned subjects were treated by Freireich and Landsberg (1946) with intravenous injections of amphetamine. Thirteen patients recovered without any ill effects except for some headache. The one death was probably due to lack of a sufficient quantity of amphetamine sulphate because no more of the drug was available.

The injection of amphetamine uniformly causes a marked blood pressure rise reaching a maximum within a few minutes after injection. This may be due to peripheral vaso-constriction (Sollman 1948). Alles (1933) noticed that amphetamine, when given intravenously produced a considerable effect in waking the animal from barbital anesthesia. In man Myerson et al (1936) reported that amphetamine sulphate subcutaneously did not affect the depth, although it definitely shortened the duration of soluble amytal narcosis, and they stated that hypertension produced by amphetamine sulfate simultaneously could be reduced by soluble amytal intravenously and also

that hypotension produced by soluble amytal intravenously could be elevated by amphetamine sulfate subcutaneously. They also observed that amphetamine sulfate considerably stimulates the respiration depressed by barbiturates. Lee and Alfredson (1952) observed that the threshold of the respiratory response sciatic stimulation, raised enormously be deep pentobarbital depression, was decreased almost to its previous level by amphetamine, thereby indicating that both these drugs acted on the central respiratory mechanism. They also found that a dose level of 2.5 mg of amphetamine per/kg would be sufficient to combat the depressant effect of large doses of pentobarbital on the blood pressure in dogs.

The treatment of coma resulting from barbiturate poisoning still takes the therapeutic skill of the physician. Amphetamine sulfate, as a drug useful in counteracting poisoning by barbiturates was first suggested by Myerson. The effect of administration is twofold: sympathomimetic action is demonstrated by a rise in blood pressure, an increase in the rate and depth of the respiration and increase in pulse rate; in its wakeful psychologic effects, amphetamine specially counteracts the soporific action of the barbiturates (Freireich and Landsberg, 1946).

Sollmann has reported that some stimulation in respiration from acute amphetamine injection was by the way of the carotid sinus reflex. Daniel et al have recently shown that barbiturates produce more depression of the cardiovascular system, even under controlled anesthetic conditions,

than was previously recognized. Thus the cardiovascular system as well as the respiratory system should be considered when attempts are made to antagonize barbiturates. Sympathomimetic amines have been considered clinically to combat hypotension in severe barbiturate intoxication in the expectation that they might overcome central depression (e.g. amphetamine) or peripheral vasodilation (e.g. phenylephrine). The study of Daniel et al suggest that the efficacy of such agents may well be the result of cardiac stimulations.

The drug is useful in counteracting poisoning by the barbiturates. The drop in blood pressure, as well as the unconsciousness, are offset. Linked with this relationship of amphetamine sulphate to the barbiturate is what is elsewhere called their "reciprocal pharmacology." If one desires to attain a sedative effect with the barbiturate and seeks to avoid the hangover and the depression which these drugs tend to produce, the addition of small doses of amphetamine sulphate is of value. Especially valuable is this conjoined use when phenobarbital is used in the treatment of epilepsy (Myerson, 1940).

Fate and Excretion:

Amines such as epinephrine are known to be rapidly eliminated, but Dr. Guttman has observed that the action of amphetamine sometimes appears to persist for more than a day. It has now been shown that the duration of action of amines in the body is determined mainly by the amine oxidases, an enzyme present in the liver, intestine and other organs. Most

amines are rapidly oxidized by this enzyme and therefore exert their action for only a relatively short time, but amines of the ephedrine series are not oxidized by this enzyme and are slowly excreted unchanged in the urine. According to Goodman and Gilman, 50% of amphetamine is destroyed in the body principally by deamination in the liver and the rest is excreted unchanged in the urine. Amphetamine resists oxidative deamination by amine oxidase which accounts in part for its long duration of action. It is a potent inhibitor of amine oxidase. However, other enzymes, e.g. phenol oxidase destroy it.

According to Beyer and Skimmer (1940), less than 50% of amphetamine is excreted in 48 hours following injection. In man the percentage of a given dose excreted generally paralleled the volume output of urine. With smaller doses, percentages excreted were greater.

There is little information concerning the fate of d-amphetamine, d-p-hydroxy-amphetamine (paredrine) and d-methamphetamine, sympathomimetic amines in the dog. D-amphetamine disappears slowly at a rate of about 8% per hour by hydroxylation and renal excretion. Norephedrine is mainly excreted unchanged at a rate of 25% per hour (Axelrod 1953), d-p-hydroxyamphetamine disappears at a rate of 40% per hour by renal excretion and conjugation. Ephedrine is rapidly metabolized at a rate of 6% per hour, primarily by demethylation (Axelrod 1953). D-amphetamine disappears slowly in the dog compared to its hydroxylated derivatives, suggesting that

in this species the major part of the pharmacological effect of the drug is due to the parent compound. A major route of metabolism of d-methamphetamine in the dog involves demethylation of d-amphetamine. D-amphetamine is bound to plasma proteins to a negligible degree but is highly localized in most organ tissue.

With ephedrine (26 mg base) approximately 100% is excreted in 24 hours, but with amphetamine (20 mg sulfate) and methylamphetamine the rates of excretion are much slower, so that only about 40% is excreted in the urine in 24 hours and the excretion continues for some 26 hours after administration (Richter 1938-39).

CHAPTER II

MATERIALS AND METHODS

Before deciding on the exact procedure for the study, various single and repeated injections of methylphenidate were tried in several dogs. Finally forty-eight dogs, including six controls, were used to observe the action of methylphenidate alone in three different dose levels and in combination with methetharimide and amphetamine in over anesthetized dogs.

The dogs were obtained from a dog pound. As there were large numbers of dogs necessary to run this project, no discrimination was made in breeds and weight of the animals. Their weights varied from 6.25 kg to 14.25 kg. But efforts were made not to use any dog anesthetized or used otherwise for any other experimental work for at least the preceeding 7 days. Sometimes the dogs were used again after the lapse of 7 days. The animals were kept in individual cages and raised on commercial dog food* and water ad libitum. Effort was made to use healthy dogs.

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*Purina Dog Chow

The following analeptics were used in this project:

**Amphetamine sulfate was a 5% aqueous solution.

***Methetharimide was a 3% solution in propylene glycol.

****Methylphenidate hydrochloride 1% solution, vial of 100 mg methylphenidate hydrochloride dissolved in 10 ml of sterile solvant. Also prepared 1% solution in sterile saline from crystalline powder.

Experimental Procedure

At the outset of each experiment every dog was carefully weighed. The dogs were then deeply anesthetized with 6% sodium pentobarbital in 10% ethyl alcohol. All the dogs were given a dose of 40 mg/kg in the beginning and the action was observed for about 10 minutes. In some cases the first injection was sufficient to induce deep anesthesia to a desired level (about 1.0 to 1.5 liters ventilation/minute). In a number of cases, one injection was not sufficient to decrease the minute ventilation to the desired level, thereby necessitating further injections according to the intensity of the depressant state of the respective subjects. The subsequent injections were either 10 mg/kg or 5 mg/kg. The

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**Amphetasul- Pitman-Moore Co., Indianapolis, Indiana.

***Mikedimide- Parlam Corporation, Englewood, New Jersey.

****Ritalin- CIBA, Summit, New Jersey

range of ventilation at the time of drug administration varied from 0.5 to 1.7 liters per minute. The intravenous injections were restricted to the radial vein for both the analeptics and the anesthetic.

The major instruments to record respiratory rate, ventilation and blood pressure were a wet-test flow meter** and the Grass model 5D Polygraph.*

The flow meter is nothing but a gas meter or wet-test gas meter. 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. The principal indicator needle is made to rotate in such a way that it can indicate each 250 cc. of air passes into the flow meter. The indicator needle makes one complete revolution for each 3 liters of air. For recording the ventilation and respiratory rate a rubber tracheal tube with an inflation cuff around its distal end was then passed into the trachea through the mouth of the dog and the cuff was then inflated to fit the tracheal tube snugly into the trachea. Considerable effort was made to inflate the cuff to fit snugly so that there could not be

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*Grass Instruments Co., 101 Old Colony Ave., Quincy, Mass.

**Cat.N.S.39445 E.H. Sargent and Co., Detroit, Mich.

any loss of the expiratory and inspiratory gas in the trachea. Degree of inflation was indicated by a pilot baloon connected with the cuff outside. This procedure allowed free passage of air into the trachea and out, but only through the tracheal tube. The tracheal tube was then connected with the wet-test flow meter in order to record and measure the expired air to find out the respiratory volume and rate. A flutter valve at the outlet of the flow meter was allowed to touch a Force-Displacement Transducer (FT.03) for recording the respiratory rate. With each expiration and inspiration there was an inflation and collapse of the flutter valve. The wet-test flow meter was then connected with the Grass model 5D Polygraph in which channel 1 and 2 were used for recording the respiratory rate and minute ventilation respectively.

Indirect blood pressure of the subjects was recorded. The idea of recording indirect blood pressure was to use the experimental subject once again after seven days if necessary. The Polygraph was adjusted in such a way each time before the start of the experiment that 1 cm deflection on the Grass paper represented 100 mm Hg. A two inch cuff fitted just below the lock of the subject was connected to a Statham Pressure Transducer (P23 AC). The transducer was connected with the Polygraph in such a way that the cuff pressure was recorded in channel 3. An electronic pulse pick up (Grass Model PTTI) was fitted in between the digits of the previously cuffed leg to record the pulse wave in channel 4. From time to time the bulb attached to the cuff was inflated

in order to build up pressure around the vessels which caused complete disappearance of pulse wave indicated by the fourth pen drawing a straight line on the Grass paper instead of the usual pulse wave tracings and the third pen was deflected up as the pressure was built up. Then the pressure was gradually released from the cuff. As a result the third pen slowly moved downward and the fourth pen gradually moved upward till the pulse wave reappeared when the pressure was completely released from the cuff and soon the cuff pressure curve returned to the baseline. Then a reading was made by drawing a straight line upward from the point of reappearance of pulse wave to the cuff pressure above, which was considered as the indirect systolic blood pressure. It was observed that an indirect blood pressure reading closer to direct blood pressure was obtained by fixing the cuff below the lock region then above the lock region. A comparison was also made to find out the differences, if any, between the indirect and direct blood pressure. It was found out that the blood pressure remained almost similar in both the cases. Indirect blood pressure was taken from time to time during the experiment. All the records were made in the standard Grass paper. The Grass model 5D Polygraph was set in such a way that the respiratory rate, minute ventilation, cuff pressure and pulse wave were recorded in channels 1,2,3 and 4 respectively. The time was recorded in one second intervals.

After setting up the machine for all the desired records, minute respiratory volume for at least 10 minutes

was observed. Effort was made to reduce the ventilation down below 1.5 liters per minute (sometimes after additional injection of 5 or 10 mg/kg of pentobarbital sodium); in some cases additional doses failed to reduce the respiratory volume below 1.7 liters per minute. In some dogs ventilation was reduced to 0.9 liters per minute while in other cases it was reduced to only 2.7 liters per minute after the first dose of 40 mg/kg body wt. in similar conditions. Occasionally some dogs showed a resistence to pentobarbital sodium to a certain level followed by an abrupt falling of respiratory volume where artificial respiration was needed.

When the ventilation was approximately 1.5 litters per minute or lower, the analeptics were administered intravenously. Single injection of methylphenidate 30 mg/kg i.v. in an over anesthetized dog resulted in a decrease in ventilation single injection of methylphenidate 15 mg/kg i.v. produced slight increase in ventilation but ventilation decreased to a minus level when the same dose was repeated after 20 minutes. A dose of methylphenidate 10 mg/kg i.v. produced the similar results. But methylphenidate 5 mg/kg i.v. produced gradual increase in ventilation in regular repetitive doses. As a result the dose of methylphenidate higher than 5 mg/kg was rejected. Three injections of methylphenidate 5 mg/kg each i.v. at 20 minute intervals produced remarkable increase in ventilation. Then 6 injections of methylphenidate 5 mg/kg each i.v. were tried which produced quite satisfactory elevation of ventilation. Finally

three different doses of methylphenidate alone were tried in six injections at twenty minute intervals. Besides this four different combinations of methylphenidate with amphetaimine or methetharimide were tried (Table 1). In each case amphetamine and methetharimide was injected first followed immediately by one injection of methylphenidate. Both the drugs were injected through the same needle. Methylphenidate was injected six times at 20 minute intervals whereas injection of either methetharimide or amphetamine was stopped after the one injection only. The idea was to see whether or not there could be any synergistic effect of methetharimide or amphetamine with methylphenidate. The last injection of methylphenidate was completed at 100 minutes and the effects were observed and recorded for one hour and thirty minutes after the last injection of methylphenidate i.e. the antagonistic actions of these drugs against pentobarbital sodium were observed for a period of three hours and ten minutes, provided the dog did not arouse to an uncontrollable extent in this observation period. In case the dog aroused and became uncontrollable, the experiment was stopped before the intended observation period.

Each combination and methylphenidate alone were tried in six dogs and the average results of these six dogs were taken into consideration as the ultimate antagonistic effect of the barbitalized dogs.

It was observed that the ventilation increased quite frequently at the time of manipulating and needle insertion

which was evidently by the reflex induced by the mechanical stimulation at the site of injection.

Six dogs were used as controls. The dogs were anesthetized in the same manner as the other experimental dogs. Effort was made to reduce the minute respiratory volume to or below 1.5 liters. The barbiturate effect was observed for a period of ninety minutes in each case.

TABLE 1. Number and groups of dogs used, dose of pentobarbital sodium administered to produce deep anesthesia, and amounts of combinations and individual antidotal drugs injected to improve breathing are shown:

Group	No. of dogs	Average wt. and ranges (kg)	Average dose and dose ranges of pentobarbital sodium (mg/kg)	Average ventilation after drug injection (liters/min)	Antidotal drugs and doses	Remarks
1.	6	10.83 (8.5-13.0)	51.66 (40-65)	1.24	None	Controls
2.	6	9.25 (8-11)	50 (40-70)	1.2	Methetharimide 40 mg/kg and methylphenidate 5 mg/kg	Methylphenidate was injected six times at the rate indicated at 20 minute intervals except in group No. 9 where methylphenidate was injected only 3 times at 20 minute intervals. In case of combination treatment first injection of methylphenidate followed immediately after the injection of methetharimide or amphetamine.
3.	6	10.2 (8-13.25)	49.16 (40-60)	1.42	Metharimide 20 mg/kg and methylphenidate 5 mg/kg	
4.	6	8.9 (6.25-12)	41.6 (40-50)	1.16	Amphetamine 4 mg/kg and methylphenidate 5 mg/kg	
5.	6	11.33 (7.75-14.25)	47.33 (40-60)	1.37	Amphetamine 2 mg/kg and methylphenidate 5 mg/kg	

TABLE 1. (Continued)

Group	No. of dogs	Average wt. and ranges (kg)	Average dose and dose ranges of pentobarbital sodium (mg/kg)	Average ventilation of drug injection (liters/min)	Antidotal drugs and doses	Remarks
6.	6	9.9 (7.5-12.5)	45 (40-50)	0.98	Methylphenidate 5 mg/kg	
7.	6	9.9 (7.5-12	47.5 (40-60)	1.16	Methylphenidate 3 mg/kg	
8.	6	9.6 (7.5-12)	44 (40-50)	1.29	Methylphenidate 10 mg/kg	
9.	6	15.4 (10.20.5)	46.6 (40-55)	1.89	Methylphenidate 5 mg/kg	

CHAPTER III

RESULTS

In order to find the standard dose for methylphenidate the author tried various doses of methylphenidate either in single dose or in repetitive doses. An over anesthetized dog treated with a single dose of methylphenidate 30 mg/kg i.v. produced a decrease in ventilation. Another dog was injected with 15 mg/kg i.v. produced a slight increase in ventilation but soon came down to a minus level when the same dose was repeated. Methylphenidate 10 mg/kg i.v. produced the similar result. Then methylphenidate 5 mg/kg i.v. was tried. This dose produced a remarkable increase in ventilation even after the regular repetitive dose. Three injections of methylphenidate 5 mg/kg each i.v. at 20 minute intervals produced an average increase in ventilation by 82% ninety minutes after the last injection. With the idea of further beneficial results, 6 injections of methylphenidate 5 mg/kg each i.v. at 20 minute intervals were tried. This dose produced a significant increase of ventilation which will be discussed later in this chapter. A comparative study of 6 injections of methylphenidate 3 mg/kg and 10 mg/kg each i.v. at 20 minute intervals has been made and described later in this chapter.

Finally the author studied four combinations and a drug individually in three different dose levels. The effect of the combinations and the individual drug on respiration in the deeply barbitalized dogs was found in the following descending order of efficiency:

1. Methetharimide 40 mg/kg i.v. (one full dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
2. Methetharimide 20 mg/kg i.v. (one half dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
3. Amphetamine sulfate 4 mg/kg i.v. (one full dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
4. Methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
5. Amphetamine sulfate 2 mg/kg each i.v. (one half dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
6. Methylphenidate 6 injections of 3 mg/kg each i.v. at 20 minute intervals.
7. Controls(deep pentobarbital anesthesia without analeptic treatment).
8. Methylphenidate 6 injections of 10 mg/kg each i.v. at 20 minute intervals (double dose).

Six dogs were used as controls in this project. The average ventilatory volume at 0 minute was 1.24 liters per

minute and average percentage increase at 90 minutes was 25 percent as shown in Fig. XII.

Single Injections of Methylphenidate:

Six injections of methylphenidate at the rate of 5 mg/kg each i.v. at 20 minute intervals produced the best results among the different dose levels of the individual drug studied as shown in Fig. IV (Dogs #19 to 24) which was the fourth best of the series of drugs studied. All the six dogs with this dosage (5 mg/kg) produced an overall increase in respiratory rate and ventilation. The ventilation increased from a predrug average of 0.98 to an average of 3.03 liters per minute, i.e. 209% increase in ventilation. The average respiratory rate increased from a predrug rate of 7.17 to 25.1 per minute. There were no remarkable changes in blood pressure in this series of dogs. The average blood pressure decreased from a predrug level of 146 to 130 mm. Hg.

The next best drug in the individual series was six injections of methylphenidate at the rate of 3 mg/kg each at 20 minute intervals as shown in Fig. VI (dog #31 to 36). In this series an overall increase in ventilation was observed in all the six dogs, but an overall increase in respiratory rate was observed in only four cases. This result indicated that increase in ventilation does not necessarily always correspond to the increase in respiratory rate. However, the average respiratory rate increased from a predrug rate of 8.5 to 11.33 per minute and the ventilation increased from a predrug average of 1.16 to an average of 1.96 liters per minute

i.e. 69% increase in ventilation. The average blood pressure decreased from a predrug level of 143 to 133 mm Hg.

No improvement was observed from the six injections of methylphenidate at the rate of 10 mg/kg each at 20 minute intervals as shown in Fig. VIII (dogs #37 to 42). The respiratory rate and ventilation per minute were, in fact, decreased after the injection of the drug in most cases. Blood pressure was decreased in most of the cases after the injection of the drug.

Combinations:

The best effect was produced by the combination of methetharimide 40 mg/kg and six injections of methylphenidate 5 mg/kg each at 20 minute intervals as shown in Fig. I (dogs #1 to 6). This combination had distinct awakening effects on four barbitalized dogs as evidenced by the return of corneal, pedal, palpebral and cough reflexes, and many times the dogs showed paddling movements, licking and swallowing symptoms and stretching of the legs. In four cases, the dogs were so uncontrollable that after 42 minutes, i.e. only after the third injection of methylphenidate in one (dog #6) experiment had to be stopped and in the other three cases (dogs #1, 3 and 5), blood pressure could not be taken throughout the entire period of the experiment due to paddling movement and stretching of the legs. There was a remarkable increase in respiratory rate and ventilation in all the cases. The ventilation increased from a predrug average of 1.2 to an average of 6.73 liters per minute, i.e. a 460% increase in

ventilation and the respiratory rate increased from a predrug rate of 10 to 77.8 per minute. There was no remarkable change in blood pressure.

The combination of methetharimide 20 mg/kg and six injections of methylphenidate 5 mg/kg each at 20 minute intervals was the second best treatment studied as shown in Fig. II (dogs #7 to 12). This combination showed distinct arousing effects in at least two dogs as evidenced by a return of the corneal, pedal and palpebral reflexes, swallowing tendencies, salivation, an effort to get up by raising the head, forcible expiration and stretching of the legs. One dog (dog #7) was so uncontrollable that the experiment had to be stopped at 150 minutes. A remarkable increase in respiratory rate and ventilation was observed. The ventilation increased from a predrug average of 1.42 to an average of 4.22 liters per minute, i.e. 197.18% increase in ventilation. The average respiratory rate increased from a predrug rate of 14 to 39 per minute. No remarkable changes were observed in blood pressure.

The third best treatment was a combination of amphetamine 4 mg/kg and six injections of methylphenidate 5 mg/kg each at 20 minute intervals as shown in Fig. III (dogs #13 to 18). Distinct arousal effects were observed in three dogs as evidenced by a return of the pedal and corneal reflexes, forceful expiration, stretching of the legs, paddling of the legs and raising the head. A significant increase of respiratory rate and ventilation were observed. The ventilation

increased from a predrug average of 1.16 to an average of 2.96 liters per minute, i.e. 155% increase in ventilation. The average respiratory rate increased from a predrug rate of 12 to 24 per minute. No significant changes were observed in blood pressure.

A combination of amphetamine 2 mg/kg and six injections of methylphenidate 5 mg/kg each at 20 minute intervals was also observed to have produced a quite satisfactory effect on ventilation and respiratory rate, although it holds the fifth position amongst the drugs studied, as shown in Fig. V (dogs #25 to 30). Although a distinct arousal effect was observed in only one, where the dog exhibited return of pedal reflexes, an overall increase in respiratory rate and ventilation were remarkable. The ventilation increased from a predrug average of 1.37 to an average of 2.93 liters per minute, i.e. 113.8% increase in ventilation. The average respiratory rate increased from a predrug rate of 10 to 23 per minute. No remarkable changes were observed in the blood pressure.

Abbreviation in the Graph:

Me	Methetharimide
A	Amphetamine sulfate
M	Methylphenidate
Ar( ) ↓	Arousal after analeptics and no more respiratory rate and ventilation and/or blood pressure record due to struggling and excitement
↕	Two drugs injected one after another

↑	One drug injected
P	Pentobarbital sodium
B.P.	Blood Pressure
R.R.	Respiratory rate
V.	Ventilation

TABLE 2. Average increase in ventilation in barbitalized dogs after the treatment with antidotal drugs.

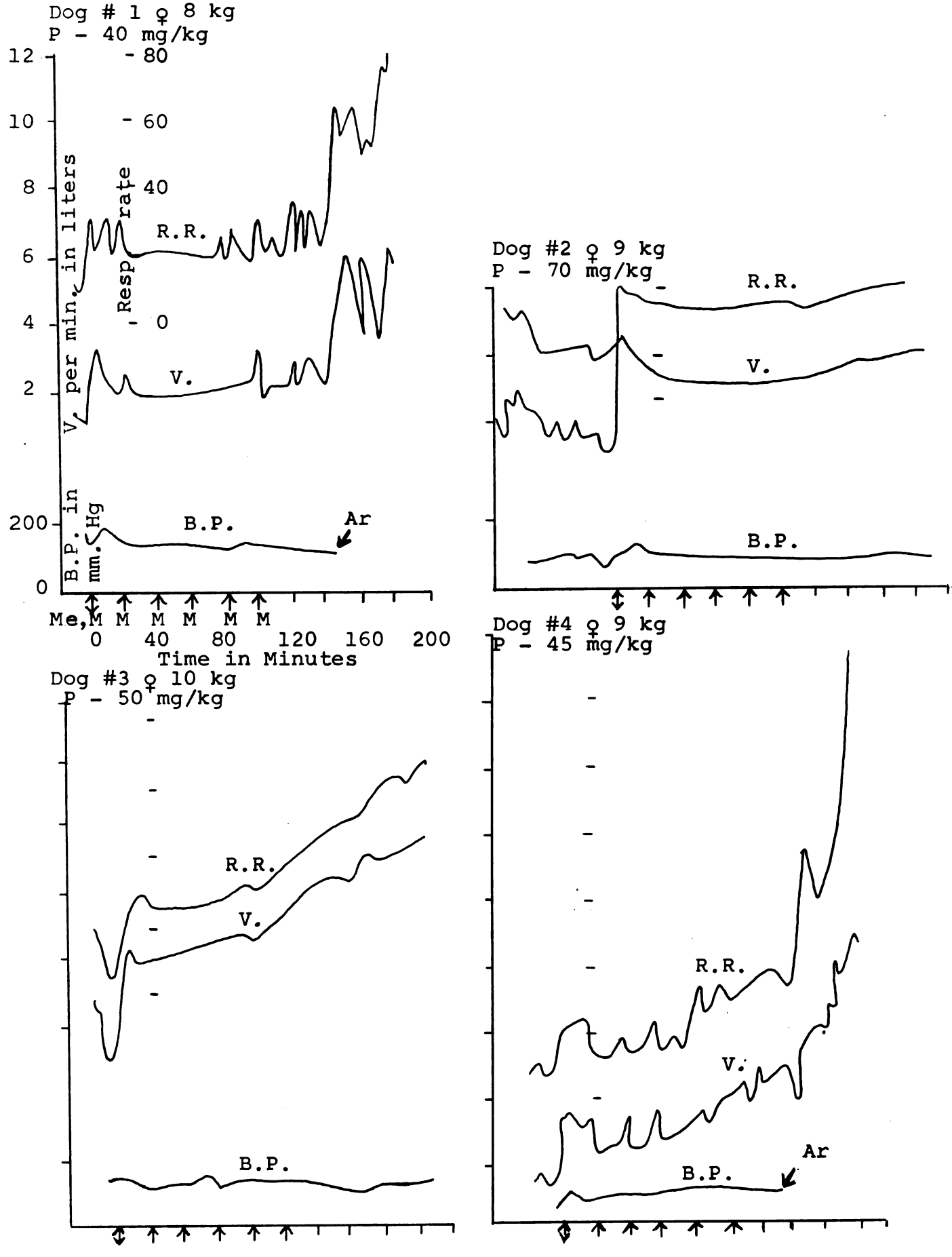
Group	No. of dogs	Antidotal drugs and doses	Average ventilation at drug injection (liters/min)	Average maximum ventilation after drug injected (liters/min)	Average maximum increase in ventilation after the drug injected (%)	Remarks
1.	6	None	1.24	1.55	25	Controls
2.	6	Methetharimide 40 mg/kg and methylphenidate 5 mg/kg	1.2	6.73	460	Methylphenidate was injected six times at the rate indicated at 20 minute intervals except in group No 9 where methylphenidate was injected only 3 times at 20 minute intervals. In case of combination treatment first injection of methylphenidate followed immediately after the injection of
3.	6	Methetharimide 20 mg/kg and methylphenidate 5 mg/kg	1.42	4.22	197.18	
4.	6	Amphetamine 4 mg/kg and methylphenidate 5 mg/kg	1.16	3.3	184.48	

TABLE 2. (Continued)

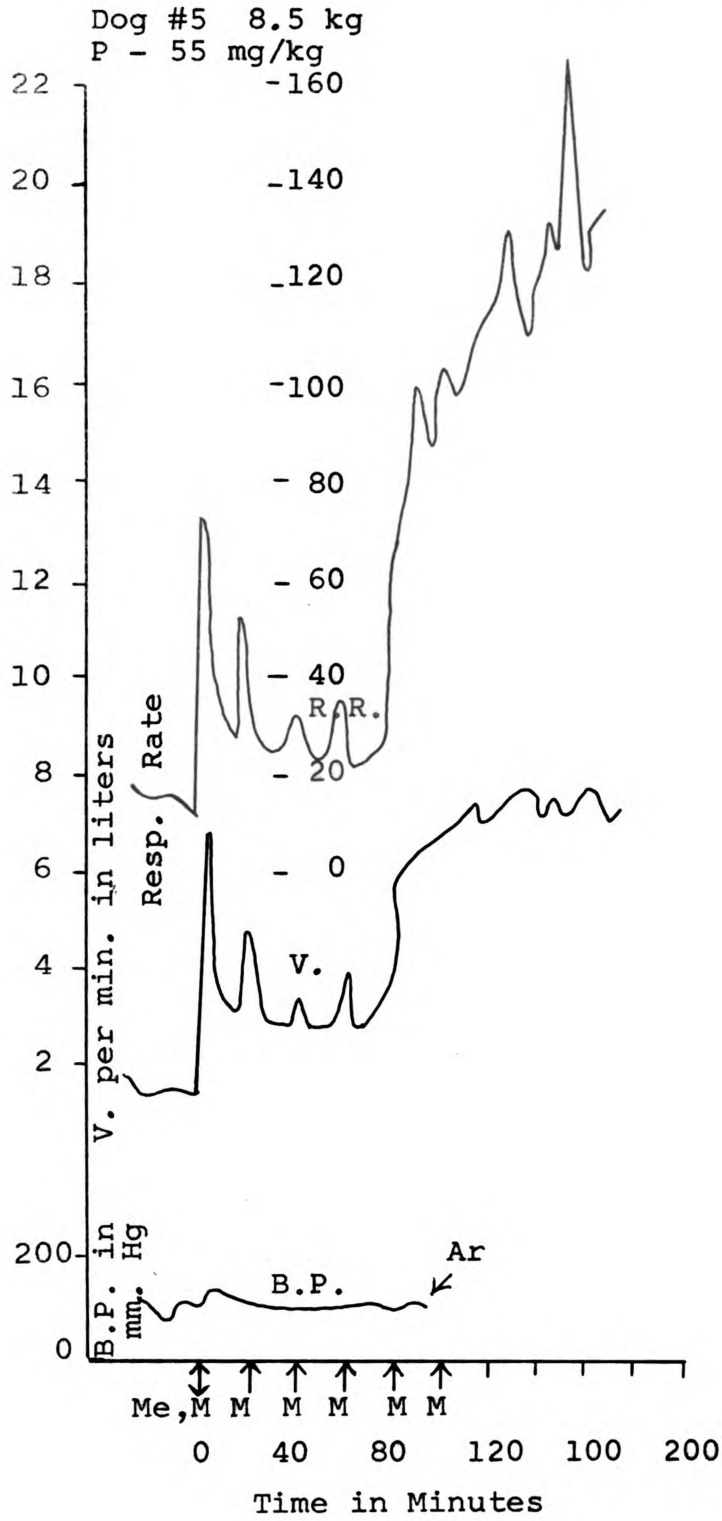
Group	No. of dogs	Antidotal drugs and doses	Average ventilation before drug injection (liters/min)	Average maximum ventilation after drug injected (liters/min)	Average maximum increase in ventilation after the drug injected (%)	Remarks
5.	6	Amphetamine 4 mg/kg and methylphenidate date 5 mg/kg	1.37	2.93	113.8	methetharimide or amphetamine.
6.	6	Methylphenidate 5 mg/kg	0.98	3.03	209	
7.	6	Methylphenidate 3 mg/kg	1.16	1.96	69	
8.	6	Methylphenidate 10 mg/kg	1.29	1.29	None	
9.	6	Methylphenidate 5 mg/kg	1.89	3.94	82	

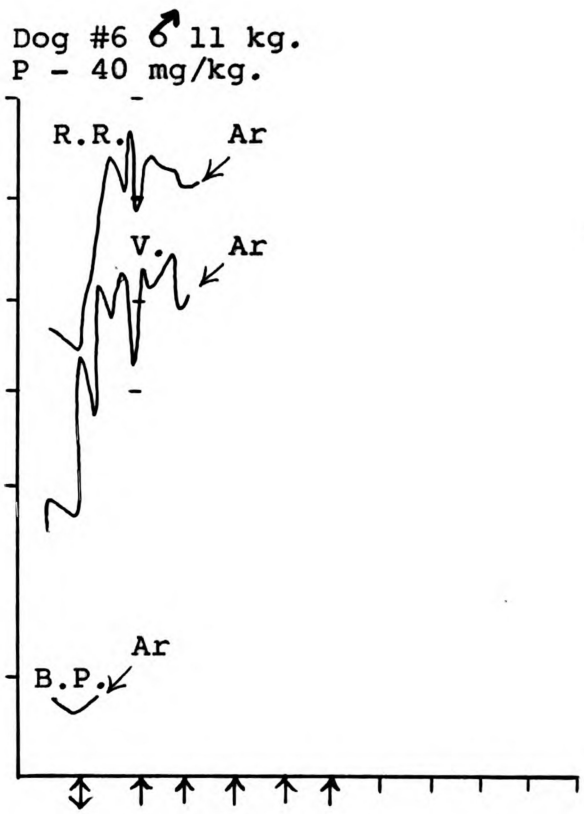
FIGURE I. (Dog #1 to 6)

METHETHARIMIDE 40 MG/KG ONE INJECTION AND 6 INJECTIONS OF METHYL-PHENIDATE 5 MG/KG EACH AT 20 MINUTE INTERVALS



METHETHARIMIDE 40 MG/KG AND METHYLPHENIDATE
5 MG/KG (Continued)





METHETHARIMIDE 40 MG/KG AND METHYLPHENIDATE
5 MG/KG (Continued)

Average for 6 dogs

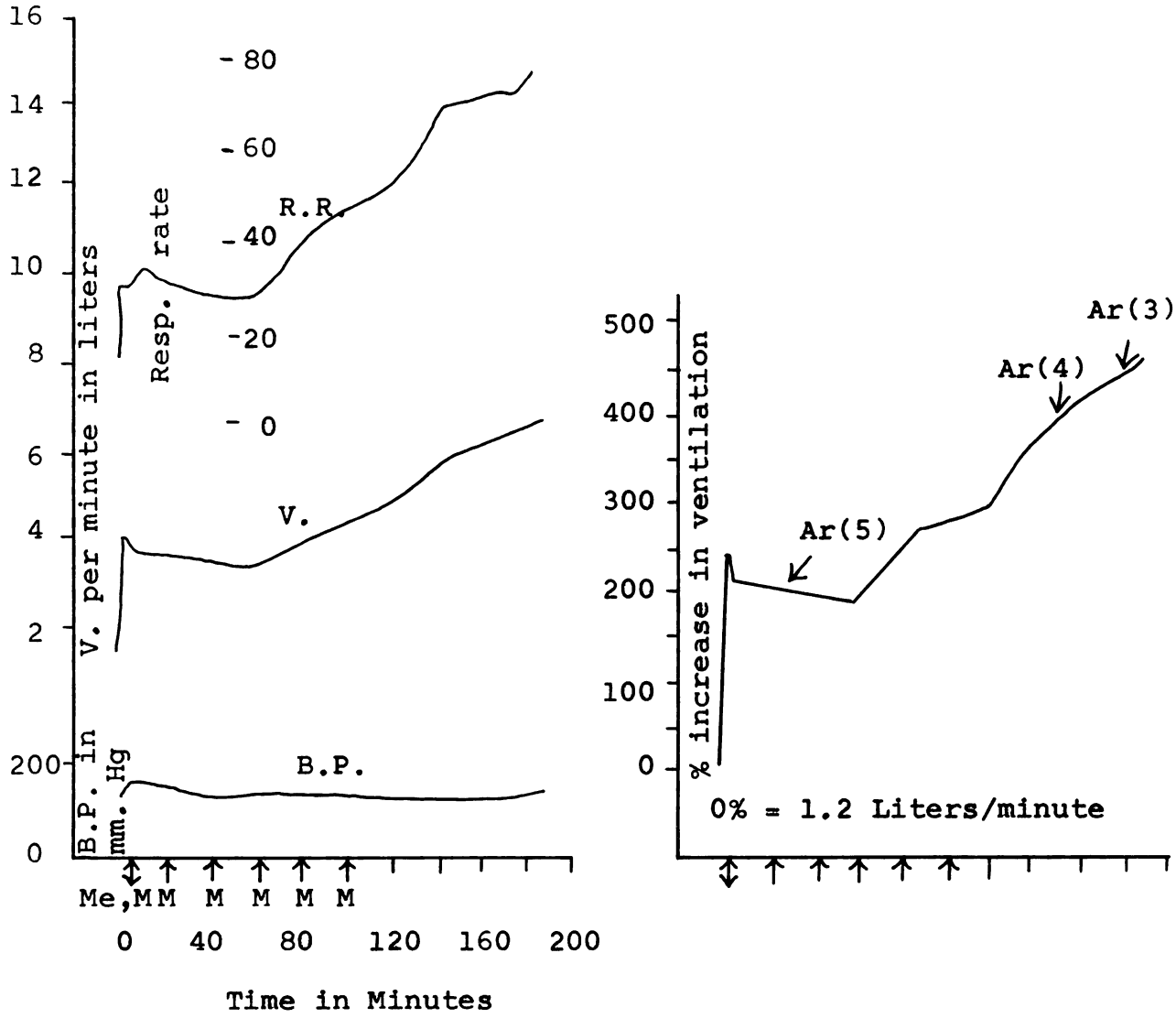
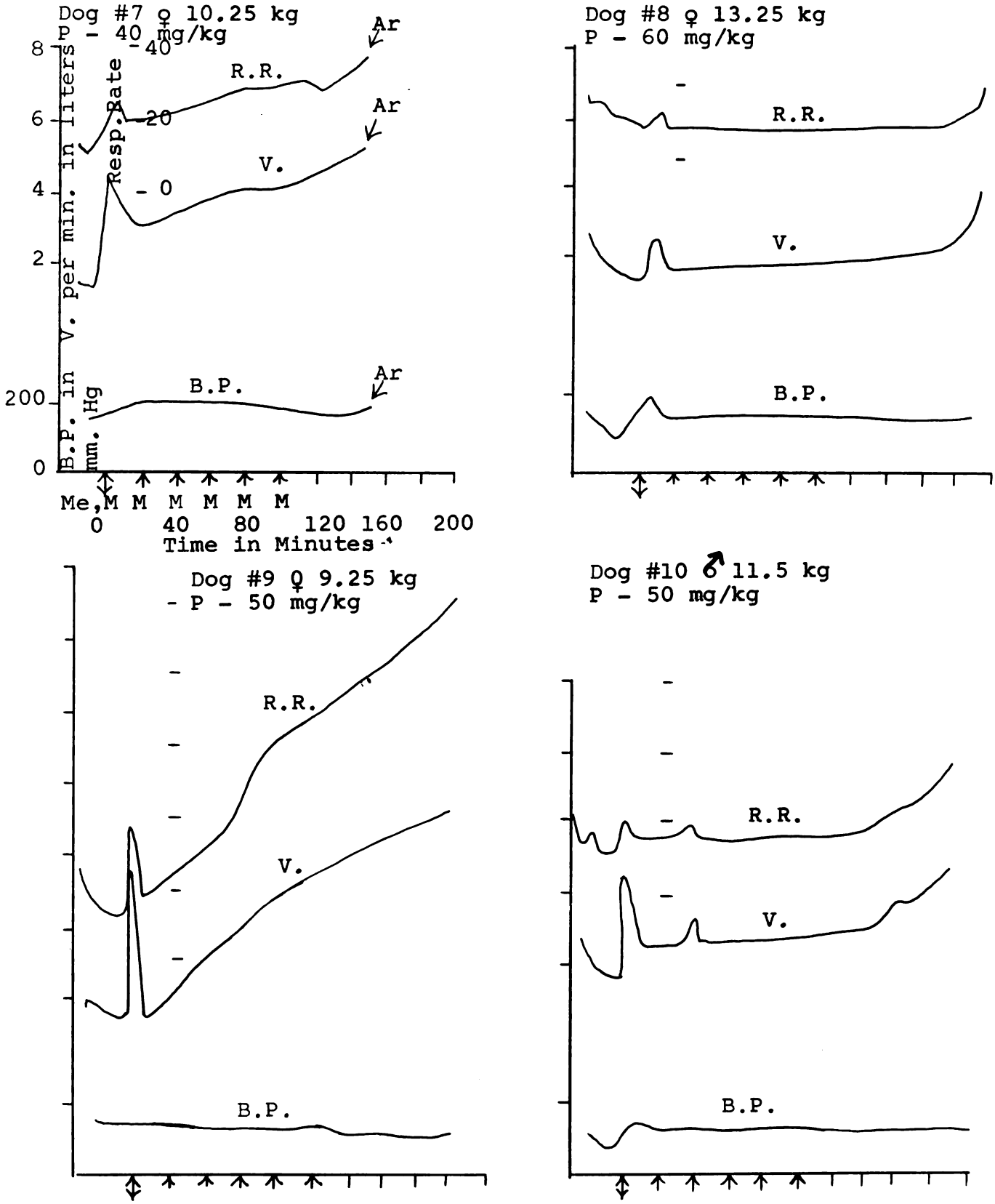
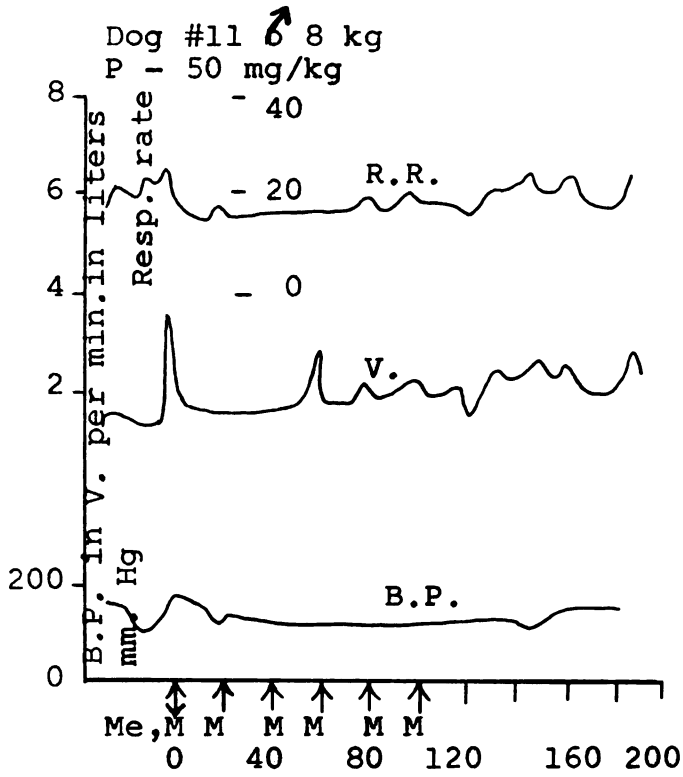


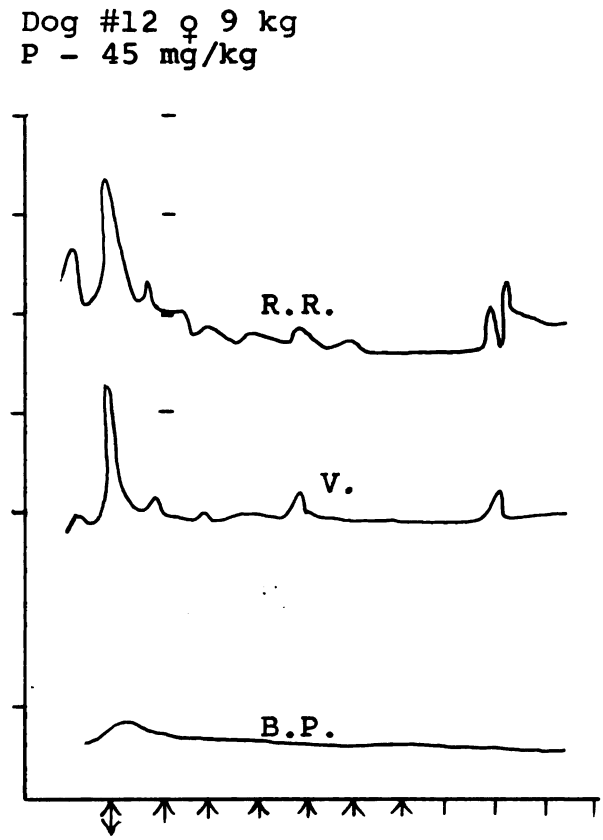
FIGURE II. (Dog #7 to 12)

METHETHARIMIDE 20 MG/KG AND 6 INJECTIONS OF METHYLPHENIDATE 5 MG/KG EACH AT 20 MINUTE INTERVALS

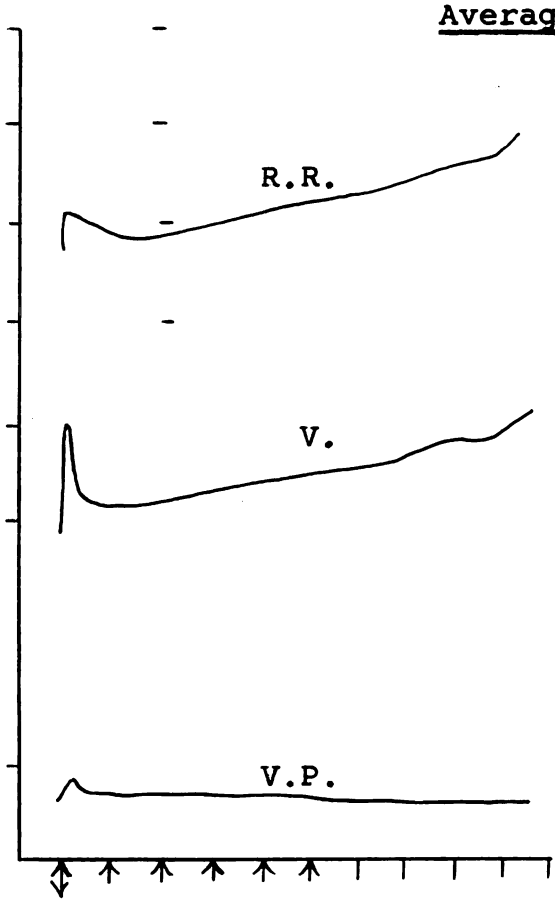


METHETHARIMIDE 20 MG/KG AND METHYLPHENIDATE
5 MG/KG (Continued)





Average for 6 dogs



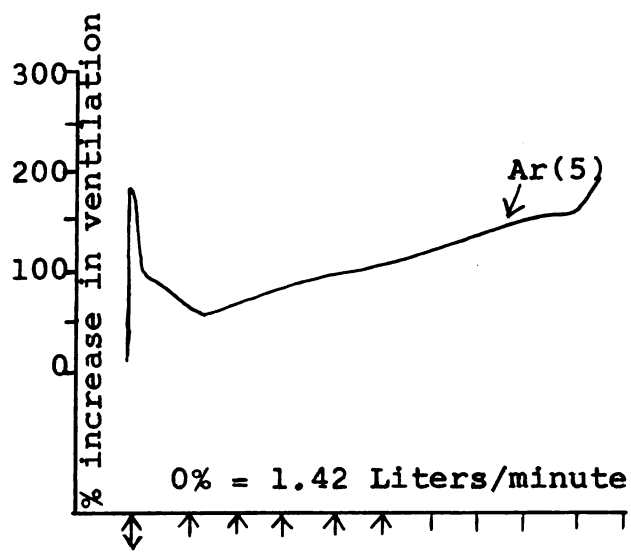
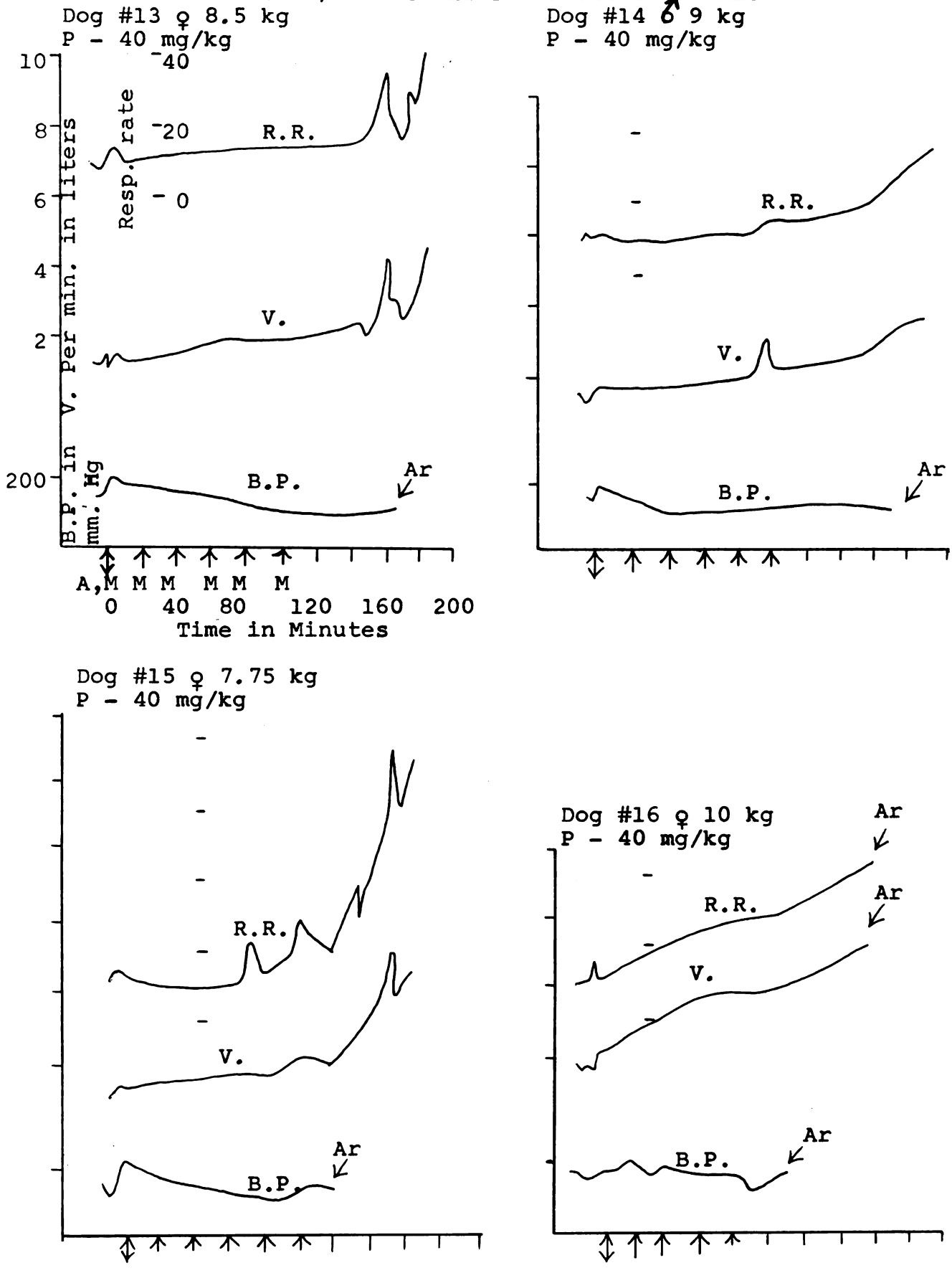
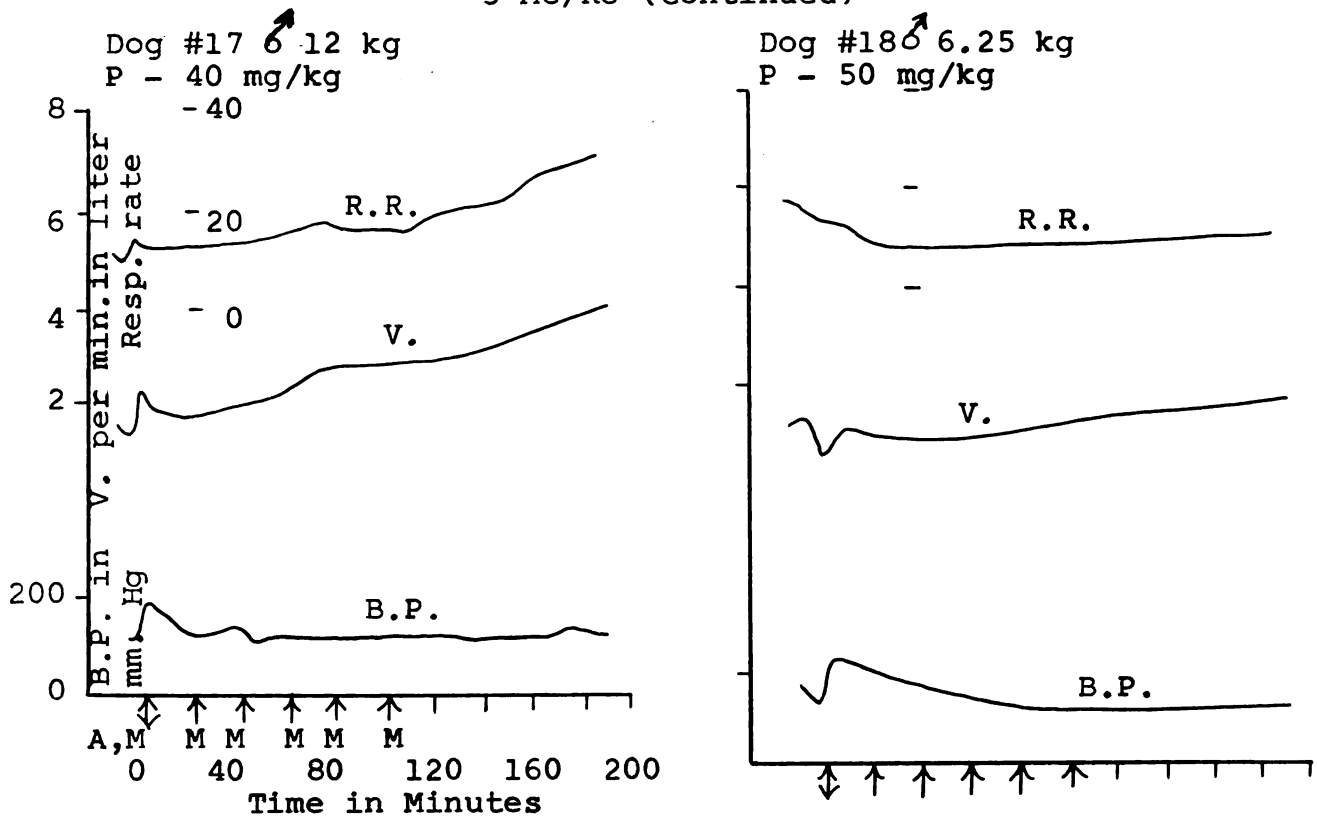


FIGURE III. (Dog #13 to 18)

AMPHETAMINE 4 MG/KG AND 6 INJECTIONS OF METHYLPHENIDATE 5 MG/KG EACH AT 20 MINUTE INTERVALS



AMPHETAMINE 4 MG/KG AND METHYLPHENIDATE
5 MG/KG (Continued)



Average for 6 dogs

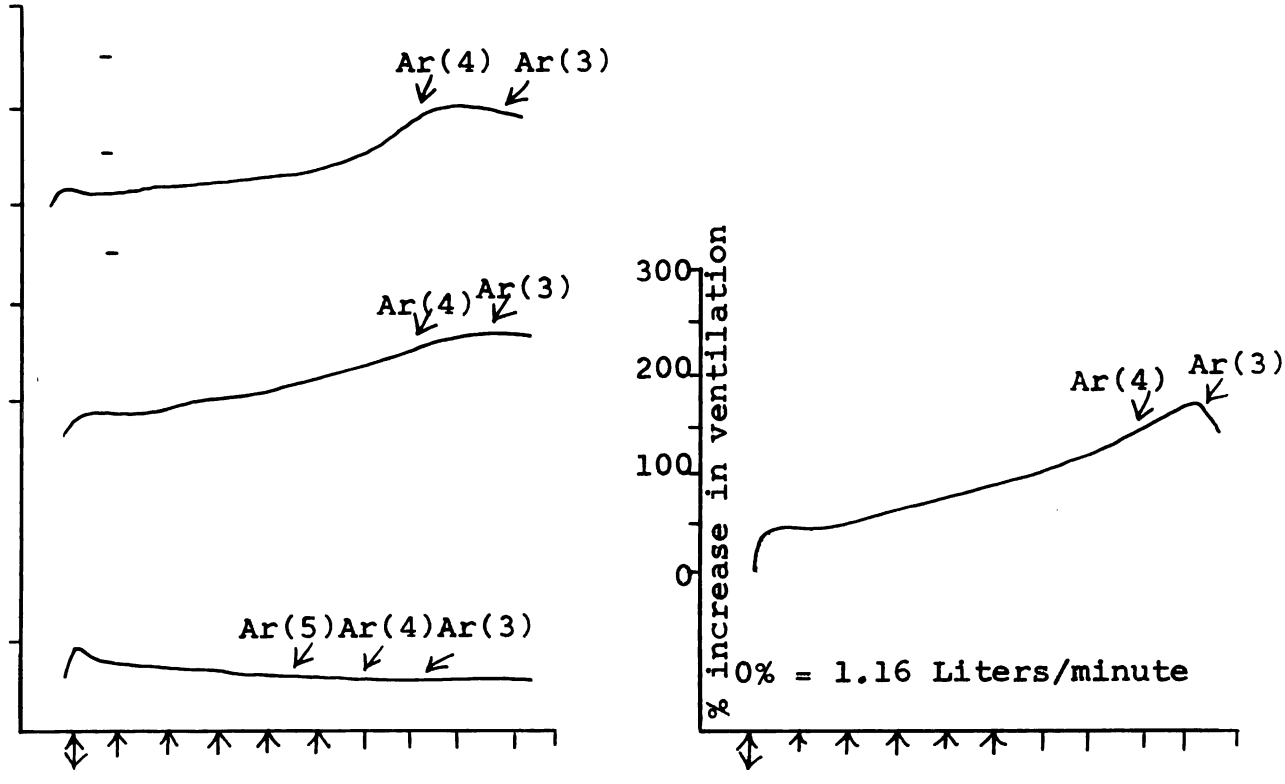
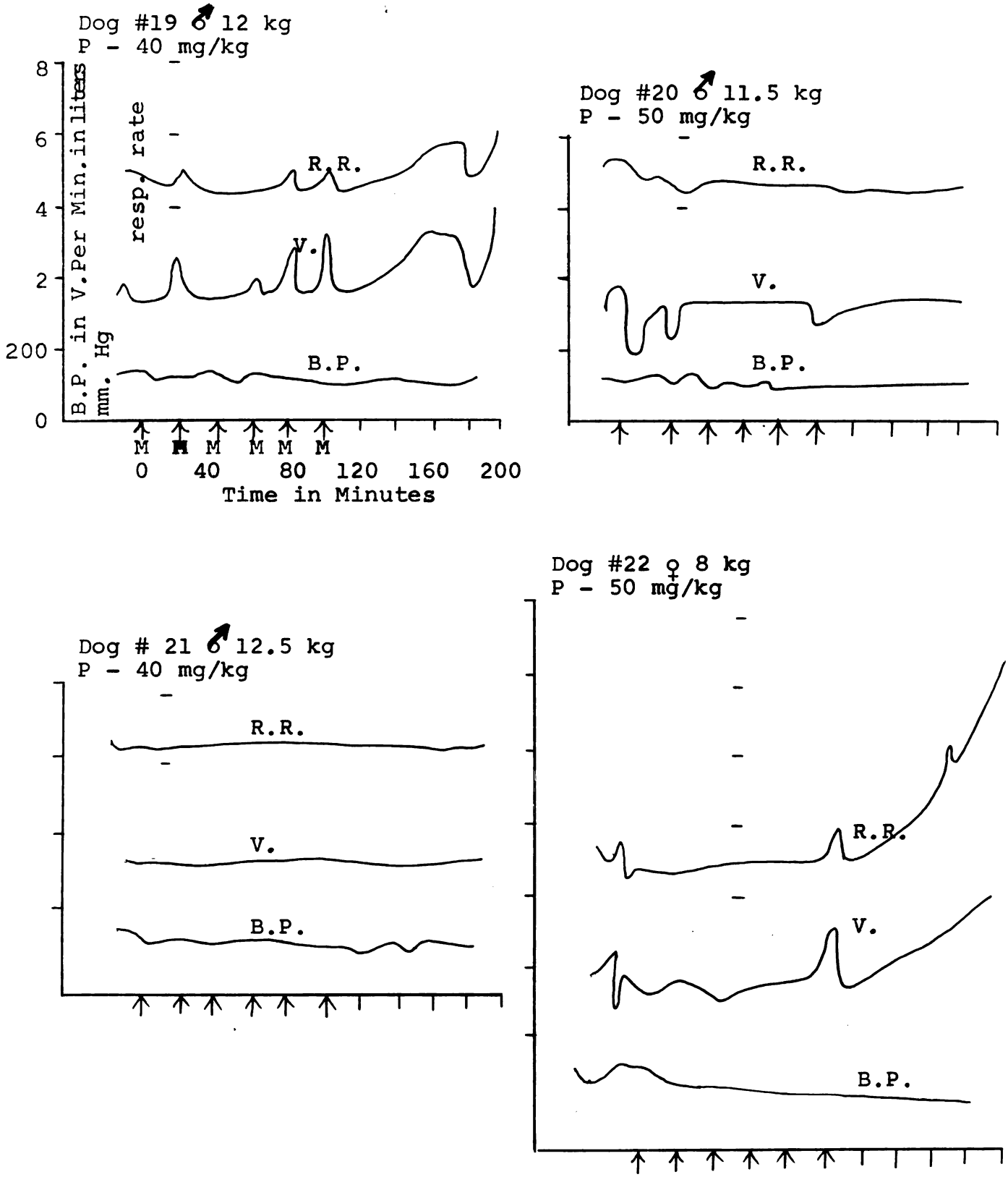
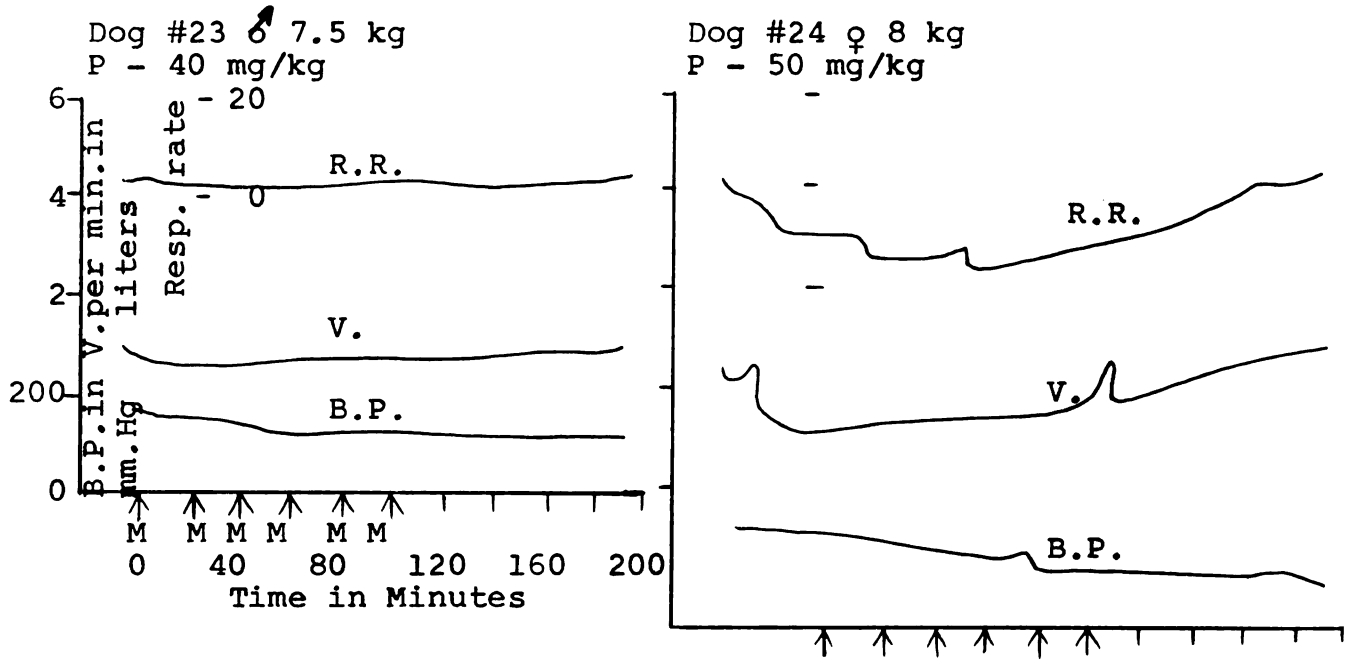


FIGURE IV. (Dog #19 to 24)

6 INJECTIONS OF METHYLPHENIDATE 5 MG/KG EACH AT 20 MINUTE INTERVALS



METHYLPHENIDATE 5 MG/KG (Continued)



Average for 6 dogs

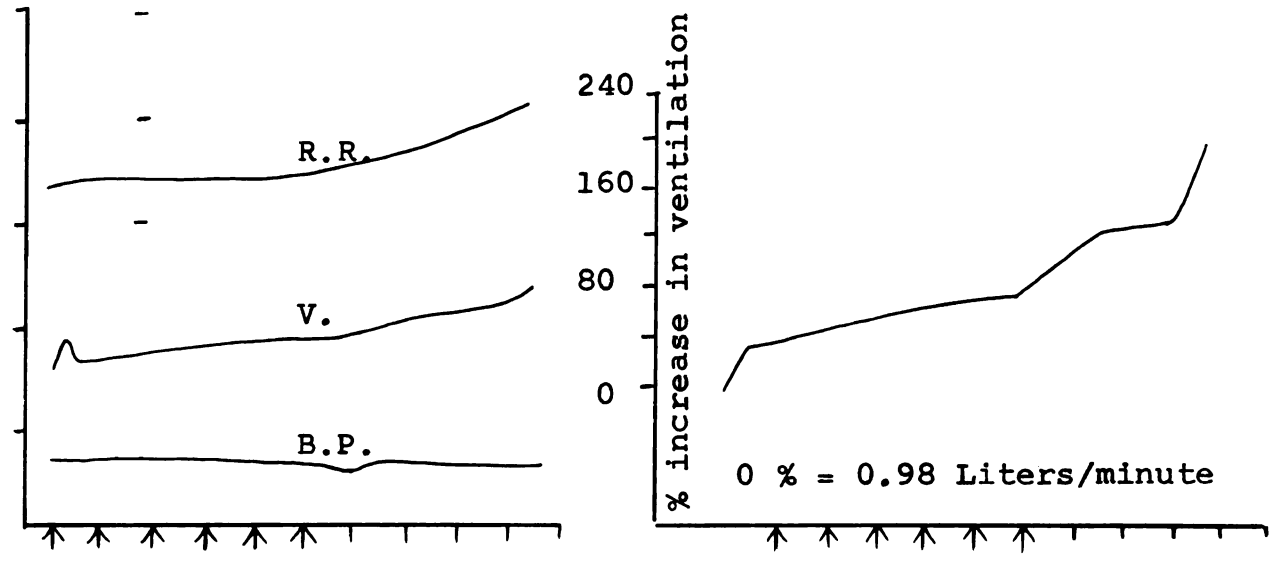
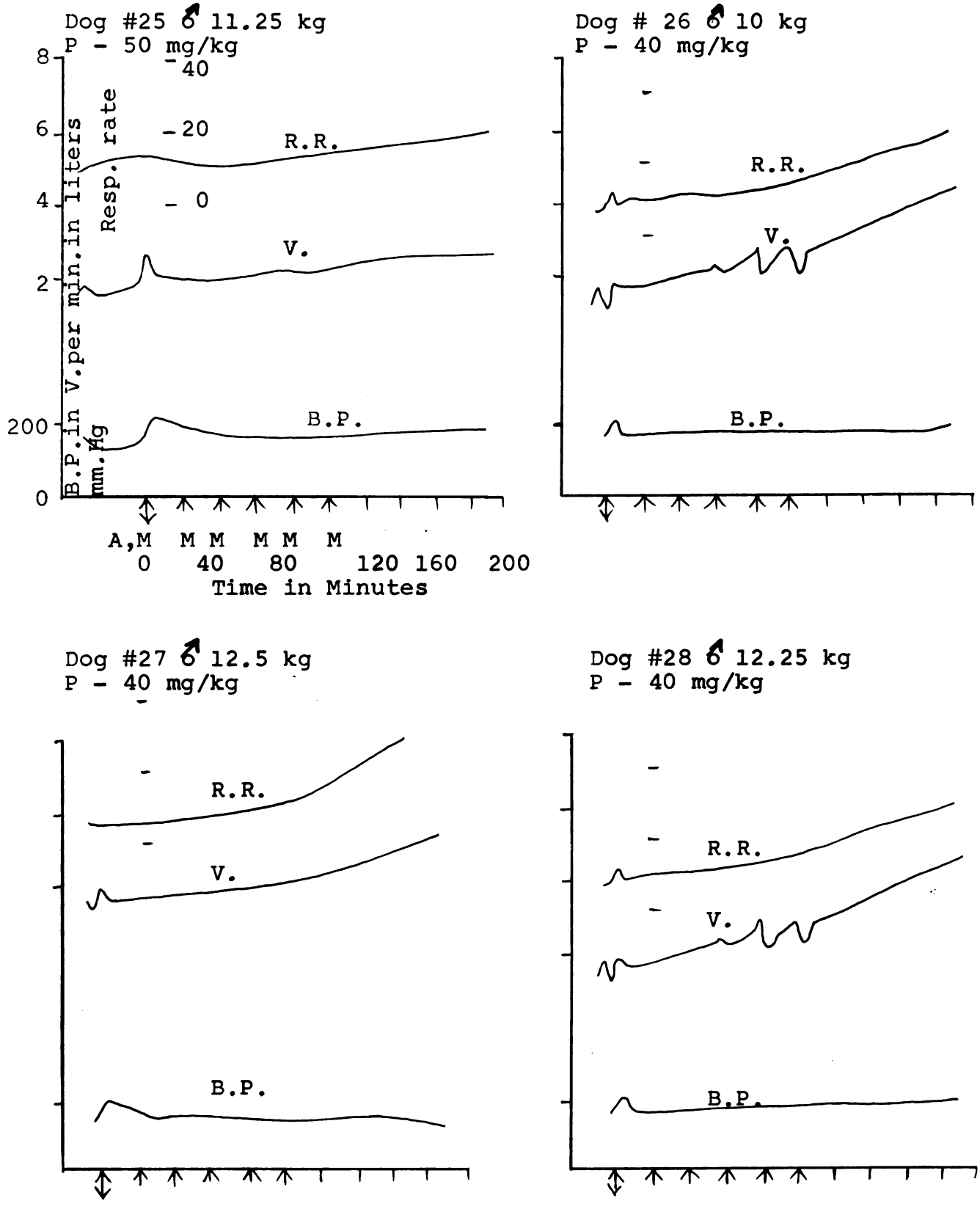
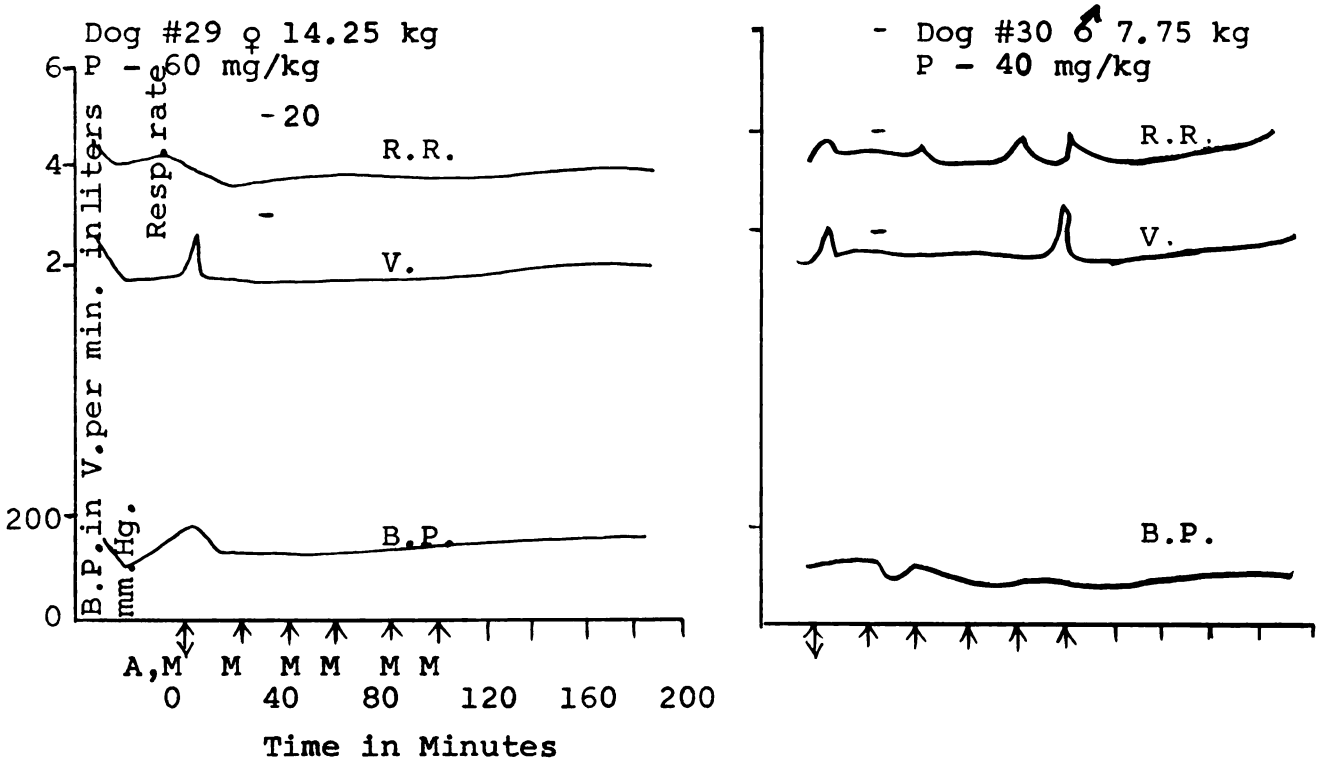


FIGURE V. (Dog #25 to 30)

AMPHETAMINE 2 MG/KG AND 6 INJECTIONS OF METHYLPHENIDATE
5 MG/KG EACH AT 20 MINUTE INTERVALS



AMPHETAMINE 2 MG/KG AND METHYLPHENIDATE 5MG/KG (Continued)



Average for 6 dogs

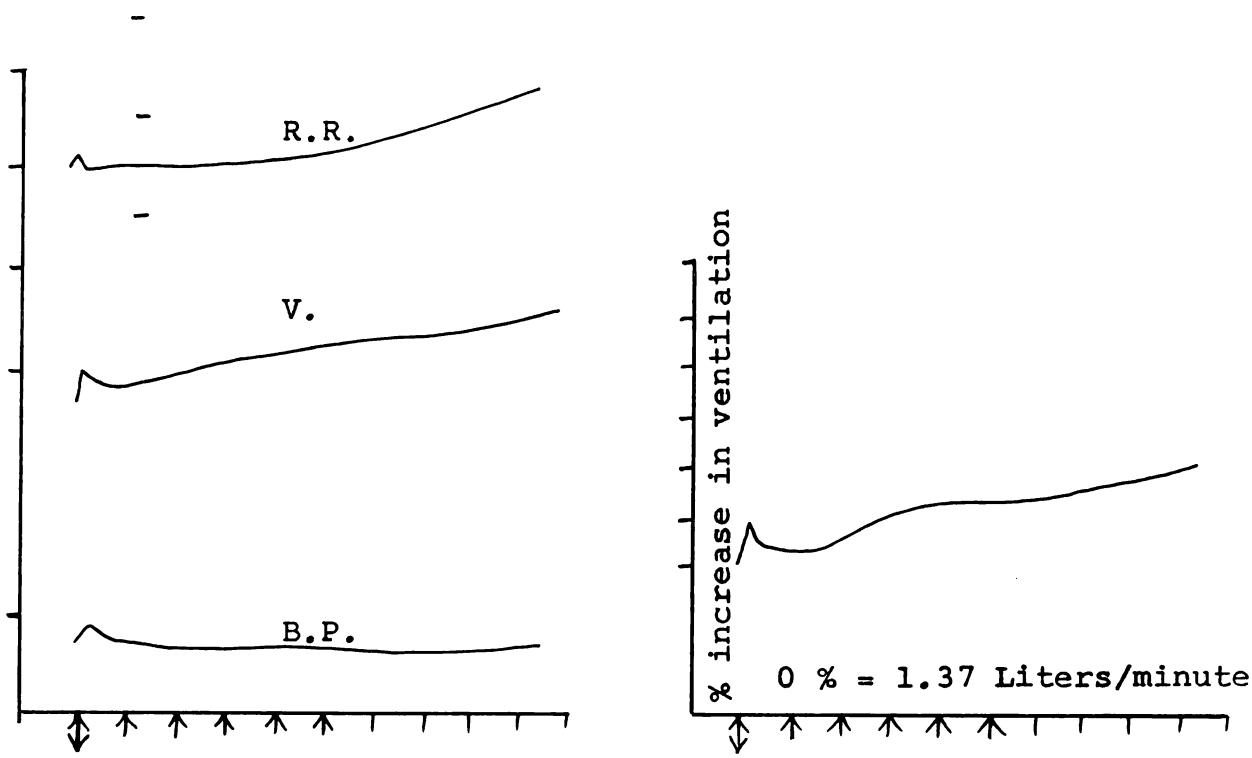
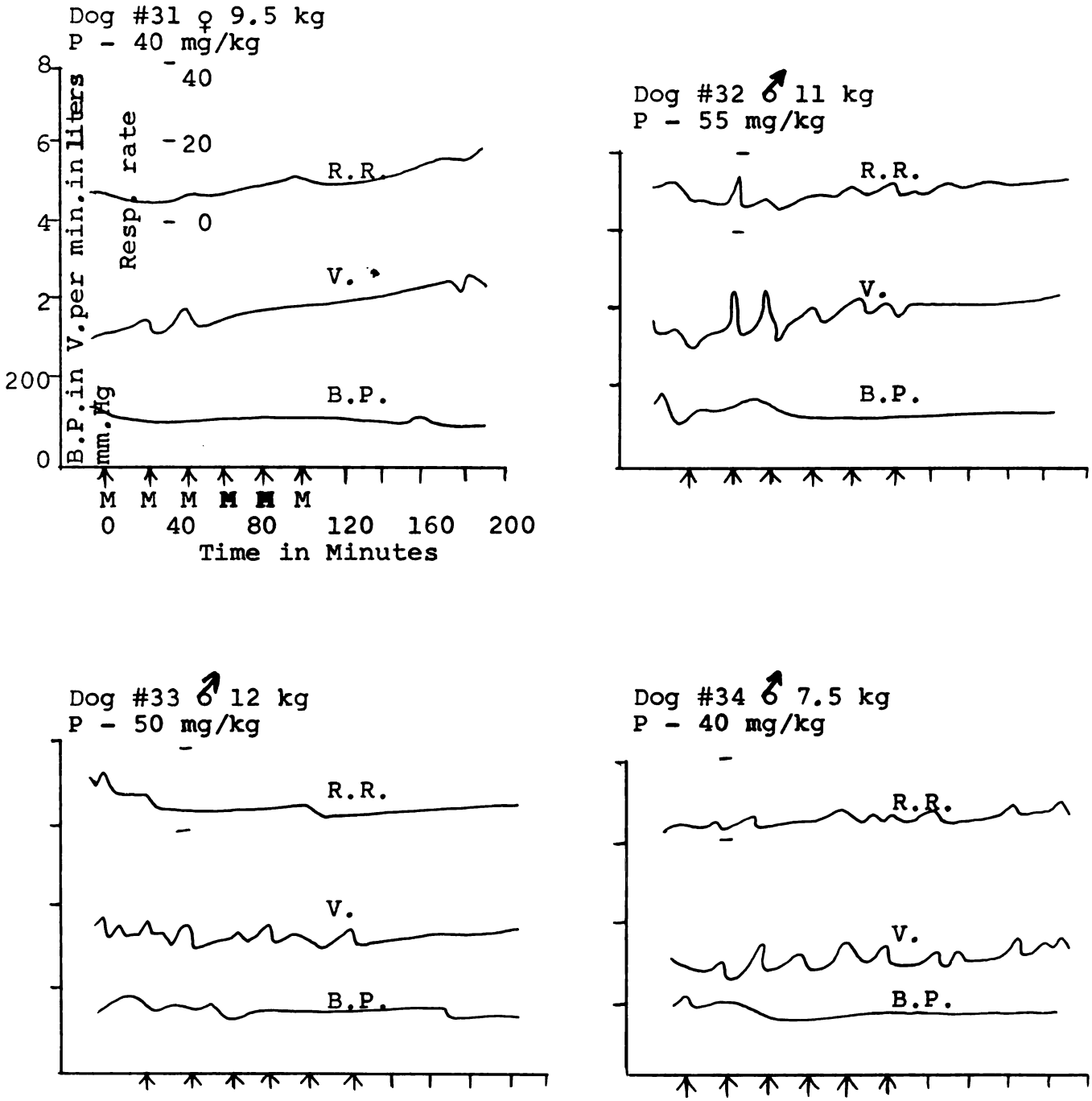
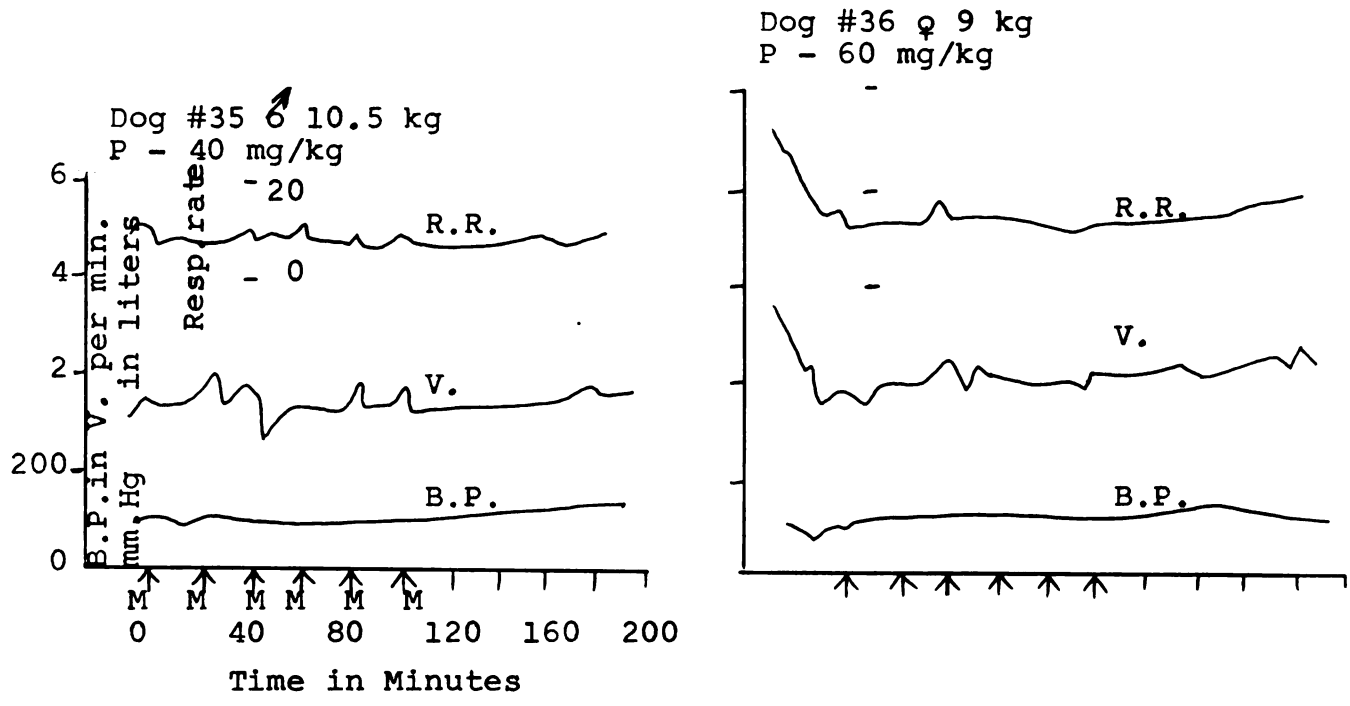


FIGURE VI. (Dog #31 to 36)

6 INJECTIONS OF METHYLPHENIDATE 3 MG/KG EACH AT 20 MINUTE INTERVALS



METHYLPHENIDATE 3 MG/KG (Continued)



Average for 6 dogs

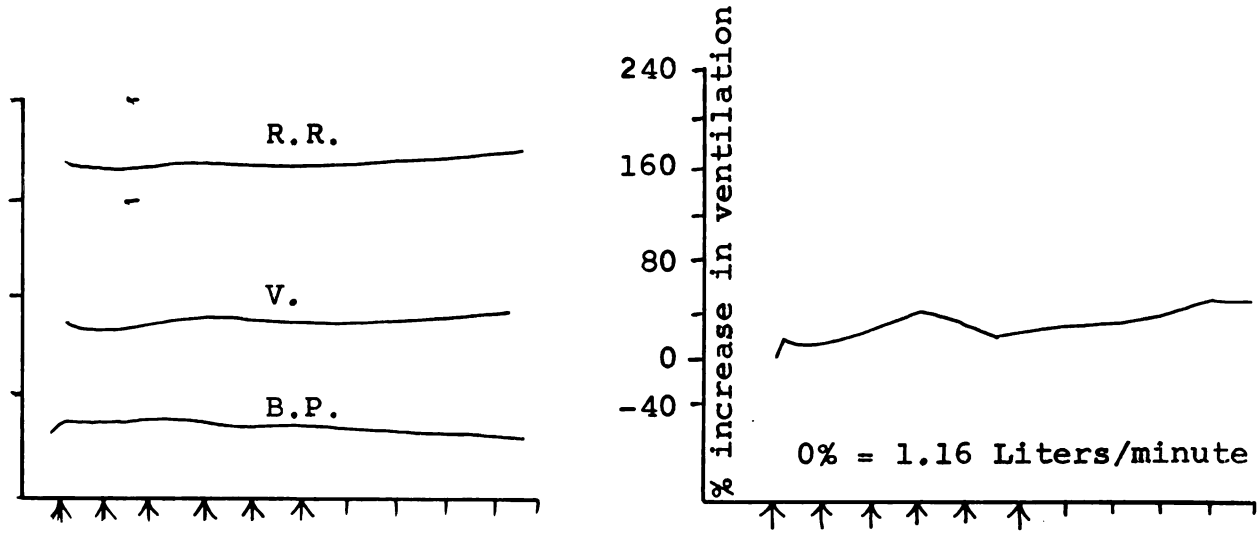
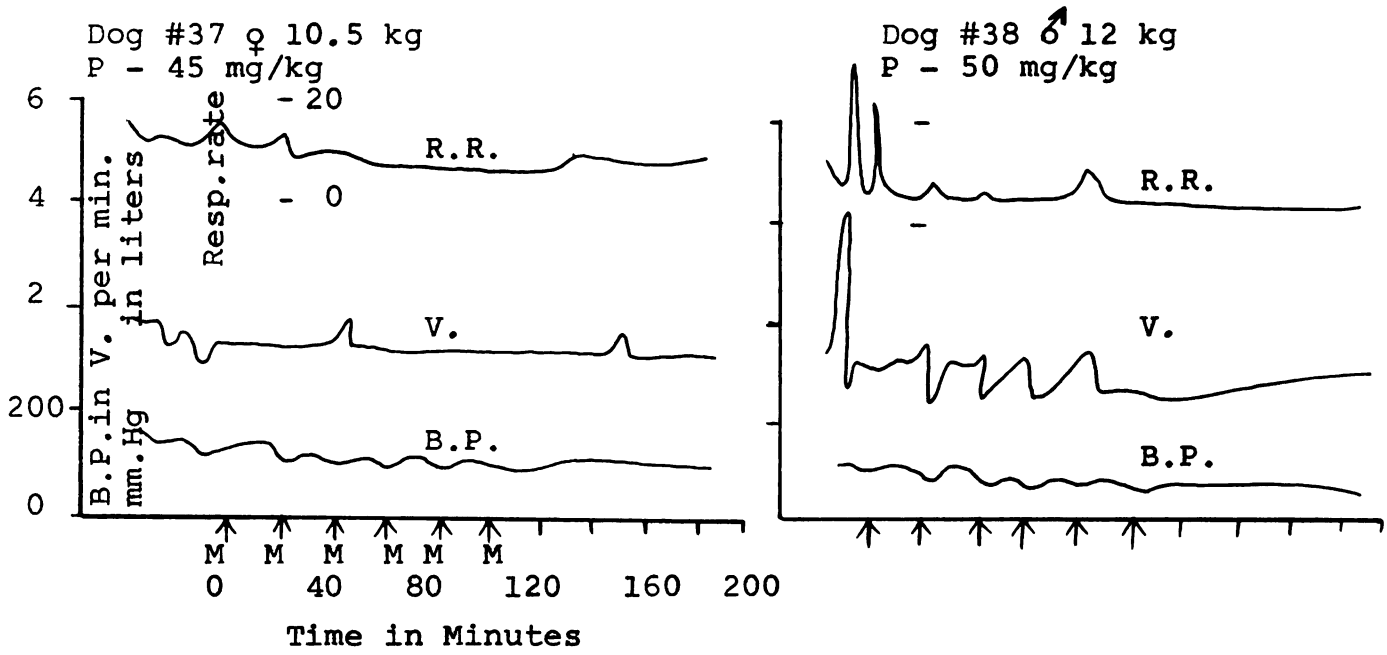
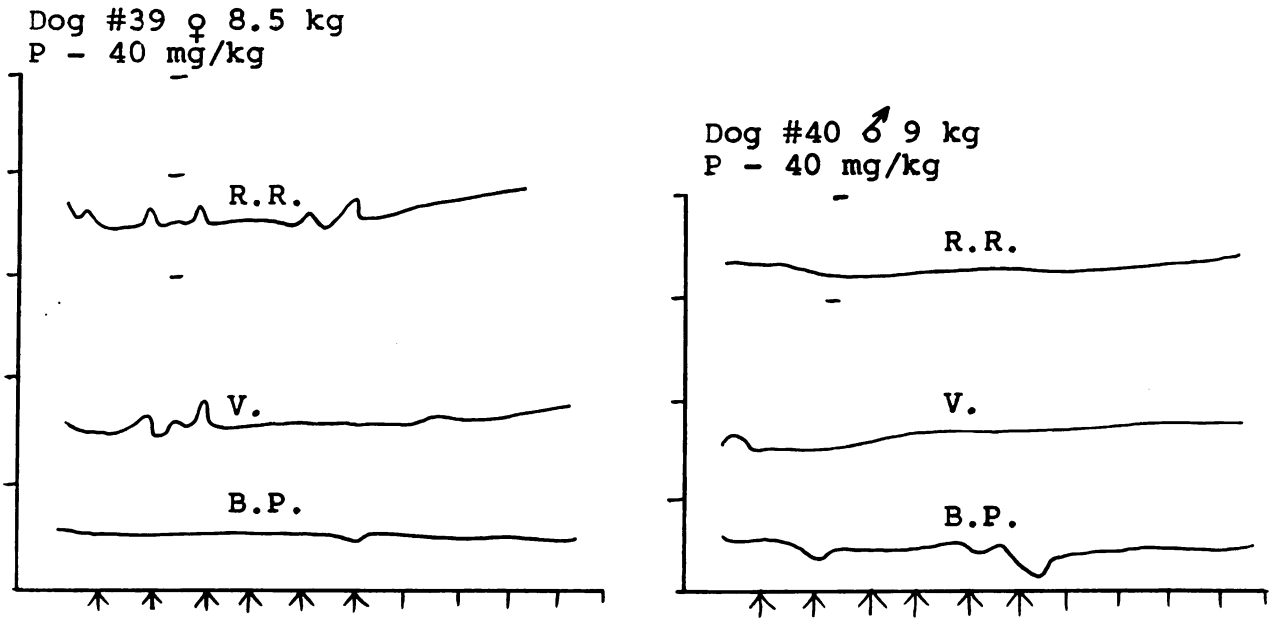


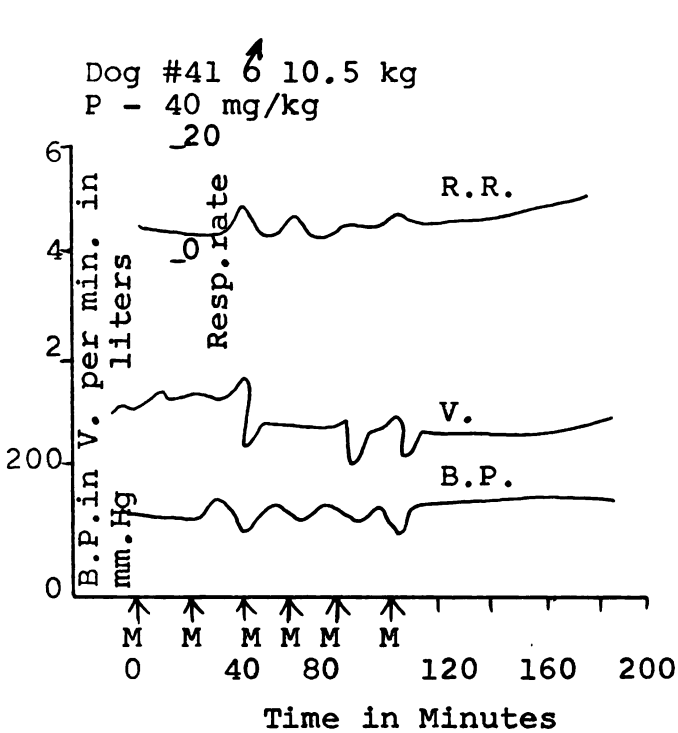
FIGURE VII. (Dog #37 to 42)

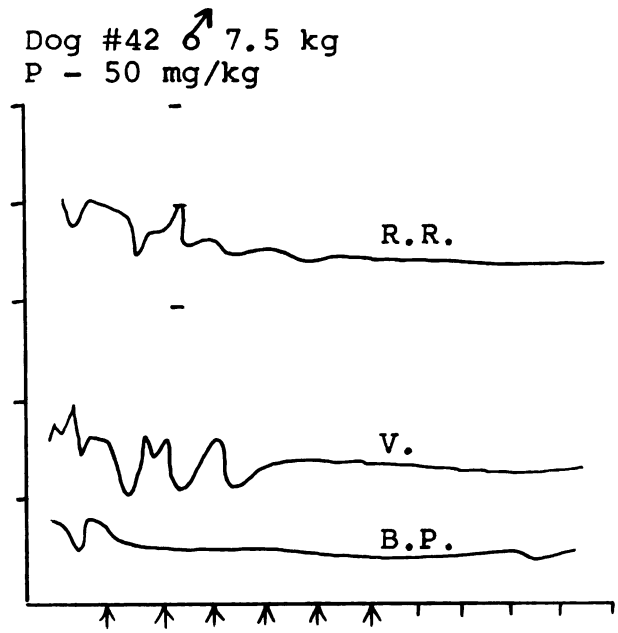
6 INJECTIONS OF METHYLPHENIDATE 10 MG/KG EACH AT 20 MINUTE INTERVALS



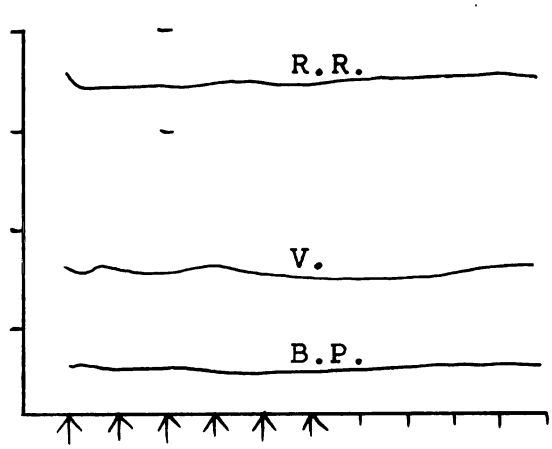


METHYLPHENIDATE 10 MG/KG (Continued)





Average for 6 dogs



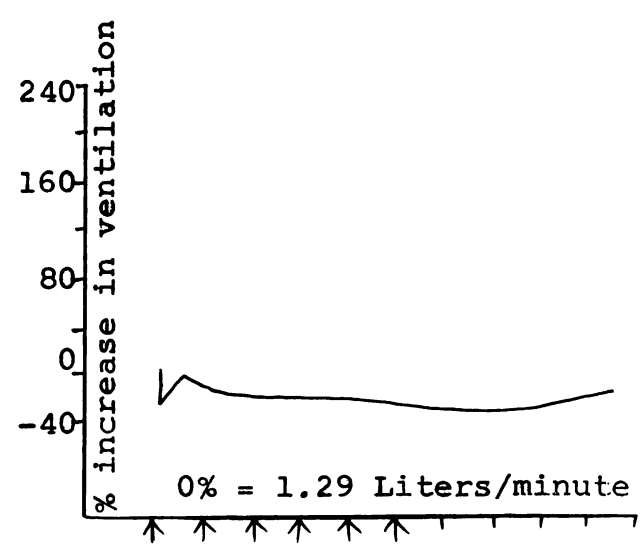
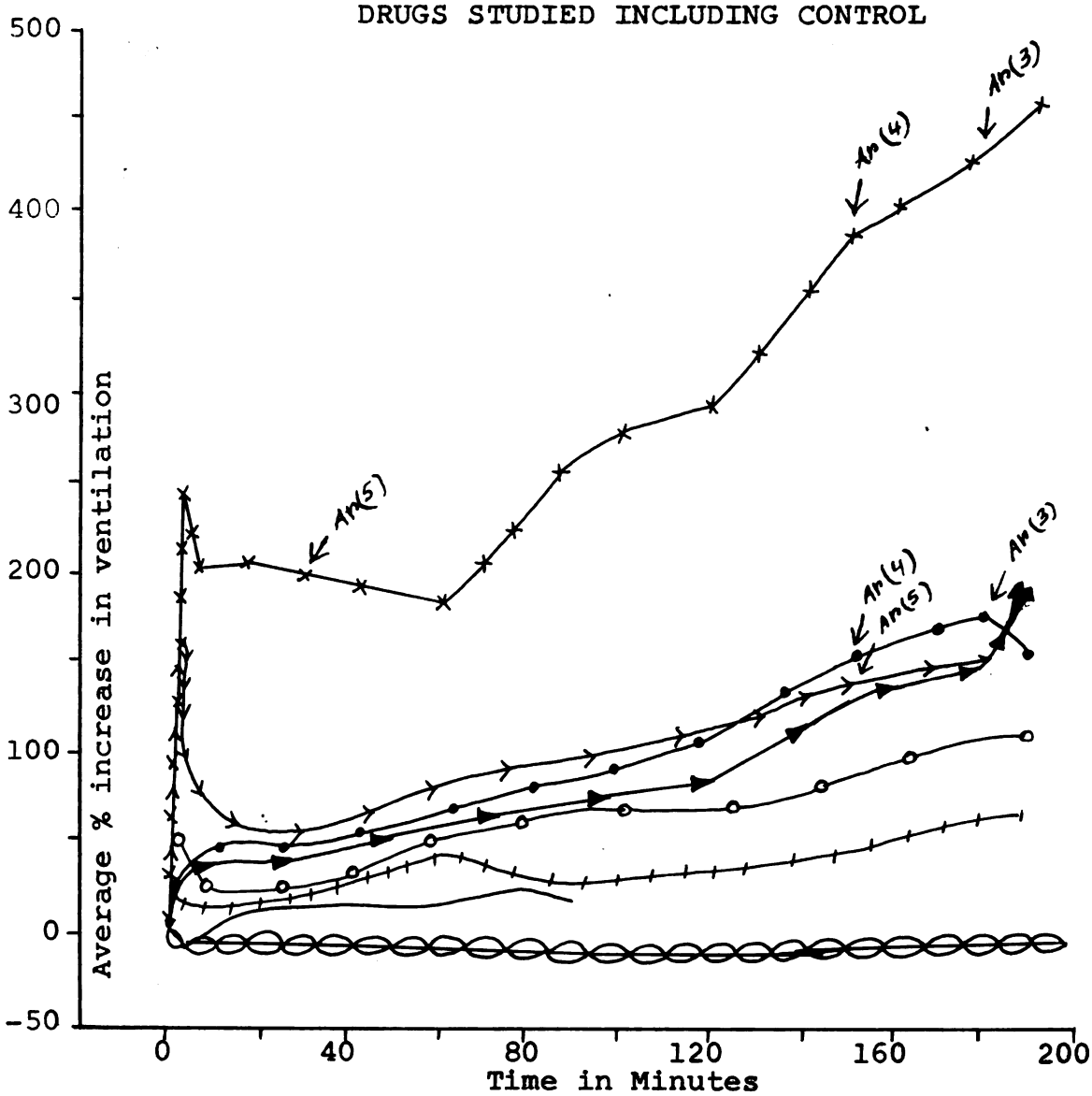


FIGURE VII.

AVERAGE PER CENT INCREASE IN VENTILATION OF ALL THE DRUGS STUDIED INCLUDING CONTROL



Methetharimide 40 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

Methetharimide 20 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

Amphetamine 4 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

Amphetamine 2 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

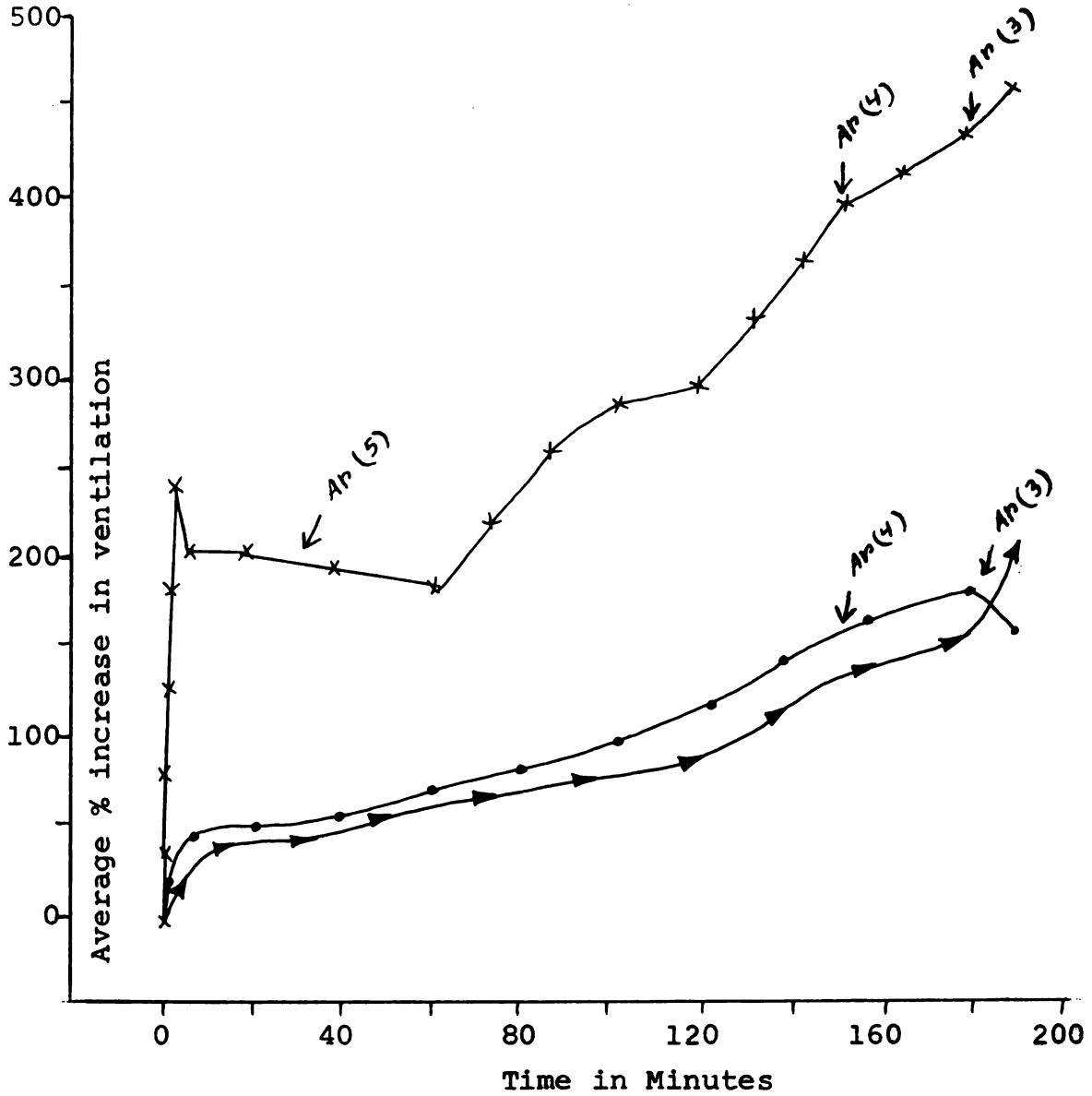
6 injections of methylphenidate 3 mg/kg each at 20 minute intervals

6 injections of methylphenidate 10 mg/kg each at 20 minute intervals

Control

FIGURE IX.

THE BEST TRIALS USING METHYLPHENIDATE ALONE AND WITH AMPHETAMINE AND METHETHARIMIDE



Methetharimide 40 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

Amphetamine 4 mg/kg and 6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

6 injections of methylphenidate 5 mg/kg each at 20 minute intervals

FIGURE X.

AVERAGE PER CENT INCREASE IN VENTILATION AT THREE DIFFERENT DOSE LEVELS OF METHYLPHENIDATE ALONE

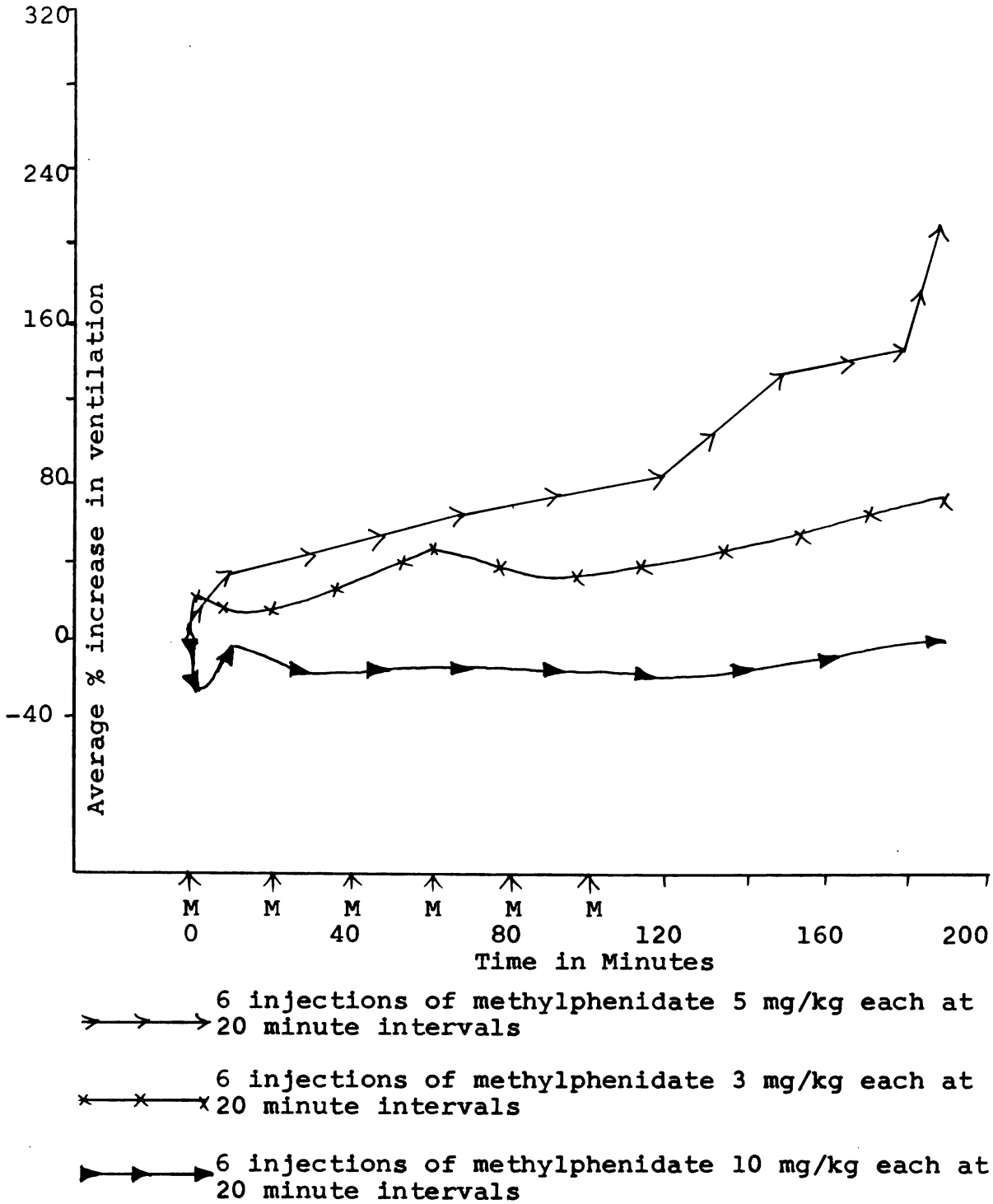


FIGURE XI.

CONTROLS

AVERAGE RESPIRATORY RATE, VENTILATION PER MINUTE IN LITERS AND BLOOD PRESSURE OF 6 DEEPLY BARBITALIZED DOGS WITH NO ANALEPTIC TREATMENT

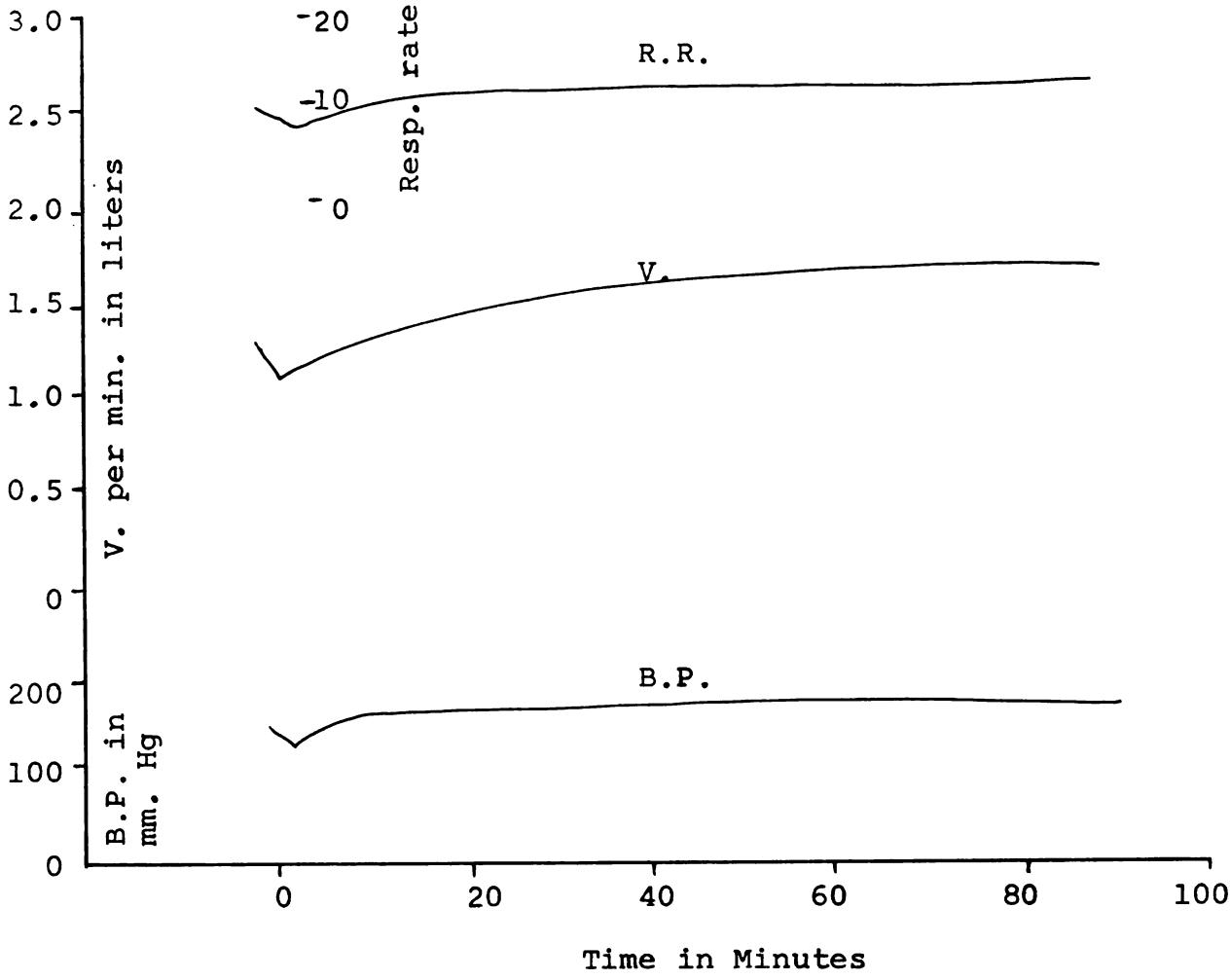
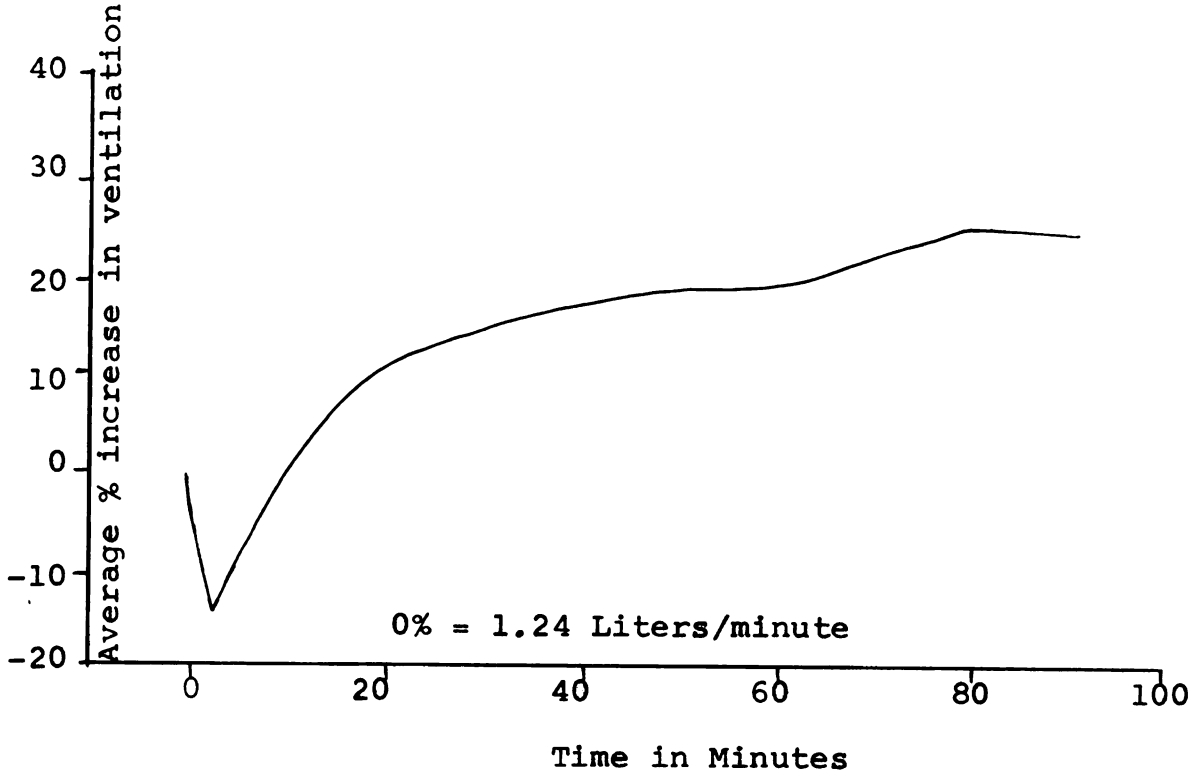


FIGURE XII.

CONTROLS

AVERAGE PER CENT INCREASE IN VENTILATION IN 6 DEEPLY BARBITALIZED DOGS WITH NO ANALEPTIC TREATMENT



CHAPTER IV

DISCUSSION

This investigation was undertaken by the author to compare the actions of a few analeptics either singly or in paired combinations in dogs overanesthetized with pentobarbital sodium. The "overansthetized" dog was meant as the one whose ventilation was decreased to or below 1.5 liters per minute with the anesthetic before the treatment with the antidotal analeptics. The main theme of this project was to find out a satisfactory drug, if any, for the treatment of severe barbiturate poisoning. With this goal in view the author tried methylphenidate singly in different dose levels and combindly with methetharimide and amphetamine sulfate. The effects of the singly administered drug and the combinations have been observed as follows:

Methylphenidate hydrochloride ("Ritalin" hydrochloride)

Single dose of methylphenidate at the rate of 30 mg/kg i.v. in an overanesthetized dog resulted in a decrease in ventilation. A dose of 15 mg/kg i.v. produced a slight increase in ventilation but ventilation came down to a minus level as the second injection was given after twenty minutes. A dose of 10 mg/kg i.v. produced a similar result. Methylphenidate at the rate of 5 mg/kg i.v. was tried in regular

repetitive doses which produced gradual elevation of ventilation. Three injections of methylphenidate at the rate of 5 mg/kg each i.v. were tried at twenty minute intervals. An average of 82 per cent increase in ventilation was observed in one hour and a half after the last injection with a minimum of arousal effects. As this result was somewhat satisfactory, another series of six dogs with the six injections of methylphenidate at the rate of 5 mg/kg each i.v. at twenty minute intervals were tried with the expectation of further beneficial result. Again the action of the drug was observed for a period of one hour and thirty minutes after the last injection. In this group a remarkable increase of ventilation, respiratory rate and depth were observed with the typical arousal symptoms and finally six injections of methylphenidate at the rate of 5 mg/kg each i.v. was considered as the best dose level for methylphenidate alone. Comparative study of 6 injections of 3 mg/kg and 10 mg/kg each i.v. at 20 minute intervals has been discussed later in this chapter.

Six injections of methylphenidate 5 mg/kg each i.v. at 20 minute intervals produced an elevation of ventilation by an average of 35 per cent at the tenth minute after first injection of the drug. At the hundredth minute, i.e. after the end of sixth injection the ventilation was gradually increased to an average of 75 per cent followed by an abrupt increase to an average of 209 per cent at the end of the experiment, i.e. after one hundred and ninety minutes

observation period. A significant increase in respiratory rate and depth was also observed. In a few cases arousal symptoms were observed perhaps due to cortical stimulation. There was no significant change in blood pressure throughout the course of the treatment.

Six injections of methylphenidate 3 mg/kg each i.v. at 20 minute intervals produced an initial fluctuation in ventilation but it did not seem to be satisfactory. An average of 20 per cent increase in ventilation was observed at the end of two minutes after the drug injection and then it decreased to 12 per cent and again elevated to 45 per cent after one hour followed by a drop to 30 per cent by one hour and thirty minutes. Finally the ventilation was gradually increased to an average of 70 per cent by the end of observation period of one hundred and ninety minutes. Respiratory rate also fluctuated during the experiment. Blood pressure was little affected.

Six injections of methylphenidate 10 mg/kg each i.v. at 20 minute intervals produced a completely different pattern of action. In this case ventilation was decreased to an average of 24 per cent from the predrug level after the injection of first dose. Then it was dropped down further to an average of -4 per cent by the end of the tenth minute followed by a further decrease to an average of -20 per cent for about one hour and forty minutes. A very slow rise was then observed and finally it rose up to the original predrug ventilation level. In this particular dose of methylphenidate,

a reduced trend of ventilation was quite significant which is contraindicatory of the antidotal treatment and it was proved to be the least effective of all the drugs studied in this project. It showed, in fact, no improvement from the pre-drug ventilatory level. Two dogs died after about twenty-four hours of the treatment as they failed to recover from severe barbiturate depression. Respiratory rate and blood pressure showed a significant decrease after the administration of the drug.

Methylphenidate is a cerebral cortical stimulant which increases psychomotor activity without appreciable sympathomimetic effects. Pharmacological and clinical trial have shown that methylphenidate stimulates the central nervous system to a degree between that of caffein and amphetamine compounds (Meier, Gross and Trippod, 1954; Drassdo and Schmidt, 1954). Originally both methylphenidate and methetharimide were considered to be specific barbiturate antagonists; more recent investigation has indicated that they are nonspecific stimulants (Gale 1961).

It is observed from this investigation that six injections of methylphenidate at the rate of 5 mg/kg i.v. at twenty minute intervals produced better results than either 10 mg/kg or 3 mg/kg in the similar experimental conditions indicating that methylphenidate bears a definite optimum dose-relationship for antidotal action. It is quite obvious that the results that doubling the standard dose (5 mg/kg) or reducing the dose to 3 mg/kg would decrease the ventilation

or produce less increase in ventilation, which indicates that an optimum dose is required for the stimulation of the central nervous system. This observation of a required optimal dosage of methylphenidate correlates with the observation of Gale (1958). No satisfactory explanation has been offered for the decreased effectiveness of the high doses, except for the general observation that other stimulants may have similar reversals in high doses.

A study (Gale, 1958) of the effectiveness of the various doses of methylphenidate compared to the amount of the thiopental administered revealed that the optimum dose of methylphendiate was independant of the dose of thiopental. This led to the assumption that methylphenidate acted not as a biological competitor of thiopental, but as an independent central nervous system stimulant. This hypotheses is further substantiated by the observation that methylphenidate apparently countered respiratory and other depressant effects by meperidine, tranquilizers and general anesthetics. Ventilation studies showed an average increase of 65 per cent in respiratory minute volume following the administration of methylphenidate.

In drug-induced barbiturate depression methylphenidate alone or in combination with methetharimide or amphetamine had no significant effect on the cardiovascular system. Although this drug alone or in combination did not raise the depressed blood pressure but it definitely protected the subject from an abrupt falling of blood pressure due to

barbiturate intoxication indicating that it acts some way in the cardiovascular center in barbiturate depression.

No side effects or depressive rebound was observed during the course of treatment, or after the treatment; instead the animals showed characteristic arousal symptoms particularly with the dose of 5 mg/kg and recovery occurred after nearly 8 hours after the end of the experiment in most of the cases. From this study and the previous studies by several other workers it is apparent that methylphenidate is a prospective antidotal drug in severe barbiturate poisoning and can be used without any visible hazard either alone or in combination.

According to the study of methylphenidate alone we observed that the standard dose is 5 mg/kg , six injections intravenously at twenty minute intervals to antagonize the effect of severe barbiturate depression with satisfactory increase in ventilation. This finding led the author to study the effect of methylphenidate with the combination of other analeptics such as methetharimide and amphetamine. The drugs for combination other than the standard drug (six injections of 5 mg/kg methylphenidate at twenty minute intervals intravenously) were tried in full and half doses with six dogs in each group of combination.

The combinations have projected the following findings revealing quite satisfactory results from most of them.

Methetharimide and methylphenidate combination

Two different doses of methetharimide were tried with methylphenidate. The following are the two combinations in the descending order of efficiency:

1. Methetharimide 40 mg/kg i.v. (one full dose and methylphenidate 6 injections of 5 mg/kg each i.v. at twenty minute intervals (one full dose).
2. Methetharimide 20 mg/kg i.v. (one half dose) and methylphenidate 6 injections 5 mg/kg each i.v. at twenty minute intervals (one full dose).

Methetharimide in full dose (40 mg/kg) with methylphenidate was observed to increase remarkably the ventilation by an average of 242 per cent at the end of two minutes after the first injection followed by slight decrease till sixty minutes where the average increase in ventilation was 183 per cent. Following that, ventilation shot up once again and increased by 270 per cent at ninety minutes, i.e. after the completion of fifth injection of methylphenidate and steadily reached an average increase in ventilation by 460 per cent at the end of the experiment, i.e. after one hundred and ninety minutes observation period. The peak increase in ventilation was considerably more than the action by methylphenidate alone or in other combinations. It may be noted that three dogs of this group produced characteristic awakening symptoms (stretching of legs, paddling of legs, swallowing, pedal and corneal reflexes, raising head, etc.) that the experiment had to be stopped in those cases before the end of the observation period.

The other combination in this series, i.e. methetharimide in half dose (20 mg/kg) with methylphenidate produced appreciable rise in ventilation. At the end of two minutes of the first injection ventilation was increased by 190 per cent on an average followed by fall to 101 per cent above the predrug level, then gradually dropped further down to 54 per cent at the end of thirty minutes. Following that, the ventilation began to rise again gradually and steadily and reached an average of 197 per cent increase in ventilation after the end of one hundred and ninety minutes. In this group one dog produced a great awakening effect at 150 minutes and the experiment had to be discontinued before the end of the observation period. Blood pressure was maintained to a satisfactory level throughout the experiment.

Methetharimide is a central nervous system stimulant and in high dosage and particularly if given rapidly will cause convulsions in both barbitalized and normal animals (Benica and Wilson, 1950; Shaw et al, 1954) has indicated this substance possesses a high therepeutic index. In therapeutic doses it is a useful analeptic against barbiturate depression. Methetharimide appears to possess a specific respiratory stimulant effect only in barbitalized animals and routinely is suggested to terminate barbiturate anesthesia. The drug appears to be a specific barbiturate antagonist on almost a milligram for milligram basis (Baker and Englewood, 1956). This view has been partly contradicted by Kimura and Richards (1958) who told the opinion that methetharimide is

not a competitive antagonist to barbiturates but merely another drug which stimulates the central nervous system as do picrotoxin and metrazol. Gale (1961) also observed that methetharimide is a nonspecific stimulant. It is also said by some workers that methetharimide behaves purely as a pharmacologic antagonist to barbiturates, since the effects of the latter persist. As a central analeptic, which methetharimide must be regarded, it is superior to early preparations in that it does not cause hypertension and overtaxing of an already intoxidated myocardium, neither does it cause hyperpyrexia. In the previous study, Cairy, Leash and Sisodia (1961) in this laboratory have observed that methetharimide alone in barbitalized dogs produces an immediate rise in ventilation of 165 per cent followed quickly by a decrease to the 70 per cent level which was maintained for about 35 minutes at which time a prompt increase to 120 per cent was recorded and further it produces the best result amongst the drugs studied (Nikethamide, Caffeine and sodium benzoate, metaraminol bitartrate, pentylenetetrazol, amphetamine sulfate). On the basis of the good result observed in this laboratory the author selected this drug to use in combination with methylphenidate which produced a gradual rise in ventilation up to the end of the experiment described before in this chapter.

It is strongly believed from the findings of the result of this project that methetharimide and methylphenidate have synergistically increased the ventilation. We know that

methetharimide immediately raises ventilation, and on the other hand methylphenidate produces a gradual and steady improvement of ventilation. Therefore, it may be expected that the immediate rise of ventilation by methetharimide followed by abrupt fall is maintained at the appreciable level by the methylphenidate synergistically with the methetharimide. It has been observed by Gale (1960) that methetharimide alone develops tremors or convulsions in the treatment of drug-induced central nervous system depression and he suggested the administration of methetharimide and methylphenidate combination in which case tremors and convulsions were not produced. The present observation further confirms the previous findings and suggestions. The side effects that were observed by the treatment of methetharimide alone was found to be terminated when used with the combination of methylphenidate indicating that the side effects of the former is cut down by the latter and therefore the combination of these two drugs can be considered as a suitable treatment in barbiturate depression.

Amphetamine and methylphenidate combination

Two series of dogs were studied in two different dose levels of amphetamine in combinations with the methylphenidate. The following are the two combinations in the descending order of efficiency:

1. Amphetamine sulfate 4 mg/kg i.v. (one full dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at twenty minute intervals (one full dose).

2. Amphetamine sulfate 2 mg/kg i.v. (one half dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at twenty minute intervals (one full dose).

Amphetamine sulfate in full dosage (4 mg/kg) with methylphenidate produced a gradual and steady increase right after the first injection. An average increase in ventilation by 49 per cent was observed at the end of ten minutes, followed by a rise by 86 per cent at ninety minute and finally elevated by 155 per cent increase in ventilation at the end of one hundred and ninety minute observation period. The respiratory rate and blood pressure were maintained to a satisfactory level except blood pressure was decreased a little at the later part of the experiment in some cases. In this group 3 dogs exhibited a great awakening effect (pedal and corneal reflex, movement and stretching of legs, paddling of legs, forceful expiration, raising head, etc.). Vomition was observed in one case, the reason for which could not be explained.

Amphetamine sulfate in half dosage (2 mg/kg) with methylphenidate produced a fluctuating increase in ventilation. At the end of two minutes an average increase in ventilation was 50 per cent which was dropped down to 32 per cent at ten minutes and again elevated to 53 per cent at the end of sixty minutes after which a slow and steady increase in ventilation was maintained and reached a peak of 113 per cent at the end of one hundred and ninety minutes observation period. In this group one dog exhibited remarkable awakening

symptoms, (pedal and corneal reflexes) during the course of treatment.

In these two combinations amphetamine in full dosage with methylphenidate produced the better results and in fact it gave the third best results in this investigation.

Amphetamine is a sympathomimetic amine and stimulates the cerebrospinal axis, especially the brain stem and the cortex. It compares well with all other drugs in analeptic effectiveness and finds considerable use in counteracting overdepression caused by anesthetics, narcotics, hypnotics, etc. Animals receiving sufficiently large amounts of amphetamine exhibit tremors, restlessness and increased motor activity. This is due to the cortical stimulation of the drug, but they may also result in part, from excitation of the brain stem. Barbiturates not only depress the respiratory system, but also the cardiovascular system considerably even under the controlled anesthetic conditions (Daniel et al, 1956). Amphetamine thus antagonizes barbiturates at the central nervous system as well as at the cardiovascular system. Amphetamine is a long-acting drug due to its slow destruction and thus it maintains a good ventilation for a longer time.

In the previous study in this laboratory by Cairy, Leash and Sisodia (1961) it was observed that with the amphetamine sulfate alone there was a slow increase in ventilation to an average of about 100 per cent above the predrug level after the drug was given. In the present study it is observed

that full dosage of amphetamine sulfate with methylphenidate produced steady rise in ventilation to 184 per cent at the end of one hundred and eighty minutes and then gradually dropped down to 155 per cent at the end of one hundred and ninety minutes indicating that these pairs act in some way additively enhancing the action of amphetamine.

The blood pressure was reduced a little in the later part of the experiment probably due to sustained action of methylphenidate as studies of Maxwell et al revealed that methylphenidate blocked the pressure response elicited by bilateral carotid occlusion and produced a prompt reduction in blood pressure which has been elevated by amphetamine or ephedrine.

The half dosage of amphetamine sulfate with methylphenidate exhibited the increase in ventilation not to a great extent but it was not either negligible indicating that perhaps half dosage of amphetamine sulfate was not potent enough to raise the ventilation and moreover it affected the usual action of methylphenidate in some way as the action of methylphenidate (5 mg/kg) alone at twenty minute intervals produced better results than this combination treatment.

CHAPTER V

SUMMARY

Methylphenidate alone in three doses and combined with amphetamine sulfate or with methetharimide at two dose levels each were studied in this project in order to observe the changes in ventilation, blood pressure and the awakening properties in deeply anesthetized dogs with the pentobarbital sodium. The following descending order of efficiency was observed:

1. Methetharimide 40 mg/kg i.v. (one full dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
   The maximum average percentage increase in ventilation was 460 per cent
2. Methetharimide 20 mg/kg i.v. (one half dose) methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
   The maximum average percentage increase in ventilation was 197.18 per cent.
3. Amphethamine 4 mg/kg i.v. (one full dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).
   The maximum average percentage increase in ventilation was 155 per cent.

4. Methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).

   The maximum average percentage increase in ventilation was 209 per cent.

5. Amphetamine 2 mg/kg i.v. (one half dose) and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals (one full dose).

   The maximum average increase in ventilation was 113.8 per cent.

6. Methylphenidate 6 injections of 3 mg/kg each i.v. at 20 minute intervals.

   The maximum average percentage increase in ventilation was 69 per cent.

7. Controls-Maximum average increase in ventilation in deeply barbitalized dogs with no analeptics was 25 per cent.

8. Methylphenidate 6 injections of 10 mg/kg each i.v. at 20 minute intervals (double dose).

   No improvement was observed.

In the individual series with the methylphenidate alone, six injections of methylphenidate at the rate of 5 mg/kg i.v. at 20 minute intervals was observed to have a better effect on ventilation than either 3 mg/kg or 10 mg/kg i.v. given six times each and the combination of amphetamine sulfate 2 mg/kg. i.v. and methylphenidate 6 injections of 5 mg/kg each i.v. at 20 minute intervals.

It may be observed from the results that a combination of methetharimide 40 mg/kg i.v. (one full dose) along with 6 injections of methylphenidate at the rate of 5 mg/kg i.v. at 20 minute intervals produced the best ventilatory and awakening effects amongst the paired and individual drugs studied in this project.

On the basis of the results of this experiment and the previous studies the author firmly believes the methylphenidate alone or in combination with other analeptics could be satisfactorily used for the treatment of severe barbiturate poisoning in veterinary practice and perhaps in human practice.

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