PHARMACODYNAMIC REACTIONS OF RESPIRATORY DEPRESSANTS AND ANALEPTICS AFTER THEIR INJECTION INTO THE GREAT CISTERN OF THE DOG

by

James C. Rice

B. S. in Ed., University of Missouri, 1922
A. M., University of Missouri, 1927

Submitted to the Departments of Physiology and of Pharmacology and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Robert M. Isenberger
Instructor in charge

Date April 14, 1934

O. O. Stoland
~~Head~~ Chairman of Department

Table of Contents

I. INTRODUCTION

Because the term "analeptic" is not used extensively by American investigators it is necessary both to define it and to show cause for its use. Neither Sollman (1) nor Bastedo (2) include the term in the indices of their textbooks. An analeptic is defined by Dorland (3) and by Webster (4) as a "restorative" or a "restorative drug." It is with the idea of restoration of respiratory function in mind that the word is chosen in preference to the word "stimulant." As an example of the use of the word, camphor is described as a "circulatory analeptic", a description to which European investigators would assent more readily than American.

Not all of the experiments in this study involved the cisternal exhibition of drugs. However, since some of the preliminary experiments were instrumental in shaping the course of the study and since all of them yielded observations of intrinsic interest, they will be presented in the experimental results. All of our experiments are essentially studies in drug antagonism.

Originally, a more customary approach to the problem of antagonism between the barbiturates and certain stimulant drugs was contemplated. The experimental procedure involved the modification of consciousness by depressants and a subsequent modification by antagonistic drugs of the

changes first produced. Elsewhere in the paper it will be shown repeatedly that this procedure is very valuable and not in the least unique. It is an experimental device used by the founders of the science of pharmacology. The desirability of a study of the antagonism between barbiturates and stimulant drugs is apparent because, at present, no drug has been proved truly efficacious in reversing barbiturate narcosis without producing effects occasionally more deleterious than the narcosis. The finding of a satisfactory antagonist would confer a boon upon those who have attempted to advance the use of barbiturates as anaesthetics, and upon those who are called upon to treat patients experiencing the accidental and suicidal crises consequent to the free and untrammelled sale of hypnotic drugs.

The utility of the Magnus (5) reflex patterns for the study of the duration of barbiturate action and for a comparison of the relative narcotic powers of various barbiturates is apparently more impressive than a possible utility of these patterns for the study of analepsis after barbiturate narcosis. In the hands of Eddy (6) the method employing the postural reflexes has yielded very significant data comparing the hypnotic potency of the barbiturates available. The very mode of injection commonly used (intravenous), however, leaves much to be desired in experiments assaying the activity of antagonists against barbiturates. Although this is the inevitable consequence

after intravenous, subcutaneous, oral or inhalation exhibition of drugs, it is not the case after topical medication in the most rigorous sense of the word.

When drugs are administered non-topically the maximum dose never reaches the site desired, and to a limited extent the same is true with topical medication. However, during the first moments after topical medication (in the absolute sense) it is possible to produce the full pharmacodynamic effect of all the drug administered. With any other type of medication this is clearly impossible. Furthermore, with topical medication it is possible temporarily to defer the effects of detoxication and of excretion. This, too, is clearly impossible with any other type of medication.

Out of the dilemma of detoxication, dilution, differential absorption, excretion and depot effect some form of topical medication offered the only solution. The pharmacologic study of isolated nerve fibers or trunks offered itself as an expedient, an expedient whose necessity was overruled by fortuitous observation.

This observation was the immediate spontaneous return of respiration after the intrathecal injection of sodium thiocyanate in the subdural space of a dog experiencing respiratory paralysis after experimental anaesthesia by subdural novocaine. This surprising result called attention to the eligibility of respiration as a function for use in studies of antagonism. However, the lumbar tap method

of producing the paralysis was far from attractive. The response to sodium thiocyanate in the experiment cited was achieved after preliminary ephedrine medication and after a lapse of time probably fully adequate to permit the spontaneous return of respiration. However, the observation aroused the hope that sodium thiocyanate might be responsible, and it pointed out a physiological mechanism which could, by artificial means, be at least partially divorced from the rest of the organism.

With respiration selected as a function to be modified and with topical or quasi-topical medication explicitly chosen, the cisterna magna suggested itself at once as a possible avenue of drug exhibition. Its choice, it must be admitted, was made with some misgiving because there is still some question concerning the continutity of the subarachnoid with the ventricular spaces. Certainly the exhibition of drugs in the cistern constitutes an act which can be performed with more nicety than lumbar tap can be effected. Furthermore, the diffusion or circulation of drugs exhibited in the lumbar subarachnoid is not clearly understood even by those who daily use spinal anesthesia upon man. LeRiche (7) recently deplored the fact that spinal anesthesia has interested the physiologist far less than it has deserved.

Respiration is rarely used in an explicit sense in the study of drug antagonism. However, it offers, after the

application of depressant drugs to its central regulators, graded and crucial changes about whose reality there can be no mistake. Respiratory paralysis is such a change and its duration is a measurable quantity. In this study the duration of respiratory paralysis has been set up as the criterion of depressant action upon the respiration and reciprocally as the criterion of analeptic potency.

It might be argued that incision of the atlanto-occipital membrane would offer an even surer approach to the medulla. Although this is true the surgical procedure is incompatible with the availability of animals for control purposes. Even if the animals do survive after such procedure, and there is little reason why they should not provided the operator is skillful and providing overdosage is avoided, there remains the almost inevitable obliteration of the comparatively small cistern by the processes of repair. Indeed,the cistern ceases to exist as such after too many punctures even with the hypodermic needle. This is particularly true if bloody taps be made at any time.

The validity of the assumption that the method of injection constitutes topical medication is likewise questionable. Whatever the merit of the objection to the validity of this assumption it must be admitted that the injection of drugs into the cistern does produce a comparatively high momentary concentration of the drug in the subarachnoid fluid. Before the dissipation of the drug from the subarachnoid cisternal fluid, it is apparent that there

will be absorption of some of the drug by any nervous tissues in contact with subarachnoid fluid. The amount of absorption will, in all probability, be dependent upon the concentration gradient between the fluid and the nervous tissue.

It must also be borne in mind that cisternal exhibition of drugs, because of greater concentration, produces localized functional modifications more profoundly than does the intravenous injection of drugs.

The study of the respiratory changes produced by cisternal injection has convinced the author that this method constitutes both a means of ascertaining the analeptic potency of drugs and a possible means of clarifying the nature of the antagonism existing between drugs. These studies do not presume to include the latter possibility. The method renders it possible to discover a species of antagonism different from and in addition to that species of antagonism which operates by changes in other functional mechanisms besides the one deliberately modified. For example, the antagonism between sodium amytal and ephedrine is probably partially due to an improvement of circulation. The sense of these studies is that it is also manifested at the site of the contact of ephedrine with the narcotized central respiratory structures. However, the mode of action of ephedrine in this latter species of antagonism is, at present, not at all clear.

I
SUMMARY OF EXPERIMENTAL METHODS USED IN THESE STUDIES

1. Preliminary Experiments
   A. Experiments using mice to test the efficacy of ethylene diamine as an antagonist to ether.

      This series is very short and quite unimportant.

      It will be described in the results.

   B. Observational experiments employing the study of modification of reflex behaviour and of consciousness by hypnotics and by stimulants.

In this group of experiments dogs were anaesthetized either with sodium amytal or with sodium amytal preceded by morphine sulphate. They were permitted to regain consciousness and to assert their spontaneous ability to walk either after intervention with certain stimulants or without intervention. Ephedrine, coramine, cardiazole, picrotoxin, and sodium thiocyanate were used to reverse the depressions invoked in the animals.

Both consciousness and the postural reflexes are elusive phenomena. They are stumbling-blocks in the hands of any except the most gifted investigators and have been responsible for much of the conflicting testimony regarding drug antagonism.

2. Major Experiments Involving Observations of the Intact Animal.
   A. The production of respiratory paralysis by the cisternal injection of drugs. The mitigation of the paralysis by the cisternal and intravenous injection of analeptics (antagonists).

In this group the dogs were first anaesthetized to facilitate entry into the cistern. At least three types of

anaesthesia were used: ether, morphine-ether, and morphine - sodium amytal. After anaesthesia tracheal tubes fitting as closely as was consistent with the necessity of no trauma to the larynx and trachea were inserted in the animals. The cistern was then tapped by a method more fully described in a later section. The desired drug was dissolved in the aspirated fluid and re-injected in the cistern. With adequate doses of depressants respiratory paralysis occurred. The animal was then artificially respired and, if the experiment was designed for control, permitted to breathe spontaneously when it regained the ability to do so. The duration of paralysis was recorded.

When the efficacy of an analeptic drug was to be tested, fluid was again aspirated and the analeptic dissolved therein. Then the fluid was re-injected and the duration of respiratory paralysis again measured. In certain experiments the analeptic and depressant were simultaneously injected but in the greater number the analeptic followed the depressant.

It was found possible to compare the duration of respiratory paralysis after different anaesthesias upon the same animal.

The safe-guards, whereby the variability of conditions was removed, are described in the general discussion.

B. Experiments in which analeptics alone were injected in the cistern

3. Acute experiments.

A. Blood pressure studies during respiratory paralysis produced by depressant drugs cisternally exhibited.

This phase of the study requires no description.

Femoral arterial blood pressure was measured.

B. Blood pressure studies during respiratory paralysis produced by depressants injected in the lumbar subarachnoid.

II
RELATION OF EXPERIMENTAL TECHNIQUE TO THE MECHANISM OF RESPIRATORY CAUSATION

It is assumed that the views of Robert Gesell (8) describe best the chemical regulation of respiration. He postulates the existence of an acid metabolism of the respiratory center unique and not identical with the acid metabolism of the rest of the body. The rate of formation of acid in and its rate of transport from the center determine the acidity of the center. Changes in the pH of the center rather than of the blood constitute the prime factor in respiratory control. Since the supply of oxygen determines the absolute and relative amounts of lactic acid and carbon dioxide formed in living tissue, and since it controls the efficiency of transport and elimination of acid it constitutes the normal and indirect regulator of pulmonary ventilation.

The effects of lactic acid and carbonic acid are additive. They are excreted indirectly by way of blood from the tissues and more directly by virtue of their formation in the respiratory center itself.

Diminished oxidation in the respiratory center leads to an accumulation there of relatively poorly diffusible lactic acid and in relatively poorly buffered cytoplasm and lymph no longer fully protected by the potential alkalinity of the blood, the dual function being disturbed by the diminution of the reduction of hemoglobin and of the liber-

ation of alkali as it passes through the center.

By virtue of its own metabolism and its extreme sensitivity to minute changes in its own hydrogen ion concentration, the respiratory center is sensitive to minute changes in its own oxidation and, therefore, to changes in the tension of oxygen in the arterial blood.

The capacity of the center to respond to changes in the arterial carbon dioxide tension consequent to fluctuations in the general metabolism, however, must also be a factor.

In our experiments the animal was, as has been stated, respired artificially by periodic blasts from an artificial respirator. It is well known that excessive ventilation produces apnea, a condition depending according to Haldane and Priestley (9) upon the depletion of arterial carbon dioxide. Since the dogs used were of variable size and since cannulation with a tightly fitting tracheal catheter was not advisable, the question of variable ventilation at once obtruded itself. Furthermore, there is great variability in the operation of the respirator depending upon atmospheric conditions impressing themselves upon the length of the leather belt driving the respirator pump. Proper inflation becomes, then, something more than a problem in the mechanics of the respiratory pump.

Although we were aware at the outset of the advisability of running carbon dioxide studies of arterial blood,

we were equally certain that it was impossible to control the inflation from the findings of such studies. It would have been necessary to make the measurements and then to adjust the apparatus in keeping with the analyses. Before this could have been done the animal would have been able to breathe of its own accord.

Gesell (8) described a manganese dioxide electrode with which the pH of blood is automatically registered. With this apparatus at one's disposal it would have been possible to control at least one variable quite accurately, but with this device all variables would not have been eliminated.

The metabolism of the narcotized center is also an unsolved problem. There are, it is true, some data describing the metabolism of narcotized tissue. Warburg (10) has shown that narcosis inhibits fission of the sea urchin egg but not its oxidation. This was confirmed by Loeb and Wasteneys (11). Winterstein (12) has shown that in the central nervous system depressed by alcohol there is increased oxidation.

If the metabolism of the respiratory center is greatly depressed by narcosis then it is quite possible that the production of acid therein is at such a low ebb that concentrations of carbon dioxide in arterial blood of even major proportions may be unsuccessful in eliciting respiration. This speculation assumes, of course, that there is

little diffusion of carbon dioxide into the center. Further, it assumes that the normal role of carbon dioxide, in the blood, in provoking respiration depends upon the fact that its concentration in the blood inhibits its transport out of the cells of the respiratory center. This possibility is far from unthinkable. On the other hand, if the metabolism of the center is increased by narcosis then the level of circulating carbon dioxide might be unbelievably low and still respiration would result from excessive concentration of metabolites in the center itself. Indeed, the fact of narcosis may even produce changes in the center favoring a diminished oxidation, and at the same time an impermeability of the center to gases. Under such conditions respiration could not result until the narcotic concentration in the center had been so reduced that permeability had again returned, and that oxidation had assumed its normal unnarcotized level. These speculations are not submitted as tentative interpretations of narcosis of nervous tissue but rather to show how difficult it is to set up proper criteria to test the irritability of a center emerging from narcosis.

We have measured the carbon dioxide level in circulating arterial blood and are led to believe from our data that respiratory response is possible under greatly differing concentrations of carbon dioxide in arterial blood. We do not presume to assert but merely suggest that the abol-

ition of spontaneous respiration by our method may be very valuable in the study of the fundamental regulation of respiration.

In the measurements of arterial carbon dioxide blood was drawn from the femoral artery under oil and was analyzed for carbon dioxide without permitting the access of air. The analyses are in no sense alkali reserve determinations.

Naturally the results of such analyses will be variable from animal to animal and even from day to day depending upon the alkali reserve. The important information to be gained from these data is that the actual carbon dioxide content of the arterial blood has been caused to fluctuate by varying the inflation. In general, the carbon dioxide content is somewhat lower during inflation after anaesthesia than the level during unanesthetized spontaneous breathing. The carbon dioxide level in arterial blood after one minute abeyance of artificial respiration is as high as the normal level and often as high as the level while the animal spontaneously breathes under morphine-amytal anaesthesia or ether anaesthesia. The latter level is slightly higher than the normal arterial carbon dioxide in the unanesthetized dog spontaneously breathing.

The tabulated results give only corrected volumes percent and not the actual volumes as read in the Van Slyke apparatus. The results and computations have been checked

Table 1

ARTERIAL CO_2 LEVELS IN VOLUMES PER CENT UNDER CONDITIONS IMPOSED EXPERIMENTALLY

EXPER.	NORMAL	AFTER MORPHINE	(A) AFTER SODIUM AMYTAL	(B) WHILE ARTIFICIALLY RESPIRED	(C) AFTER 1 MIN DENIAL OF ART. RESP.	(D) SPONTANEOUS BREATHING	DIFFERENCE C - A	DIFFERENCE D - A	DIFFERENCE C - B
162	39.0	—	42.8	37.6	43.8	41.4	+1.0	-1.4	6.2
161	4..	—	40.4	41.1	43.1	45.8	+2.8	5.4	2.0
160	37.6	—	41.2	36.6	41.2	—	0.0	—	+4.6
158	40.4	—	43.0	38.6	44.3	44.5	+1.3	+1.5	+5.7
157	3..9	—	31.9	—	—	—	—	—	
155	44.9	—	37.4	39.3	—	—	—	—	
154	—	36.5	40.1	—	—	—	—	—	
153	38.4	—	—	37.4	—	36.5	—	—	
151	—	40.6	—	33.4	36.0	34.2	—	—	+2.6
150	—	40.5	—	37.7	39.6	44.0	—	—	+1.9
149	37.3	—	40.9	32.6	35.4	34.4	-5.5	-6.5	+2.8
148	38.4	—	44.0	—	30.8	40.1	—	-3.9	—
147	38.0	37.8	37.8	29.0	38.4	45.0	+6.0	+7.2	+9.4

Table 1 (conc.)

Arterial CO_2 Levels In Volumes Per Cent Under Conditions Imposed Experimentally

Exper.	Normal	After Morphine	After Sodium Amytal (A)	While Artificially Respired (B)	After 1 Min. Denial (C)	Spontaneous Breathing (D)	Difference C – A	Difference D – A	Difference C – B
146	37.3	—	42.9	39.1	39.1	38.2	-3.8	-4.7	0.0
* 145	39.6	—	47.0	37.2	39.6	47.0	-7.4	0.0	+2.4
143	42.9	—	50.4	42.9	48.5	42.9	-1.9	-7.5	5.6
142	36.6	—	36.6	—	—	36.6	—	0.0	—
** 141[a]	36.6	—	46.3	42.4	—	36.5	—	—	—
141	40.1	—	—	36.3	45.9	45.9	—	—	+9.6
140	39.4	—	38.55	36.6	—	42.37	—	—	—
139	42.5	—	46.38	42.5	46.38	49.29	0.0	2.91	+3.90
138	52.4	57.0	—	46.56	52.4	51.3	—	—	+5.84

* ** Nearly Died from Anaesthetic

by two persons and are the results of consistent findings in which a check was secured in all except a few cases.

Sometimes animals were observed to breathe after paralysis in response to levels even sub-normal for the animal. Such data give a sense of security in the validity of the choice of the one minute periods as adequate for eliciting spontaneous respiration in the artificially respired dog. In some cases the animals were patently over inflated for various reasons. The data in such cases indicate the accuracy of the observers' judgment of over-inflation.

When combined with the other criteria mentioned in the general discussion these findings lead one to the inescapable conclusion that the results of these experiments can in no sense be dependent upon relative degrees of acapnia consequent to variable inflation. The fact that in only one instance was it impossible to secure breathing after abeyance of artificial respiration strengthens one's conviction. This case involved an animal which never was able ultimately to breathe under any conditions.

It must also be remembered that in normally respiring animals the respiratory center is functioning and that volleys of impulses are originating in the center. The metabolism of nervous tissue is not high but its oxygen needs are great. Just what happens in a narcotized center with respect to the metabolism consequent to the product-

ion of these volleys is entirely unknown.

Confronted with the necessity of choice of some definite standard to test the return of spontaneous breathing and cognizant of the perils of asphyxia to centers, we were forced to adopt a procedure which would minimize variations in the automatic capacity of the breathing mechanism consequent to overventilation and at the same time to minimize the dangers of asphyxial damage to animals whose survival was earnestly desired. Our choice was not the concentration of carbon dioxide in the blood nor was it the concentration of oxygen in the blood. Indeed, we were forced to forego measuring oxygen content because it demanded additional arterial puncture in the animals. Our choice was the interruption of artificial respiration for periods of one minute with the animal so ventilated that an additional abeyance of artificial respiration would lead to a quickening of the pulse and the appearance of cyanosis in the mucous surfaces in the periphery of the tongue. Often we lengthened the period of abeyance of artificial respiration and were able to elicit respiration. In this connection we have found that under all conditions of ventilation the respiration elicited by withholding artificial aid from the animal for periods as long as one and one half minutes produced, if it did so produce, respiration entirely inadequate for life. By using this expedient we have experienced the unnecessary loss of animals. When the respiration returned after one minute's abeyance the animal was generally

able to respire adequately.

Abeyance of artificial respiration for one minute is, we found, sufficient to restore spontaneous breathing in animals frankly overinflated. However, it is not difficult to give an inflation which approximates normal. This is done by observing the thoracic thrust of the animal when normally breathing and approximating it with the respirator, taking into account, of course, difference in frequency between the machine and the normal respiratory response. It must also be borne in mind that with a loosely fitting tracheal catheter the inflation of the lungs depends partly upon their inherent elasticity. Under such conditions there is ample avenue for escape of air around the catheter, a fact which makes for inflation similar to the normal.

In the presence of an unquestioned acapnia produced by overinflation, artificial respiration has been denied animals as long as two minutes. Under such conditions there was invariably a rapid decline in pulse frequency after a preliminary asphyxial increase. After the decrease the femoral pulse became quickly impalpable and cardio-circulatory collapse with intense cyanosis supervened. Recovery from such collapse was easily produced by reinstitution of artificial respiration if action was taken promptly. The sense of such observations is that the arbitrary choice of one minute for respiratory abeyance is really a satisfactory choice.

In our experiments the ability to carry on adequate breathing rather than the appearance of a first abortive thoracic or diaphragmatic movement has been selected as a crucial chronological observation. In the case of coramine disconcertingly abrupt diaphragmatic movements were often observed; in the intact animal spontaneously breathing coramine was observed to produce hiccoughs. Manifestly, such misleading movements do not constitute true respiration.

In the tabulated data the results obtained are based upon denial of respiration for one minute periods. Although early in the respiratory depression neither one minute nor longer sufficed to elicit respiration, very late in the respiratory depression the additional time often did suffice to produce respiration of inadequate character.

Rarely respiration provoked by one minute's denial was inadequate but if it chanced so to be then the animal was again respired until a subsequent one minute denial of artificial respiration produced adequate breathing. In connection with the phenomenon of inadequate respiration the protocol of a striking experiment peculiarly related to this phenomenon is adduced.

Experiment 148--Dog # 56 July 29, 1933

This animal was anaesthetized with subcutaneous morphine sulphate 4 mg.per kg. and intravenous sodium amytal 30 mg.per kg. Into its cistern 25 mg. ephedrine sulphate and 84 mg. sodium amytal were introduced

simultaneously and well mixed with the subarachnoid fluid by washing in and out. That the cistern tap was good was evidenced by the ability to inject and withdraw fluid at will. The animal continued to breathe for six minutes. In spite of an apparently adequate respiration the animal ceased to breathe abruptly. With the cessation of respiration came complete cardio-vascular collapse with impalpable femoral or precordial pulse and with total abolition of reflexes. No cardiac movements could be felt through the needle-syringe assembly. Artificial respiration was immediately instituted and adrenalin, 1 c.c. of 1/1000, introduced into the heart. After a short period of precordial massage the heart started to beat and within one minute the circulation had begun to improve. Within four minutes the hind-limb extensor jerk could be elicited. In about six minutes the protruding eyes had receded and the reflexes had improved. The animal made an eventless recovery.

One more fact regarding this experiment merits especial consideration. The animal was, after its cardio-respiratory collapse, patently over-inflated for obvious reasons. In spite of the over-inflation the animal breathed thirteen minutes after the collapse in the face of abeyance of artificial respiration of only forty seconds. It is suggested that in this case there was respiratory analepsis in its most intimate sense because this experiment demonstrates the return of irritability to

a mechanism depressed to a point approximating the lethal limit and stimulated by one of its proper stimulants (carbon dioxide) in a concentration deliberately made minimal by over-inflation.

****

Artificial respiration was periodically denied every five minutes. Such procedure introduces the possibility of errors of as much as five minutes in the recorded durations of respiratory paralyses. However, the deep preliminary anaesthesia suffices so to lengthen the duration of respiratory paralysis as to minimize this error. It is believed that too frequent denial of artificial respiration to test the return of spontaneous ability to breathe implies the danger of asphyxial damage to the centers. In our concern for ultimate recovery this danger has been scrupulously avoided.

It must also be remembered that the administration of ephedrine conduces to variability of carbon dioxide in the blood as a consequence of improved circulation. Although such improvement makes for an increased elimination of carbon dioxide it can hardly make for an improvement in the oxygen supply because the mechanism governing oxygen supply works at high efficiency. The responses to ephedrine administration just mentioned would certainly conduce to an increase in the duration of respiratory paralysis as a result of what the author likes to call "circulatory acapnia." Both Schmidt (13) and

and Wright (14) have observed this acapnic apnea after the impact of the effects of powerful pressors upon the cardio-respiratory mechanism. The latter observer attributes the phenomenon to reflexes mediated by the carotid sinus and the nerve of Hering. However, an improved circulation serves to dissipate the concentration of the narcotic in the central structures and in so doing tends to produce a more speedy recovery from respiratory paralysis. The former credits oxygen surfeit with the improvement in irritability of the central structures. We believe that in our experiments the analeptic produces an additional effect: that it increases the sensitivity of the central structures to stimuli or that it supplants or nullifies the narcotic in some undetermined fashion. In studies of analepsis using consciousness as a criterion it is easy to talk loosely about the effects of an improved circulation. With our experimental procedure a mechanism was used in which an improvement of circulation might, quite conceivably, produce changes conducing to an actual increase in the duration of the depressant effects. Our studies impressively deny the production of any such increases in the duration of depressant effects.

If the effect of elimination of carbon dioxide excessively or of the carotid sinus reflexes should chance to cancel the effects of elimination of the narcotic from the central structures then the observed effects must

be attributed to intrinsic stimulant properties of the analeptic operating at the very site of depression. We do not presume to assert the truth of this possibility; we merely offer it as a possible explanation of our results.

III. THE CHOICE OF THE CISTERNA MAGNA AS THE AVENUE OF DRUG EXHIBITION IN THE STUDY OF THE PHARMACODYNAMIC REACTIONS OF DRUGS AND FOR THE STUDY OF EXPERIMENTAL SPINAL ANAESTHESIA

1. Anatomical Relations

The cisterna cerebello-medullaris, one of the reservoirs of the subarachnoid system is also called the "great cistern" and the "cisterna magna." The pial-arachnoideal relations are not identical at all levels of the neuraxis. At the bulbar level the arachnoid is less closely applied to the cord. The separation from the neuraxis is most extensive dorsally where the arachnoid passes from the cord to the surface of the antero-dorsal aspect of the cerebellum. This separation of the meninges is the cause of the existence of the cistern as a reservoir.

The limiting structures of the cisterna magna are: in the superior sense, the inferior vermis and the mesial aspect of the cerebellar hemispheres; in the dorsal sense, the diverging arachnoid; in the lateral sense, the arachnoid; and in the ventral sense, the inferior medullary velum and the tela choriodea inferior.

Although the continuity of the subarachnoid with the ventricular spaces is still in dispute it is not expedient to enter into the controversy at length. The dispute hinges upon the patency of the foraminae of Luschka and Magendie. The situation was summarized by Weed (15) who insisted upon the existence of a mechanism for mediating osmotic exchange

from the ventricular fluid to the subarachnoid fluid. He described ependymal structures in the roof of the fourth ventricle which, by virtue of their differentiated character, might serve as the medium of such osmotic exchange. Weed (16) also asserted that the existence of the Luschka foraminae are not controverted. In this connection, Frazier and Peet (17) remarked the almost instantaneous appearance in the subarachnoid space of phthaleins injected into the lateral ventricles.

Whatever the facts about the patency of these foraminae, it is demonstrably clear that the injection of drugs into the cisterna magna produces physiological changes in the structures lying in the floor of the fourth ventricle. It has been found so in the case of the paralyzing local anaesthetic, novocaine,and the barbiturate, sodium amytal. Other observers cited elsewhere in this thesis have found it to be true with stovaine and other local anaesthetics.

That an intact cistern is necessary for the diffusion of drugs to the medullary centers was clearly demonstrated by Cotui and Standard (18). They found that methylene blue cisternally injected did penetrate to the fourth ventricle whereas the same dye applied to the surgically exposed roof of the fourth ventricle failed to produce a stain in the ventricle. They assert that hydrostatic pressure in the cistern is necessary for such penetration. Furthermore, the same workers found that novocaine applied

to the roof of the fourth ventricle failed to elicit respiratory paralysis whereas the same drug injected into the cistern produced prompt paralysis.

If the foraminae are existent as openings and are not artifacts then the penetration of the drugs into the fourth ventricle when cisternally administered is easily explicable. Riquier and Ferraro(19) have described a pressure differential between the cistern and lateral ventricles of 21m.m. of water. The pressure, as far as the cistern is concerned, is unquestionably linked with the fact of dural elasticity, a phenomenon which has had excellent mathematical treatment in the hands of Flexner, Clark and Weed (20). The withdrawal of cisternal fluid to the amount of 3 c.c. must produce a fall of cisternal pressure to a level lower than that of the ventricles. Such a fall would elicit the flow of ventricular fluid into the cistern. After the reinjection of the fluid into the cistern the pressure therein would again increase and if there had been drainage of the ventricular fluid into the cistern such a pressure would become presumably greater than that of the ventricular fluid. Consequently subarachnoid fluid would flow into the ventricles. That the existence of an appreciably decreased pressure in the cistern by the withdrawal of fluid is not idle speculation is shown by the aspiration of air through the detached needle into the cistern after the withdrawal of the cisternal fluid. If the needle be corked after withdrawal then the only other possibility of pressure equalization lies in the

superior pressure of the ventricular fluid.

In our experiments the viability of certain reflexes constituted the test of diffusion of the drugs introduced into the cistern. It is common practice to use methylene blue as a test of diffusion but this is impossible in experiments which demand the survival of the animals. Unfortunately an interpretation of distribution based upon reflex behavior is open to criticism because of the existence of arachnoid channels around each artery and capillary intimately communicating with the perineural and perivascular spaces of the nervous substance itself. This fact is attested by those competent observers Cushing (21) and Weed (16).

The diffusion into systemic channels of the drugs administered cisternally is another moot question. Possibly the Pacchionian granules as well as the other channels just described are responsible for the movement of dissolved substances out of the cistern. Dandy and Blackfan (22) described the excretion of dyes into the bladder 6-10 minutes after their cerebral subarachnoid administration. Pacchionian granules are not present in the spinal levels nor are they present in dogs. In spite of this fact, Frazier and Peet (17) described the excretion into the bladder of drugs administered in the spinal subarachnoid in an equally short period of time. They found excretion by the venous rather than by the lymphatic avenues. In early life the arachnoid villi are present but not the Pacchionian

granules. Weed (16) insisted that the arachnoid villi constitute a filtering apparatus allowing passage into the venous sinuses. He also postulated the activity of the perineural and perivascular lymphatics in the diffusion of drugs. If the perivascular lymphatics alone are concerned in the absorption of fluid and consequently of drugs therein dissolved then it is very difficult to explain the rapid appearance of drugs in the bladder after exhibition in the subarachnoid because such drugs must first traverse the cervical lymphatic system before reaching the circulation.

2. The choice of doses for cisternal injection

The use of doses based upon the body weight of the animal is probably not as logical as the suggestion of Cotui (23). He determined the cisternal dose of novocaine adequate to arrest respiration in terms of the length of spine from atlas to base of the tail. He found 1.3 to 1.5 mg. per cm. of length of the spine adequate. Because his observations were only recently published we were unable to avail ourselves of this choice of dosage and were forced to resort to a choice of dosage based upon body weight.

In animals which survive the experimental procedure the choice of dosage is not so important because they serve as controls. In these experiments various doses sufficient to produce respiratory paralysis were used. However, since it was necessary to produce paralysis with one injection in the cases of novocaine and of sodium

amytal, doses of 6.2 - 6.3 mg. per kg. body weight were used as the ultimate empirical choice.

3. Relation of cisternal puncture to spinal anaesthesia.

Although these experiments were not planned explicitly to contribute to the study of spinal anaesthesia, many of the observations have an intimate relation to that import- and pre-surgical procedure. A few workers have used the cistern as a medium of study of spinal anaesthesia. This use is becoming progressively more important in the light of the type of regional anaesthesia which has been described by Jonnesco (24) as " General Regional Anaesthesia."

Bowers and his associates (25) who administered stovaine intrathecally in the lumbar subarachnoid and in the cistern observed a difference in the respiratory failure consequent to the different procedures. The paralysis from cisternal stovaine they found to be central; that from spinal stovaine they found to be partly intercostal. They believe deaths from spinal anaesthesia fall into three classes: cardiac, cardio-respiratory and respiratory. They do not consider the pooling of the splanchnic blood as primarily important in spinal crises.

North and Ferguson (26) also minimized the importance of the pooling of splanchnic blood in spinal anaesthetic accidents. They insist that the failure of respiration is produced by the abolition of thoracic movements. They reject the importance of the systemic absorption of the

drug used (novocaine).

The cause of collapse of blood pressure in spinal anaesthesia is well summarized by Seevers and Waters (27) as follows: "Cellular oxygen want per se is one of the principal factors in the circulatory depression accompanying spinal anaesthesia." To combat the circulatory depression they suggested the use of the Drinker respirator and of ephedrine prophylactically, not remedially. One of their assertions is quite interesting:" The fall of blood pressure in spinal anaesthesia tends to be synchronous with and proportional to the amount of intercostal muscle paralysis."

On the other hand, Koster and Kasman (28) asserted that the fall of blood pressure in spinal anaesthesia is dependent upon effective block of splanchnic vaso-constrictor fibers. Their work was concerned with spinal anaesthesia but it is presented here because in it they minimize the danger of respiratory depression. Their feeling of security against respiratory depression was gained by the topical administration of neocaine to the exposed medullas of frogs and cats. We do not share their feeling of security.

If this paper presumed to study the cause of death or depression in spinal anaesthesia we should discuss at greater length the experimental data of spinal anaesthesia.

4. The use of the cistern in administration of drugs.

The use of the cistern for the administration of drugs is comparatively uncommon, partly because of the comparative youth of the cistern tap. The first occipital puncture was

described in 1905 by Westenhofer (29) who admitted his trepidation in approaching the task.

As early as 1913 Camus (30) was toying with the idea of the cisternal exhibition of drugs. It is true that the cistern offered to earlier workers an excellent opportunity for the administration of antisyphilitic drugs. Furthermore, its suitability for the administration of sera to combat meningitis was quickly apparent.

In 1925 Janossy (31) reported the introduction of lobelia into the cistern. Later, Jonnesco and Jiano (32) reported the production of respiratory paralysis by the cisternal introduction of novocaine. It is difficult to state from their data unsupported by graphic records whether the depression resulting in paralysis was central or peripheral.

Very convincing evidence of the ability of cisternally injected stovaine to produce respiratory paralysis was submitted by Bloch, Camus, and Hertz (33). They demonstrated the use of artificial respiration in saving their animals. Furthermore, they found caffeine beneficial in mitigating the cisternally produced depressions. Later, Camus (34) showed with graphs the same phenomena with novocaine.

Recently Vehrs (35) described the production of respiratory paralysis by the cisternal injection of novocaine. He also described the measurement of the concentration of novocaine in the subarachnoid fluid at periodic intervals after its exhibition. Vehrs did not interest himself in the

concentration of the drug in the nervous tissue itself. Such a consideration is a more elusive question than is the problem of concentration in the subarachnoid fluid. In the light of the Meyer-Overton theory of narcosis the differential fixation of the cisternally administered drug is infinitely more important than the concentration in the subarachnoid fluid.

In all probability Vehrs(35) over-emphasized the greater resistance to depression of the motor nervous elements in comparison with the resistance of the sensory elements. He believes that total regional anaesthesia involves no more vaso-motor depression than does lumbar block. His explanation of death in the thorough-going anaesthesia just alluded to is dual: death results from brain-stem anaemia without respiratory block or with respiratory block due to paralysis of respiratory nerves or centers; or death results from cardiac anaemia.

The central theme of Vehrs' postulates for the safe practice of profound spinal anaesthesia is that the vital motor elements of the organism are protected from the consequences of drugs administered in the subarachnoid by chemical, anatomical,and physiological safety devices depending upon the large cisternal volume. Vehrs considers the motor elements lower in the neuraxis much more vulnerable to the effects of depressants administered in the subarachnoid spaces.

Some of the impressiveness of Vehrs' papers is, in our opinion, sacrificed by his insistence that grave bulbar anaemia can exist without respiratory paralysis and that only parasympathetic elements of the autonomic system are depressed by cisternal medication whereas only sympathetic elements are depressed by lumbar medication.

The lethal dose of novocaine cisternally exhibited has been found by Cotui (36) to be influenced by previous medication. Morphine and sodium amytal seem in his experiments to sensitize the respiratory center or centers to depression. Our studies confirm this observation. He has found scopolamine incapable of potentiating novocaine depression.

The availability of the canine cistern for repeated taps has found little if any space in the literature. The two factors militating against repeated puncture are danger of infection and anatomical changes consequent to trauma. With the dog the danger of infection is remote. In our experiments we have never observed the signs of meningitis. Frazier and Peet (17) using the drastic procedure of implanting aleurone granules in the Sylvian aqueduct also reported the resistance of the dog to meningitis. We have at times aspirated sticky fluid from the cistern but not from dogs manifesting meningitic or meningismic signs. Our results are not supported

by bacteriological studies because the behaviour of the surviving animals was so manifestly non-meningitic. It must be remembered that no attempt was made to produce sterile taps.

Plaut (37) described the difficulty of repeated punctures in rabbits even with sterile technique. With dogs we have experienced the same difficulty but apparently in lesser degree. The canine cistern is easily accessible but is not large and it does become obliterated after bungling punctures. Autopsy findings conduce to the belief that obliteration is the result of exuberant inflammatory changes in the arachnoid or from hemmorhage in the tela. Sometimes true adhesion of pia to the arachnodural complex was observed. In such cases blunt dissection was necessary to separate the meninges from the nervous tissue.

5. The Technique of Cistern Puncture in the Dog

Greatest success in tapping the canine cistern was attained in our experiments with the animal in the prone position. While in this position the head was sharply brought at right angles to the spinal axis by flexing the neck as far as was consistent with the maintenance of free access of air through the tracheal tube which had been previously inserted.

Ordinary hypodermic needles (gauge #20 or #22) were found most serviceable. Blunt bevelled needles were not

found at all superior to the ordinary needle in expediting experimental procedure and they are probably inferior because they invite trauma.

The needle was introduced while affixed to the syringe. Even with the affixed needle the feeling of puncturing parchment was observed as the dura was transfixed. Since the cistern is surprisingly superficial it was never necessary to penetrate very deep. We have never found it necessary to puncture deeper than 2 cm.

The landmark to guide penetration into the cistern is the cephalic prominence of the spinous process of the axis. The process is easily demonstrated in all except very fleshy dogs. If the finger of the operator be moved forward from this landmark it will experience the firm resistance of the bony dorsal arch of the atlas on which the process rides. Suddenly the finger meets less firm resistance as it comes in contact with the caudal portion of the atlanto-occipital membrane. This place is the proper one for entrance into the cistern.

The needle was carefully inserted at right angles to the spinal axis and in the mid-line while negative pressure was applied to the plunger. Almost invariably fluid was withdrawn to the amount of 4 or 5 c.c. It was just as easily re-injected. We consider the statement of Bower and his associates (25) that under ether the fluid spurts forth to be an over-statement for emphasis.

The pulse rhythm can be readily detected in the

welling fluid. It is, we believe, a certain criterion of entrance into the cistern.

The accompanying photographs, Fig.1(a dorsal view) and Fig. 1a (lateral view) show the relations of the structures proximal to the cistern. Particular attention is called to the caudal extension of the occipital condyle. This structure extends so far back that with the neck unflexed cistern tap is almost impossible. Under the most favorable conditions a rhomboidal area about 1 cm. by 1 cm. is exposed. In this area, the needle will encounter only the atlanto-occipital membrane and no osseous structures. This area constitutes, in the dog, practically all of the membrane which is not very closely applied to the occipital condyle.

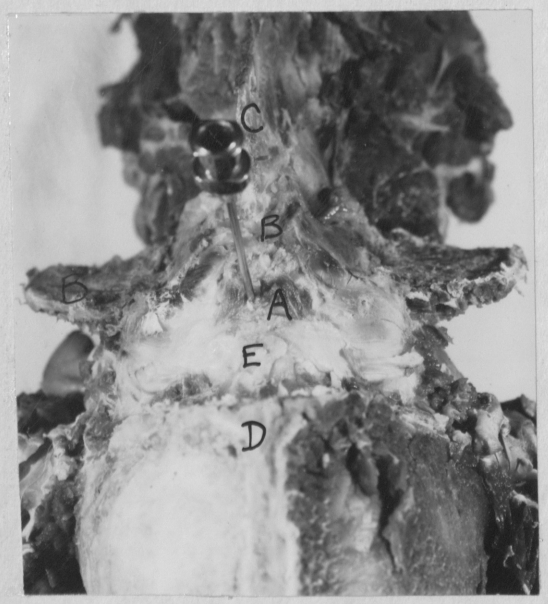


Fig.1

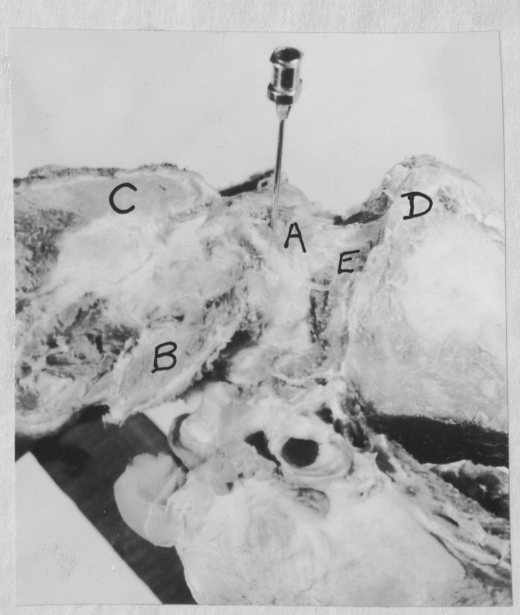


Fig.1a

Legend for both photographs: A. Site of puncture of atlanto-occipital membrane; B. Atlas; C. Axis; D. Occiput; E. Occipital condyle

IV. DRUG ANTAGONISM AND SYNERGISM IN THE BARBITURATE GROUP

1. Discussion of Literature on the Barbiturates

It is assumed that what is true for other barbiturates is also true for sodium amytal , the barbiturate used in these studies, in greater or lesser degree. This assumption is pertinent to observations on antagonism and likewise to observations on site of localization, tolerance, and cumulative action. The latter observations are decidely germane to the problem of antagonism because the choice of proper antagonists contemplates all these phenomena.

Apparently the incidence of accidental and suicidal crises from barbiturate administration involves vernnal and luminal more seriously than it does sodium amytal. The comparative youth of sodium amytal is probably responsible for this fact. However, sodium amytal epitomizes the pharmacodynamics of the barbiturates and studies directed at antagonism to its action confer any practical utility which they may possess upon the whole problem of barbiturate action, whether the action be designed or studiously avoided.

Bastedo (38) summarizing without citation, states that from large doses of the barbiturates the respiratory and cardiac vagus centers are depressed. The respiratory phase of the action is made apparent by the ease with which animals can be killed from respiratory failure by

too rapid administration of intravenous sodium amytal. Bastedo's statements do not apply to the subarachnoid administration of the barbiturates but rather to other modes of administration. There is little if any record of the effects of barbiturates administrated in the subarachnoid in the literature to date.

To combat severe barbiturate depression Bastedo recommends among other treatments the use of strychnine sulphate--3 mg. and caffeine sodium benzoate--0.5 g.; and ephedrine sulphate 50 mg. Later we shall endeavor to show that the recommendation of ephedrine is probably more valid than that of the other drugs. Certainly the actions of strychnine and caffeine are exerted in locales remote from those most profoundly affected by the barbiturates. Furthermore, there has been adduced by Schoen (39), in studies of the labyrinthine reflexes, evidence that caffeine may actually further depress centers already experiencing barbiturate depression.

With our knowledge of the proper tactics for antagonizing the barbiturates in its present fragmentary state it is essential that we attempt to know at least the site of their action. Keeser (40) reported the constant finding of barbiturates in the diencephalon. He found only small amounts of luminal; dial, and veronal and slightly larger amounts of somnifen, noctal and pernocton in the cord. He also demonstrated the latter drug

in the medulla. Quite significantly, he found that somnifen, noctal and pernocton depress blood pressure rather than respiration. However, he found that in combination with morphine and scopolamine they do depress the respiratory centers. His studies lead to the interesting speculation that synergism and potentiation may possibly be dependent upon a directive action upon the drug synergized or potentiated with respect to its site of localization. The Keeser (40) experiments are based upon the interesting technique of volatilizing the drugs from nervous tissue and identifying them by crystalline form. In addition this investigator has prepared iron derivatives of the barbiturates which he identifies by treatment with ferrocyanide. The results obtained in both experimental procedures are concordant.

At present to combat barbiturate depression it is necessary to employ the method of direct physiological stimulation. Furthermore, it is necessary to choose for the purpose drugs which exert their stimulating influence on structures which are most probably depressed by the barbiturate in question. In spite of the evidence presented in the foregoing paragraph the site of localization of the barbiturates is far from categorical solution.

An antagonism dependent upon the production of crucial chemical changes in the depressant would seem to be more serviceable than an antagonism dependent upon the stimulation of depressed protoplasmic structures. Another

mode of antagonism would possibly find its expression by the production of physico-chemical changes in protoplasm which would preclude the phenomenon of depression.

That the site of action of the barbiturates can be established beyond peradventure of a doubt grows out of the fact that these drugs are administered in doses which are easily amenable to chemical identification. Although the possibilities with the stimulant drugs are far less impressive from the standpoint of chemical identification, their peculiar physiological properties serve very nicely to identify the site of their localization. Picrotoxin excellently exemplifies the unsuitability of stimulant drugs for chemical identification. It is active in infinitesimal doses and is chemically a neutral principle.

Attempts to produce colored barbiturates or derivatives which can be transformed into dyes in nervous tissue are under way. Rising, Shroyer, and Stieglitz (41) recently synthesized barbiturate derivatives possessing no hypnotic properties. Leulier and Postic (42) synthesized non-hypnotic nitro and amino derivatives of luminal and rutonal, derivatives which they had hoped to convert into dyes in the nervous tissue of narcotized animals.

Since the introduction of sodium amytal as an intravenous anaesthetic by Page (43) much concern has been felt because of the prolonged after-sleep produced. Attempts

have been made to circumvent this difficulty by the synthesis of barbiturates whose duration of action is brief. Both detoxication and excretion seem to constitute the key to the problem but the fact of similarity of fundamental action has remained an obstacle to success.

Johnson and others (44) reported in 1930 that dextrose shortens the recovery time in barbiturate narcosis at least one-half. Their observation is in agreement with that of Gower and Tatum (45) who found that tolerance to the action of barbiturates is proportional to the rate of excretion. Apparently the tolerance is related, as Marx (46) reported, to the fact that barbiturates inhibit diuresis. Eddy (47) found that the cumulative effects of the barbiturates are associated with a lag in excretion. Gower and Van de Erne (48) found that it is important in barbital poisoning that the diuresis invoked be limited by thoughtful concern for the possibility of over-taxing cardiac and renal function. They used intravenous glucose and insisted that the preliminary use of picrotoxin does not preclude the necessity of a subsequent diuresis.

In Munch's monograph, " Bioassays " (49) fifteen medullary stimulants are listed. Such stimulants while they are not asserted to be stimulant for areas presumably depressed by the barbiturates are stimulant for areas not far removed from the barbiturate-fixing areas. Only one

of these stimulants is at all common and not one is official. The fairly common member of this group, picrotoxin, was successfully used by Koppen (50) to reverse the action of chloral in rabbits. This same stimulant was successfully employed by Fitch, Maloney and Tatum (51) to gain survival in barbiturate poisoning in rabbits. They found ephedrine, coramine, strychnine, brucine, cocaine physostigmine, calcium gluconate and insulin ineffective.

Caffeine was not used in our studies because its action is almost certainly cortical, a fact which was remarked most tellingly in this connection by Isenberger(52). However, Bloch, Camus, and Hertz (53) seem to have mitigated the severity of medullary depressions produced by cisternal stovaine by the cisternal administration of caffeine. This observation is not adduced because stovaine can be satisfactorily placed in the category with barbiturates, a manifest impossibility, but rather because the mode of administration definitely localizes its action at a site deliberately aimed at by our cisternal administration of sodium amytal. Camphor was not used in this study because its action is always uncertain and because its solubility is practically nil. Further reference to the behavior of barbiturates in the face of hypothetical antagonists will be made later when the specific stimulants are discussed.

2. Ephedrine as an Antagonist to the Action of Depressants

The ability of ephedrine to reverse depressed states may be dependent upon circulatory changes, upon stimulation in an intrinsic sense of depressed physiological mechanisms, or upon the production of physico-chemical changes in depressed structures, which changes are in some obscure sense incompatible with the phenomenon of depression. It might even be possible that chemical change between the aqueous solutions of barbiturates and the aqueous solutions of ephedrine is responsible for the effect. Sodium amytal is in aqueous solution quite alkaline because the compound is produced by the reaction of a strong base and a weak acid. Ephedrine sulphate, is on the contrary, produced by the reaction of a strong acid with the weak base ephedrine. Its aqueous solutions are acidic. Measurement of the of the hydrogen ion concentration of mixtures of the aqueous solutions of the two drugs indicate an increase in the acidity of the barbiturate, a fact which is known to conduce to an increase in the toxicity of the depressant for respiration.

Airila (54) and Morita (55) reported the easy awakening of chloralized rabbits by ephedrine. Doyle and Daniels (56) reported the antagonism of ephedrine to the barbiturates and to morphine. The consensus of pharmacological opinion seems to be that the circulatory improvement is primarily responsible for the abbreviation of narcosis by ephedrine. However, it is difficult to see how the

improvement of an already adequate circulation, such as obtains in narcosis when respiration is adequate, can account for the rapid action of ephedrine manifested after its cisternal exhibition. An improvement in circulation conduces to the more rapid elimination of the depressant by increased excretion and detoxication but it can hardly conduce to immediate crucial modification of the irritability of an already adequately irritable center. In fact, as has been pointed out, the most immediate effect of an improvement in circulation might possibly be reflex inhibition of respiration mediated by the channels subserved by the carotid sinus. It is almost a truism that the detoxication and excretion of depressants is as dependent upon the equilibrium between fixed depressant in nervous tissue and dissolved depressant in circulating blood as it is upon the minute-volume of circulating blood. If a drug be stable and if it be avidly fixed by protoplasm its elimination will be slow regardless of the condition of the circulation.

In contradistinction to those changes which must of necessity be slow, the rapid return of the conjunctival reflex abolished by cisternal sodium amytal after cisternal ephedrine repeatedly asserted itself in these studies. Often its return was noted within five minutes. It is difficult to explain how the impact of an improved circulation upon the depressed centers and nerves mediating

this reflex can be responsible for the stimulation of these structures. If there were the possibility of asphyxia, and there never was, the matter could be readily interpreted in terms of the more rapid access of oxygen to the centers. However, the oxygen transport mechanism functions at splendid efficiency under the hegemony of normal tension in alveolar air and of the acid-base relations of hemoglobin combined with the definitely limited stoichiometrical possibilities of hemoglobin as a reducing agent.

Ockerblad and Dillon (57) advocated the use of ephedrine prophylactically in spinal anaesthesia. Something of the same sort is advocated by most anaesthetists. In the light of our experiments the suggestion of Ockerblad and Dillon is enthusiastically endorsed. Jonnesco (24) advocated the use of strychnine for the same purpose but on much less convincing pharmacodynamic grounds. Probably the former were more interested in avoiding the hypothetical consequences of the pooling of splanchnic blood than they were in any true respiratory analepsis by ephedrine. Since the publication of their paper very convincing evidence minimizing the dangers of vasoconstrictor paralysis in spinal anaesthesia has been presented by Ferguson and North(26) and by Seevers and Waters(27). The very pertinent remark that the so-called "bloodless Caesarean sections" coupled with solicitude for the danger from splanchnic paralysis constitutes paradoxical thinking is vouchsafed

by the latter investigators. In addition to their very convincing explanation of the untoward events of spinal anaesthesia in terms of respiratory embarrassment Seevers and Waters showed experimentally that ephedrine prophylactically and not remedially is good therapy.

The writer of this paper believes that ephedrine should be credited with intrinsic analeptic properties. Chen(58) asserts that it is stimulant to the cardio-vascular mechanism both in a central and a peripheral sense. He also asserts that it is the best respiratory analeptic at present available combining, he says, the properties of caffeine and of epinephrin. In these studies a deliberate attempt has been made to disentangle the central analeptic effects of ephedrine from the more apparent peripheral effects and it is believed that in some small measure the attempt has been successful.

The observation that ephedrine increases blood sugar, lactic acid and oxygen consumption was presented by Calton (59) in 1932. Since lactic acid constitutes, according to the Gesell interpretation, one of the proper stimulants for respiration it is not at all unlikely that ephedrine serves to stimulate a depressed center by the production, in excess, of this catabolite in the narcotized protoplasm of the center.

The ability of ephedrine to interrupt avertin narcosis has been attested by Raginsky and Bourne (60). They

achieved their results with dogs and with man. On the other hand Moritsch (61) reported the synergism between ephetonin and chloretone. Ephetonin is a synthetic inactive (optically) isomer of ephedrine which agrees but in lesser degree pharmacodynamically with ephedrine. Incidentally, Collins(62) advocated the use of ephedrine for the treatment of narcolepsy in man.

Although the observations of Maloney, Fitch and Tatum (51) present a very discouraging picture of the analeptic potency of ephedrine in barbiturate poisoning, our experiments have found it so effective that it has been chosen as a criterion of analeptic potency with which to compare the potency of other drugs.

That it is improper to treat the matter of analepsis as a categorical matter is attested by the observations of Tartler (63) who found that the response of rabbits to the synthetic analeptics, coramine and cardiazole after their narcosis by medinal depended upon the dose of the analeptic. This worker found actual synergism between depressant and analeptic when the dose of the latter was large.

V. PRELIMINARY EXPERIMENTS

1. Ethylene Diamine as an Antagonist to Depressed States

The choice of ethylene diamine to reverse the depressed white mouse after ether inhalation is entirely without precedent. However, under the stimulus of the Bancroft hypothesis that peptization of the colloids of the brain tends to reverse anaesthesia the drug was so tested. Merck's Index (64) points out the value of ethylene diamine in producing emulsification of proteinaceous systems. The compound is known to cause solution of fibrin and albumin. Ethanolamine and triethanolamine possess similar properties.

The pharmacology of ethylene diamine was studied by Barbour and Hjort (65) who found it a true depressor base agreeing pharmacodynamically with the other depressor amines. Since its action is not asserted in pithed animals it is probably central.

After preliminary subcutaneous medication of white mice with ethylene diamine in doses of 10 mg. in 10% aqueous solution the animals were anaesthetized with ether or with chloroform. After the onset of anaesthesia the animals were removed from the jar in which they were subjected to the vapors of the anaesthetics and permitted to recover. The results were entirely equivocal and could in no sense be construed to show any antagonism to ether or chloroform by the amine.

In the strengths used ethylene diamine produced in the surviving mice severe necrosis at the site of injection. There is a belief current among the industrial users of ethylene diamine that its contact in the smallest amounts produces a severe eczematoid rash. Hahn and Taeger(66) reported that euphyllin, which is technically theophyllin-ethylene diamine, produced certain inflammatory changes. We did not subject the drug to experimental test in connection with its irritant properties for human tissue. That ethylene diamine is immediately irritating was evidenced by the quick motor and respiratory response of mice to its subcutaneous injection. The observation was controlled by merely pricking the animals with blank hypodermics. Marked blanching of the feet was occasionally observed in the course of experiments involving about twenty-five mice.

2. The Antagonism of Synthetic and Other Analeptics to Sodium Amytal in Depressed States of Consciousness

Group A. This comprises a series of experiments upon the same animal, a dog, # 10, a white male terrier of 10.5 kg. body weight. The animal was a very tractable one in which true anaesthesia could be easily invoked by sodium amytal intravenously without preliminary morphine.

The sense of this short group of experiments is that coramine in doses of 50-60 mg. per kg. can momentarily break through the anaesthesia produced by sodium amytal.

Strangely enough, this power to cut through sodium amytal anaesthesia with coramine apparently became less in the course of the experiments.

With doses as high as 120 mg. per kg. of coramine spastic diaphragmatic seizures and sneezing occurred. We have observed this phenomenon with cardiazole also. Even with doses in this range coramine did not elicit convulsions in the presence of sodium amytal. This finding is as true for intramuscular injection as it is for subcutaneous.

The data are sufficiently extensive to warrant the assertion that in the amytalized dog coramine increases the pulse frequency often as much as 42 beats per minute. The blood pressure judged by the crude criterion of femoral palpation was apparently little changed.

In doses from 40-120 mg. per kg. of coramine the respiration of the amytalized dog was modified in a variable sense. Both increases and decreases in frequency were observed. Depth was apparently increased but only minute-volume studies produce data justifying categorical statement.

Group B. In this group are contained several experiments seeking the crucial expression of analeptic properties by the agents used. As analeptics, sodium sulphocyanide, cardiazole, and magnesium thiosulphate were empirically selected. In comparison none of these is very

effective, with coramine as a standard.

Doses of sodium thiocyanate (sodium sulphocyanide) up to 350 mg. per kg. were tolerated by the animals (dogs) after sodium amytal anaesthesia. Sometimes the depression was apparently deepened by the thiocyanate and followed by severe post-experimental diarrhea. As an analeptic for barbiturate depression this drug is probably useless according to our results. The pulse frequency is probably decreased up to 20 beats per minute, after the drug.

The one experiment using picrotoxin was projected to gain a rough comparison of its well authenticated potency with that of coramine and cardiazole. In this case picrotoxin, a powerful medullary stimulant, broke through the narcosis of sodium amytal but in so doing produced severe medullary convulsions. Although the seizures could be controlled by additional sodium amytal intra-peritoneally, the animal succumbed. The explanation lies probably in the fact that after the picrotoxin effects have worn off there remains still an enormous quantity of barbiturate to be disposed of. No doubt there is also a species of depression predicated upon the overstimulation. Such profound depressions have in our experience led invariably to respiratory embarrassment culminating in death.

Condensed Protocols of Preliminary Experiments Involving Dog # 10 Male white 10.5 kg.

Experiment 15 June 18 1932

Preliminary anaesthesia 11:04 A.M. morphine 4 mg. per kg. Sodium amytal, 30 mg. per kg. (vein)

Metrazole 150 mg. 12:04 P.M. (subcut.)

Sneezes violently 1:04 P.M.

Conscious 6:00 P.M.

Experiment 16 June 22 1932

Sodium amytal	30 mg. per kg.	9:42 A.M.	(vein)
Coramine	250 mg.	9:52 A.M.	(muscle)
Coramine	250 mg.	9:55 A.M.	(muscle)
NaSCN	1000 mg.	10:11 A.M.	(vein)
Conscious		10:44 A.M.	
Walks		11:15 A.M.	
Became lethargic		11:47 A.M.	
Depression very deep		1:00 P.M.	
Wakeful		5:30 P.M.	

Experiment 17 June 24 1932

Sodium amytal	30 mg. per kg.	11:05 A.M.	(vein)
Coramine	500 mg. per kg.	11:18 A.M.	(muscle)
Coramine	500 mg. per kg.	11:42 A.M.	(muscle)
Walked		1:05 P.M.	
Lapsed into deep lethargy		3:00 P.M.	
Not wakened by rough treatment		6:00 P.M.	

Experiment 19 July 2 1932

Sodium amytal	30 mg. per kg. (vein)	11:13 A.M.
Coramine	500 mg. per kg. (vein)	11:43 A.M.
Coramine	500 mg. per kg. (vein)	12:00 A.M.
Coramine	250 mg. per kg. (vein)	12:50 P.M.
Still asleep		5:13 P.M.

Experiment 20 July 7 1932 CONTROL

Sodium amytal	30 mg./kg. (vein)	10:25 A.M.
Stands on feet		1:30 P.M.

Experiment 23 July 14 1932

Sodium amytal	30 mg. per kg. (vein)	10:55 A.M.
Coramine	500 mg. (muscle)	11:44 A.M.
Coramine	500 mg. (muscle)	11:48 A.M.
Violent sneezing		11:50 A.M.
Spastic diaphragm		11:51 A.M.
Very drowsy		5:45 P.M.

****

Miscellaneous Preliminary Experiments

Experiment # 5 Dog # 1 Female mongrel 10 kg.
March 25 1932

Morphine	4 mg. per kg. (subcut.)	4:00 P.M.
Sodium amytal	15 mg. per kg. (vein)	4:06 P.M.
Sodium amytal	5 mg. per kg. (vein)	4:45 P.M.
Narcotized		5:00 P.M.
NaSCN	3500 mg. (vein)	5:42 P.M.
Forelimb rigidity		5:52 P.M.
Cannot arouse		6:10 P.M.

March 26-- The animal is still unconscious. There

is great irritability almost reaching the convulsive level. 10:00 A.M.

Severe diarrhea bloody stools 3:00 P.M.

Can stand ; coarse tremors 10:00 P.M.

Distressing bloody diarrhea 10:00 P.M.

Recovery in three days

Experiment # 6 April 1 1932 Dog # 2 Female 16 kg.

Sodium amytal	30 mg. per kg. (vein)	10:28 A.M.
Sodium amytal	6 mg. per kg. (vein)	11:09 A.M.
Sodium amytal	4 mg. per kg. (vein)	11:30 A.M.
Sodium amytal	6 mg. per kg. (vein)	11:40 A.M.
Can be aroused		4:20 P.M.
Up and around		8:30 P.M.

Experiment # 7 April 2 1932 Dog # 2 Female 16 kg.

NaSCN	67 mg. per kg.(vein)	4:15 P.M.
Sodium amytal	46 mg. per kg.(vein)	5:20 P.M.
NaSCN	30 mg. per kg.(vein)	5:50 P.M.
NaSCN	3 mg. per kg.(vein)	6:50 P.M.
Return of righting reflex		8:00 P.M.

The degree of anaesthesia less than in the control

Experiment # 9 April 8 1932 Dog #4 Female 11.0 kg.

Sodium amytal	30 mg. per kg.(vein)	3:42 P.M.
NaSCN	90 mg. per kg.(vein)	3:44 P.M.
NaSCN	90 mg. per kg.(vein)	4:00 P.M.
Cannot be aroused		4:30 P.M.

NaSCN	45 mg. per kg.(vein)	4:53 P.M.
NaSCN	45 mg. per kg.(vein)	5:15 P.M.
Still cannot be aroused		10:00 P.M.

Experiment # 11 April 30 1932 Dog #6 Male 8 kg.

Morphine (subcut.)	4 mg. per kg.	11:00 A.M.
Sodium amytal (vein)	30 mg. per kg.	11:10 A.M.
Sodium amytal (vein)	5 mg. per kg.	11:25 A.M.
Sodium amytal (vein)	5 mg. per kg.	11:50 A.M.
Magnesium thiosulphate	6 mg. per kg. (vein)	1:37 P.M.
Magnesium thiosulphate	12 mg. per kg. (vein)	2:00 P.M.
NaSCN (vein)	30 mg. per kg.	2:17 P.M.
Can be aroused		2:30 P.M.

Experiment # 13 June 14 1932 Dog #8 Female 7 kg.

Morphine (subcut.)	4 mg. per kg.	10:30 A.M.
Sodium amytal (vein)	30 mg. per kg.	10:45 A.M.
Picrotoxin (vein)	5 mg. per kg.	11:25 A.M.
Attempts to raise head; strong forelimb rigidity; whines		11:46 A.M.
NaSCN (vein)	30 mg. per kg.	11:50 A.M.
Fully awake; development of spastic seizure		12:00 M.
Convulsion		12:10 P.M.
Sodium amytal(muscle) also ether; convulsion controlled	15 mg. per kg.	12:15 P.M.
Sodium amytal (muscle)	3 mg. per kg.	12:45 P.M.
Convulsion		1:20 P.M.
Sodium amytal(muscle)	3 mg. per kg.	1:30 P.M.
Death of animal during night		

Experiment #14 June 17 1932 Dog # 9 Male 7 kg.

Morphine	2 mg. per kg.	(subcut)	10:15 A.M.
Sodium amytal	30 mg. per kg.	(vein)	10:35 A.M.
Cardiazole	7 mg. per kg.	(vein)	11:24 A.M.
NaSCN	14 mg. per kg.	(vein)	12:15 P.M.
Animal is restless			12:20 P.M.
Animal rights self			12:25 P.M.

VI. EXPERIMENTS TO TEST AN ANTAGONISM OF EPHEDRINE TO SODIUM AMYTAL AFTER THE CISTERNAL EXHIBITION OF THE LATTER

1. Rationale

Because the experimental procedure in this group of experiments constitutes the pattern for all experiments of similar kind in these studies it is at the risk of duplication, minutely described. Since cistern puncture in the unaesthetized animal is nearly impossible, preliminary anaesthesia was in all cases invoked. With ether, results were produced in the presence of a minimum of anaesthetic depression.

2. Results obtained with morphine-sodium amytal anaesthesia

Preliminary anaesthesia was produced by the subcutaneous injection of morphine sulphate, 4 mg. per kg. and sodium amytal intravenously, 30 mg. per kg. The latter was administered only after the development of morphine action as evidenced by nausea and vomiting, responses which develop within from 8 to 13 minutes after the administration of morphine. Sodium amytal was always given in 5% aqueous solution and very slowly. Morphine was administered as the sulphate in aqueous solution containing 4 mg. per c.c. Two lots of sodium amytal were used. In the experiments before June 17, 1933, the drug was supplied in glass ampoules containing 1 gram of powdered sodium amytal. After that date the bulk drug was used. There is no

reason to believe that the physiological changes produced by the two samples were different. In all cases a very profound anaesthesia was produced, often with abolition of the conjunctival reflex. Recovery from this type of anaesthesia never transpired without interference sooner than in five hours. Eight to ten hours seemed to constitute the mode.

After anaesthesia rubber tubes of caliber slightly smaller than the tracheal diameter were inserted. The type of inflation secured with these tubes must certainly more closely approximate normal breathing than that secured with tightly fitting tubes. With loosely fitting tubes there is less danger of the brutal over-riding of the elastic structures of the lungs by inrushing air than there is with tightly fitting tubes. At all times there was a sense of satisfaction with the adequacy of ventilation, an adequacy certainly not inferior to that achieved with a small Drinker type respirator built expressly for this study and discarded because it interfered with observations.

In one group of experiments in this series, after anaesthesia, sodium amytal was introduced into the cistern after its solution in aspirated subarachnoid fluid. For dissolving the drug 3 c.c. aliquots of fluid were used. To secure proper mixing fluid was injected and withdrawn and re-injected so that at least five complete interchanges

of the contents of the syringe and of the cistern were made. If the drug produced respiratory paralysis the animal was permitted to regain spontaneous breathing. To test the return of spontaneous breathing, artificial respiration was denied the animal every five minutes or thereabouts for intervals of one minute starting with the end of the five minute period. The results obtained serve as controls. In spite of the hazards of repeated puncture and of repeated medication of the same animal it was possible to secure control data in the absolute sense by the use of the same animal both for control and for medication with antagonistic drugs. All the restrictions prescribed in the description of the mode of eliciting spontaneous respiration were scrupulously observed.

Analysis of all experiments using cisternal sodium amytal shows that doses ranging from 2.6 to 8.8 mg. per kg. are adequate to produce respiratory paralyses. A dose of 6.3 mg. per kg. came to be the mode because it is adequate to produce respiratory paralysis and because in the presence of morphine-sodium amytal anaesthesia it is generally consistent with recovery in all except the most inclement weather. Even in rigorously cold weather it was possible to avert disaster by causing the animals to recover from narcotic depression in a warming box.

Young animals were used in all cases except when otherwise indicated. Moist air was supplied the dogs in

only a few experiments and it is possible that the lack of moisture in the air from the respirator may have contributed to some of the fatalities. A more plausible explanation is that death was almost invariably due to the inability of the animal to throw off the hypnotic depression. It must be clearly understood that the cisternal injection of depressants produces physiological changes which can be produced by intravenous exhibition only in much larger doses. The fundamental act in our experimental procedure involves the production of changes which transcend those produced in experiments dealing deliberately with the phenomena of intoxication. We do not presume to interpret the percentage of recoveries although we have recorded them. We are content to study one factor of the complex met in intoxication with depressants, respiratory paralysis.

The depressions following the cisternal exhibition of sodium amytal were produced with doses in the aggregate of anaesthetic sodium amytal and cisternal sodium amytal which do not even distantly approach the lethal dose of the drug when intravenously injected. In the latter case over 50 mg. per kg. approaches the hazardous limit whereas in our experiments the summated doses of cisternal and anaesthetic (intravenous) depressant were clustered about 36 to 37 mg. per kg. In spite of this disparity and assuming that depression was always the cause of death we adduce the fact of three deaths in ten experiments. These transpired

within two days and there was one death within six days.

Autopsy findings disclosed graded pulmonary changes ranging from oedema to frankly purulent pneumonia. The usual dilated right heart was a constant finding. There was little evidence grossly of damage to the central structures in the zone of cistern puncture except one hemorrhage at the base of the cerebellum. This latter finding followed tap by a method which was later superseded by the safer and more feasible method described earlier in this thesis. Those exuberant fibrotic changes which sometimes obliterated the cistern after multiple tap are not interpreted as consequential trauma to the zonal areas.

An occasional opisthotonos was found in the surviving animals. This observation does not apply merely to the material described in this section but to all of the experiments. Likewise the material of the preceding paragraph also so applies. With two exceptions this sign rapidly cleared up. There was also the occasional appearance of ataxic phenomena with some atonia and asthenia approximating in a rough sense the classic "Luciani triad." Strangely the gross cause of these signs eluded observation at autopsy.

The dose of cisternal ephedrine sulphate varied from 1.1 to 3.1 mg. per kg. Since a safe maximum dose was necessary the arbitrary dose of 2.3 mg. per kg. came to

be the mode. With all doses in these limits the blood pressure was greatly increased, sometimes to an alarming degree.

In this series there are eleven experiments in which cisternal ephedrine sulphate was used to combat the depression of cisternal sodium amytal and three deaths. These data should not be construed as indicative of the ability of the medication to avert casualties because they include results obtained with different doses of sodium amytal and of ephedrine sulphate. The proper dose of cisternal ephedrine had not been satisfactorily established before the inception of these studies. Consequently our experiments served the dual purpose of supplying data on the proper dose of the drugs used as well as on antagonism.

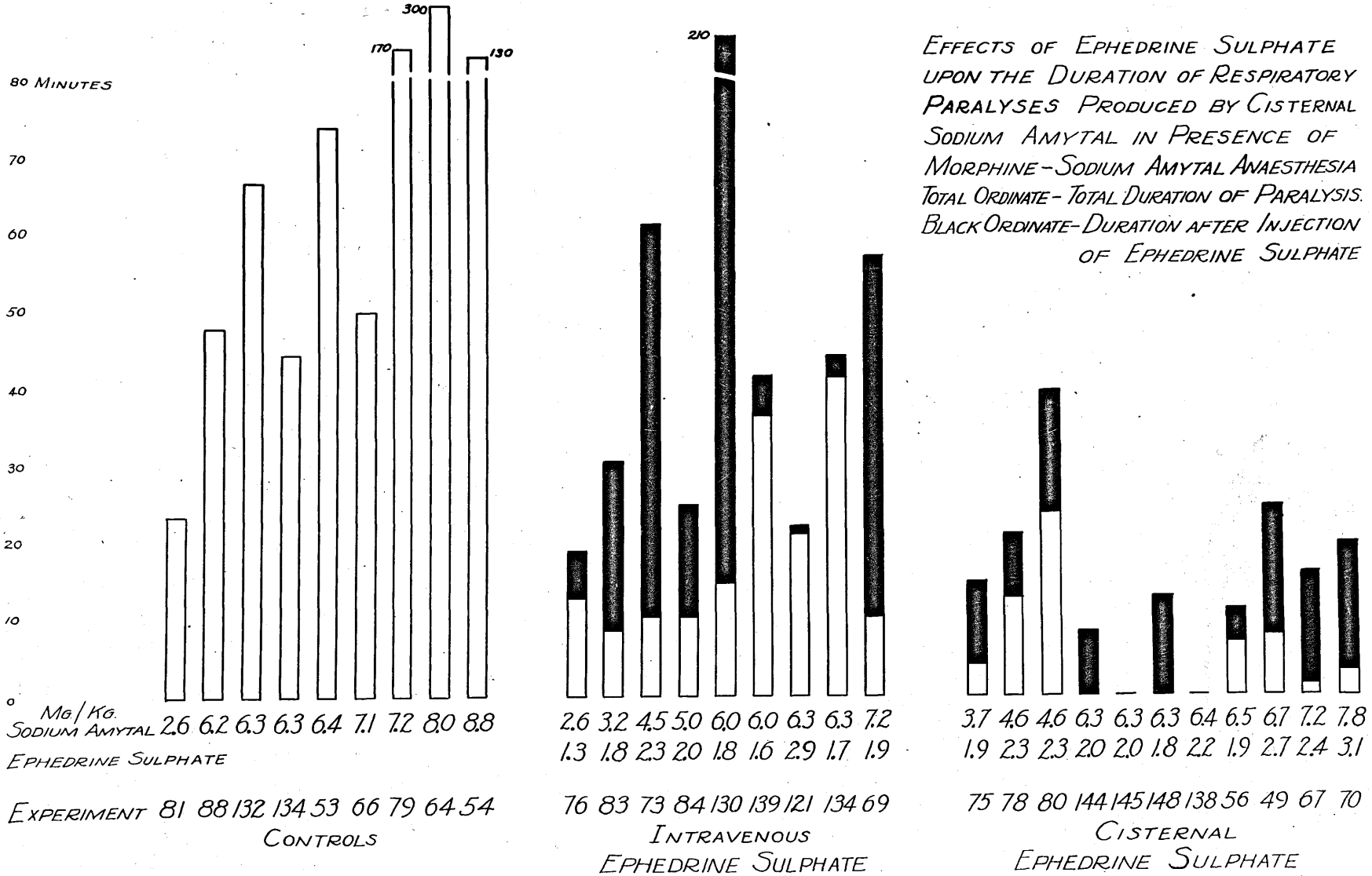
In a group of experiments employing intravenous ephedrine to combat the depression of cisternal sodium amytal there are two fatalities in twelve cases. The dose of cisternal sodium amytal ranged from 2.6 to 7.2 mg. per kg. and that of ephedrine sulphate from 1.3 to 3 mg. per kg.

The circulatory response of the dogs to cisternal sodium amytal in doses adequate to paralyze respiration was a decrease in pulse frequency. To the effects of the depressant the vasomotor system seemed particularly resistant. Elsewhere in this paper it has been stated that after intravenous sodium amytal there is vagus stimulation.

This can hardly have been the case with such massive doses as were used in these experiments. In certain experiments after respiratory paralysis by cisternal sodium amytal, drugs capable of stimulating the central vagus produced the characteristic cardiac inhibitory effects of such stimulation. A better explanation of the decrease in pulse frequency is, we believe, depression of the cardio-accelerator mechanism. The infrequent increases in pulse rate after cisternal sodium amytal were associated with small doses and can be attributed to stimulation of the cardio-accelerator mechanism. This result is not at all surprising in the light of the fact that depressants often manifest stimulant action before the depressant phase.

After the injection of ephedrine sulphate into the cistern no matter what dose is employed there is an increase in pulse frequency and in blood pressure. This effect is observed in spite of the presence of sodium amytal. This is further evidence of the resistance of the sympathetic cardiac centers to depression. Our results in this regard cause us to wonder if the crises in spinal anaesthesia ever involve the vasomotor center until a depressed respiration has produced that change which the center is least capable of withstanding, asphyxia. The acceleration of pulse is much more persistent after cisternal ephedrine than it is after intravenous ephedrine because it escapes the effect of reflex vagus stimulation.

Figure 2.



Effects of Ephedrine Sulphate upon the Duration of Respiratory Paralyses Produced by Cisternal Sodium Amytal in Presence of Morphine-Sodium Amytal Anaesthesia
Total Ordinate - Total Duration of Paralysis.
Black Ordinate - Duration after Injection of Ephedrine Sulphate

An analysis of the data on the return of respiration after its paralysis by cisternal sodium amytal and after the subsequent medication with cisternal or intravenous ephedrine sulphate indicates that this latter drug is capable of greatly abbreviating such paralyses. Cisternal ephedrine was found to be much more effective than intravenous ephedrine.

In a group of experiments, numbers 53,88,132, and 134, 6.3 mg. per kg. of cisternal sodium amytal produced respiratory paralyses lasting respectively 74,46,67, and 45 minutes. In four experiments, numbers 121,130,134, and 137 the same dose of paralyzant produced paralyses lasting 22, 210,45, and 42 minutes respectively after doses by vein of ephedrine sulphate of 2.9,1.8,1.7 and 1.6 mg. per kg. respectively. The time of the injection of the antagonist after the institution of respiratory paralysis was variable because it was not always easy to effect the introduction of the second drug into the cistern. Measuring time after the injection of the analeptic the paralyses lasted 1,195, 3, and 5 minutes respectively. The duration of 210 minutes after induction of paralysis and 195 minutes after intervention is not characteristic. In more than 20 experiments using intervention with cisternal or intravenous ephedrine there was no instance of a paralysis lasting more than 45 minutes.

In the group of experiments employing cisternal

sodium amytal in doses clustered about 6.0 mg. per kg. accompanied or followed by cisternal ephedrine in doses of 2.7, 1.9, 2.2, 2.2, and 1.8 mg. per kg. respectively, respiratory paralyses lasting in the total 25,11,0, 8 and 0 minutes were obtained. Zero duration occurred when the drugs were mixed before administration. The duration after the administration of the analeptic was in the individual cases as follows: 17,4,0,8,and 0 minutes. The experiments producing these results were 49,56,138,144 and 145. In experiment 148 despite the simultaneous administration of 1.8 mg. per kg. of ephedrine sulphate with the sodium amytal, paralysis lasted 13 minutes, a duration which we interpret as quite long under the conditions.

There are several other experiments which do not lend themselves well to expository treatment because of variability of doses. They are represented in Fig. 2 along with the graphic representation of all experiments of this type. The singular fact brought out by the graph is the failure to produce clean-cut abbreviation of paralysis manifested by ephedrine intravenously.

If the effectiveness of ephedrine in reversing depressed states is dependent upon improvement of circulation and upon that alone then it becomes impossible to assign a mechanism of action to the drug when paralysis is not produced by sodium amytal administered simultaneously with ephedrine. Later in this thesis blood pressure tracings

will be shown which conduce to the belief that circulatory failure is implicated in a most negligible degree in depressions produced by the cisternal injection of drugs. Furthermore, the tracings seem to point out very impressively the minor importance of the sympathomimetic factor in ephedrine action when that drug is caused to abbreviate the respiratory paralyses produced by the injection cisternally of depressants.

A measurement of the pH of an aqueous solution of sodium amytal containing 63 mg. of the drug in 6 c.c. of water gave a value of 8.7. Six c.c. was used as the volume for measurement because it was our practice to withdraw 3 c.c. of cisternal fluid and a residual volume of cisternal fluid of 3 c.c. was assumed. 63 mg. was chosen because it represents a standard dose of 6.3 mg. per kg. for an average size dog (10 kg.). The pH was measured by comparison of the color developed in the solution of the drug by the addition of the indicator thymol blue with Clark and Lubs color standards. When ephedrine sulphate, 25 mg., was added to the solution the pH changed to 8.6. These pH readings were checked with others obtained with the quinhydrone electrode. The agreement was good but the quinhydrone readings were discarded because they are subject to error introduced by oxidation-reduction effects. Despite the fact that the alkalinity of the sodium amytal solution was reduced it was always possible in the animal

experiments to obtain clear solutions of sodium amytal before injection. Zerfas, McCallum,and others (67) showed that a shift in the hydrogen ion concentration of solutions of sodium amytal unleashes toxic potentialities which find their expression in respiratory depression. For this eventuality they advocated the use of caffeine and ephedrine. Assuming the accuracy of these observations our results which seem to disclose an antagonism between ephedrine and sodium amytal gain in impressiveness because they were obtained under conditions wherein the hydrogen ion concentration of the solutions of sodium amytal were definitely rendered more acidic, really less alkaline, by the addition of ephedrine. Our colorimetric studies have disclosed the fact of the shift toward the acid range.

The pH of solutions of novocaine should, theoretically, be in the acid range. They were found to be acid when prepared in concentrations identical with those of sodium amytal in the colorimetric study just described, 63 mg. in 6 c.c. of distilled water. The pH of such a solution was found to be 6.2. The addition of ephedrine sulphate to the solution of novocaine should either increase the acidity or should leave it unchanged. When 25 mg. of ephedrine sulphate was added to the novocaine solution the pH was found to be unchanged. The indicator used in this phase of the colorimetric work was chlorphenol red.

If the injection of drugs into the cistern can be construed as constituting topical exhibition then it becomes imperative to define the localization of the drugs after injection. It is believed that the observation of the reflex behaviour of the animal permits the assignment of limits to the diffusion caudad of drugs cisternally injected.

The forelimb extensor jerk elicited by tapping the superficial tendons has been observed to be absent after some cisternal injection of depressants and present after others. Since the reflex is not easy to elicit, the observation has not been limited to jerks obtained by tapping the collateral ulnar ligament close to the prominence of the olecranon but has been extended to include any jerk produced by tapping one of the several sensory ligamental areas of the forelimb. The nerves mediating reflexes of the forelimb are the ulnar, radial, and the median, all of which are part of the brachial plexus, a structure derived from nerves none of which emerge from the cord lower than the first thoracic dermatome. Uniform and constant abolition of the reflexes mentioned would not definitely prescribe a lower limit to the penetration of cisternally injected drugs but the inconstant abolition of the reflexes points out, at least inferentially, to a penetration which seems to find its lower limit in the region of the first thoracic dermatome. Sisson (68) asserts

that the innervation of the dog's forelimb is analagous to the innervation of the arm in man.

When one considers the fact that the intercostal innervation begins also at the level of the first thoracic dermatome, the interpretation in the foregoing paragraph takes on additional meaning for this study. The evidence already adduced would be totally incompetent to define the nature of the respiratory paralyses which we have studied but the additional graphic evidence obtained in our work very definitely indicates that the central factor in these paralyses is fundamental. This statement in no way minimizes the role played by paralysis of the emerging intercostal rootlets.

The use of methylene blue has not been invoked to fix the areas of penetration of drugs in our experiments. Ultimate recovery has been the goal in our work and the utility of methylene blue depends upon sacrificing the animal. Ferguson and North (26) questioned the utility of methylene blue in fixing the limits of penetration of the local anaesthetics after their lumbar subarachnoid administration. Certainly the diffusion of molecular novocaine differs from that of colloidal methylene blue.

The penetration cephalad, of cisternally administered depressants, except as far as the respiratory center is concerned is not so susceptible of analysis as its penetration caudad. The cisternally administered drug can be

transported toward the cortex,in the immediate sense,by two channels; the subarachnoid spaces and the intra-ventricular spaces. In the former the drug is destined to encounter nerve roots while in the latter it is destined to meet nerve centers. In the experiments employing ether anaesthesia results have been obtained under conditions approximating the absence of anaesthesia. In such experiments immediate narcosis was produced, a narcosis which could not have been dependent upon residual ether because the cisternal injection was effected while the animal struggled out of the ether depression. Since it is quite unlikely that the drug could have penetrated as far as the cortical areas the evidence is presumptive that the depressant encountered, in the sub-cortical zones, centers or larger structures concerned in the maintenance of consciousness. At the level of the aqueducto-ventricular juncture Pick (69) has described centers responsible for the phenomena of sleep and consciousness. It so happens that these areas have been thought to be implicated in the lethargic states consequent to epidemic encephalitis because in this disease degenerative changes have often been there described. Not forgetful that access to diencephalic structures may be afforded by channels other than those just described we submit that our results indicate, at least by inference, penetration of cisternally injected depressants at least

as far as the diencephalon and probably through ventricular channels.

Manifestly the phrenic nerves which comprise fibers originating at the second, third, and fourth cervical levels are paralyzed by the injection of depressants into the cistern in adequate doses. The site of penetration in cistern tap is just cephalad to the atlas at a distance of only a few centimeters from the nucleus subserving in the dog this element (the phrenic apparatus) of the respiratory mechanism.

Tilney and Riley (70) describe the conjunctival reflex as involving the trigeminal nerve, the substantia gelatinosa of the pons, the nucleus of the facial nerve, the facial nerve and ultimately the proper effector, the orbicularis palpebrarum. The conjunctival reflex is always abolished by the injection of depressants in the cistern in doses adequate to paralyze respiration. The reflex returns generally a few minutes before the animal can spontaneously breathe and occasionally with spontaneous breathing or a few minutes later. The profound depression of any of the centers or nerves described accounts easily for the abolition of the reflex. However, in the light of our observations it would be improper definitely to state by which depression it is effected.

The pupillary reflex (direct light reflex) involves retinal cells, the optic nerve, the superior colliculus, the oculomotor nucleus, and the motor effectors of the iris.

The pupillary reflex is invariably abolished by cisternal depressants, novocaine and sodium amytal, in doses which paralyze respiration. The pupillary reflex returns much later than the conjunctival reflex, requiring generally a couple of hours.

The blink reflex (emergency light reflex) has in these experiments invariably returned before the direct light reflex. Its recovery parallels that of the conjunctival reflex. After intervention with cisternal ephedrine following cisternal depressants both the conjunctival reflex and the emergency light reflex have been observed to return within one-half minute. Tilney and Riley (70) describe the emergency light reflex as mediated by the retina, the superior colliculus, the facial nucleus, and the facial nerve. The reappearance of the pupillary reflex after the return of the emergency light reflex may be interpreted as predicated upon the sympathomimetic effects of ephedrine upon the radial fibers of the eye.

It must be reiterated that the return of the conjunctival and emergency light reflexes in one-half minute after the cisternal ephedrine in the presence of grave depression constitutes a phenomenon which the intrinsic analepsis of ephedrine alone can explain. The slightest possibility of anoxaemic damage to the centers mediating these reflexes has been studiously avoided. Whereas the routine demonstration of the abbreviation of barbiturate narcosis by intravenous ephedrine can be explained in terms of cir-

Legend to accompany condensed protocols on opposite page

Exp.	Time of administration and dose of morph. 4 mg./kg.	Time of administration and dose of sodium amytal	Time of initial injection
53	4:00 P.M.	4:08 P.M. 30 mg./kg.	4:21 P.M.
54	4:30 P.M.	4:19 P.M. 30 mg./kg.	5:00 P.M.
64	4:20 P.M.	4:30 P.M. 30 mg./kg.	4:40 P.M.
66	8:30 A.M.	8:40 A.M. 25 mg./kg.	9:25 A.M.
79	9:57 A.M.	10:09 A.M. 30 mg./kg.	11:50 A.M.
81	4:30 P.M.	4:45 P.M. 25 mg./kg.	5:17 P.M.
88	8:42 A.M.	8:50 A.M. 25 mg./kg.	9:34 A.M.
132	2:11 P.M.	2:20 P.M. 30 mg./kg.	2:38 P.M.
134	3:04 P.M.	3:13 P.M. 30 mg./kg.	3:45 P.M.
69	4:35 P.M.	4:55 P.M. 25 mg./kg.	5:37 P.M.
73	9:40 A.M.	10:00 A.M. 30 mg./kg.	10:45 A.M.
76	4:20 P.M.	4:30 P.M. 25 mg./kg.	5:21 P.M.
83	2:15 P.M.	2:29 P.M. 30 mg./kg.	3:03 P.M.
84	3:50 P.M.	4:00 P.M. 25 mg./kg.	4:15 P.M.
121	9:05 A.M.	9:16 A.M. 30 mg./kg.	10:37 A.M.
130	12:20 P.M.	12:26 P.M. 30 mg./kg.	12:45 P.M.
134	3:04 P.M.	3:13 P.M. 30 mg./kg.	3:45 P.M.
139	10:06 A.M.	10:22 A.M. 30 mg./kg.	10:55 A.M.
49	12:05 P.M.	12:20 P.M. 35 mg./kg.	1:32 P.M.
56	4:40 P.M.	4:40 P.M. 30 mg./kg.	5:20 P.M.
67	10:30 A.M.	10:40 A.M. 25 mg./kg.	11:10 A.M.
70	4:40 P.M.	4:55 P.M. 25 mg./kg.	5:25 P.M.
75	4:05 P.M.	4:17 P.M. 30 mg./kg.	4:42 P.M.
78	3:40 P.M.	3:50 P.M. 30 mg./kg.	5:52 P.M.
80	5:04 P.M.	5:17 P.M. 30 mg./kg.	6:00 P.M.
138	10:30 A.M.	10:42 A.M. 30 mg./kg.	11:32 A.M.
144	9:00 A.M.	9:15 A.M. 30 mg./kg.	9:26 A.M.
145	9:50 A.M.	10:04 A.M. 30 mg./kg.	11:01 A.M.
148	9:20 A.M.	9:35 A.M. 30 mg./kg.	9:52 A.M.

This legend has been supplied to describe the type of anaesthesia used in the experiments tabulated on the opposite page. Since the limitations of space in the table made it impossible to include information fixing the initial acts of the experiments in the forenoon or afternoon, that information is recorded in the last column.

Table 2.

MORPHINE SODIUM AMYTAL ANAESTHESIA — CISTERNAL SODIUM AMYTAL

	CONTROLS									INTRAVENOUS EPHEDRINE SULPHATE									CISTERNAL EPHEDRINE SULPHATE									
EXPERIMENT	53	54	64	66	79	81	88	132	134	69	73	76	83	84	121	130	134	139	49	56	67	70	75	78	80	138	144	145	148
DATE	10/11/32	10/12/32	11/15/32	11/19/32	12/17/32	12/23/32	1/14/33	6/15/33	6/28/33	11/21/32	12/0/32	12/16/32	12/27/32	12/26/32	5/21/33	6/14/33	6/28/33	7/5/33	10/1/32	10/18/32	11/19/32	11/23/32	12/15/32	12/17/32	12/21/32	7/3/33	7/18/33	7/22/33	7/29/33
DOG NUMBER	30	31	18	9	35	39	41[a]	51	52	35	37	39	40	41	47	50	52	53	28	30	35	36	38	37	33	52	54	55	56
WEIGHT AND SEX	15.5F	8.5F	12.5M	7F	10.4F	19M	12.3F	12.8F	11.4M	10.4F	11M	9M	22M	30M	8.7M	10.9F	11.4M	12.3M	7.5F	15.5F	10.4F	6.4F	13.5F	11M	11F	11.4M	12.3F	14.6M	13.6M
MG/KG PARALYZANT	6.4	8.8	8.0	7.1	7.2	2.6	6.2	6.3	6.3	7.2	4.5	2.6	3.2	5	6.3	6	6.3	6	6.7	6.5	7.2	7.8	3.7	4.6	4.6	6.4	6.3	6.3	6.3
MG/KG ANTAGONIST										1.9	2.3	1.3	1.8	2	2.9	1.8	1.7	1.6	2.7	1.9	2.4	3.1	1.9	2.3	2.3	2.2	2	2	1.8
TIME INJECTION PAR.	4:21	5:00	4:40	9:25	11:50	5:17	9:34	2:38	3:45	5:37	10:45	5:21	3:03	4:15	10:37	12:45	3:45	10:55	1:32	5:00	11:10	5:25	4:42	5:52	6:00	11:32	2:55	11:30	9:52
TIME INJECTION ANT.										5:47	10:55	5:34	3:12	4:25	10:58	1:00	4:27	11:32	1:40	5:07	11:12	5:29	4:46	6:00	6:24	11:32	2:55	11:30	9:52
TIME RETURN RESP.	5:35	7:10	9:40	10:15	2:40	5:40	10:22	3:45	4:30	6:35	11:47	5:40	3:34	4:40	10:59	4:15	4:30	11:37	1:57	5:11	11:26	5:45	4:57	6:13	6:40	11:32	3:03	11:30	10:05
DURATION RESP. PARALYSIS	74	130	300	50	170	23	48	67	45	58	62	19	31	25	22	210	45	42	25	11	16	20	15	21	40	0	8	0	13
DURATION AFTER ANT.										48	52	6	22	15	1	195	3	5	17	4	14	16	11	8	16	0	8	0	13
PUPILLARY RESPONSE TO PARALYSIS	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A		A	A	A	A	A	A		N.A.	A	A
CONJUNC. REFLEX TO PAR.	A	A	A	A	A	A	A.	A	A	A	A	A	A	A	A	A	A	A		A	A	A	A	A	A		N.A	A	A
FORELIMB REFLEX RESPONSE TO PAR.		N.A.	A	A	N.A	N.A	A	A	N.A	A	A	NA		A		A	NA	A		A	A	A	A	A	A		N.A.	A	A
NORMAL PULSE	160	100	140	172	136	152	152	180	188	140	160	120	156	160		132	156	132		176	160	140	96		148	116	144	144	139
PULSE AFTER PAR.	120	84	136	144	124	128	124	140	140	112	120	136	128	140		100	188	100			140		160		180	110	200	132	212
PULSE AFTER ANT.										68	240	210	200	200		164	160	88	200	200	220	250	252		188	110	200	132	212
TIME RETURN CONJ. REFLEX	5:02	5:45	5:15	10:03	12:24	5:40		3:25	4:30	5:58	11:16	5:37	3:16	4:35			4:30	11:34		5:08	11:23	5:35	4:48	6:03	6:17	NA	NA	10:45	10:10
TIME RETURN PUPILLARY REFLEX									4:35				3:26				4:35						5:01	6:16		NA	NA		
TIME RETURN FORELIMB REFLEX		N.A	5:20		N.A	N.A.			N.A.	6:01	11:36	N.A.	3:25	4:27			NA	11:45					5:03	6:06	6:35	NA	NA	11:21	10:17
TIME RETURN CONSCIOUSNESS	MUCH LATER	AFTER 8:30	GREAT LAPSE					IN NIGHT	IN NIGHT		IN NIGHT	IN NIGHT	IN NIGHT	IN NIGHT	IN NIGHT	IN NIGHT	IN NIGHT	LATE AFTER-NOON					5:20					IN NIGHT	IN NIGHT
NATURE RESTORED RESP.	12 R	16 GOOD	20 VERY SHALL.	GOOD	GOOD	12 R	14	POOR	6 VERY POOR	POOR	POOR	20 GOOD	14 POOR	40 POOR			6 POOR		20 R	16 GOOD	32 GOOD	16 GOOD	12 IRR.	12 R	10 IRR.	20 GOOD	POOR		20 R
DURATION PRORATED	119	93	248	44	150	94	48	67	45																				
FATE OF ANIMAL	RE.	RE.	DEATH	RE.	DEATH	RE	DEATH	DEATH	RE.	RE.	RE.	RE.	RE.	DEATH	RE.	RE.	RE	RE	RE	RE	RE	DEATH	RE	DEATH	RE.	RE.	DEATH	RE.	RE.
NOTATION			PNEU-MONIA											PNEU-MONIA			+ PICRO-TOXIN						WALK 5:32	PNEU-MONIA					

* A - ABOLISHED , NA - NOT ABOLISHED , R - REGULAR , RE - RECOVERED

culatory improvement, the intense analepsis of the depressed reflex mechanisms just described demands the explanation of intrinsic central stimulation, by ephedrine.

3. Results obtained with sodium amytal and ephedrine sulphate cisternally injected in the presence of ether and morphine-ether anaesthesia.

This series of experiments indicates the difficulty with which cisternal sodium amytal produces respiratory paralysis when a pre-existing anaesthetic depression produced by that drug and morphine is wanting.

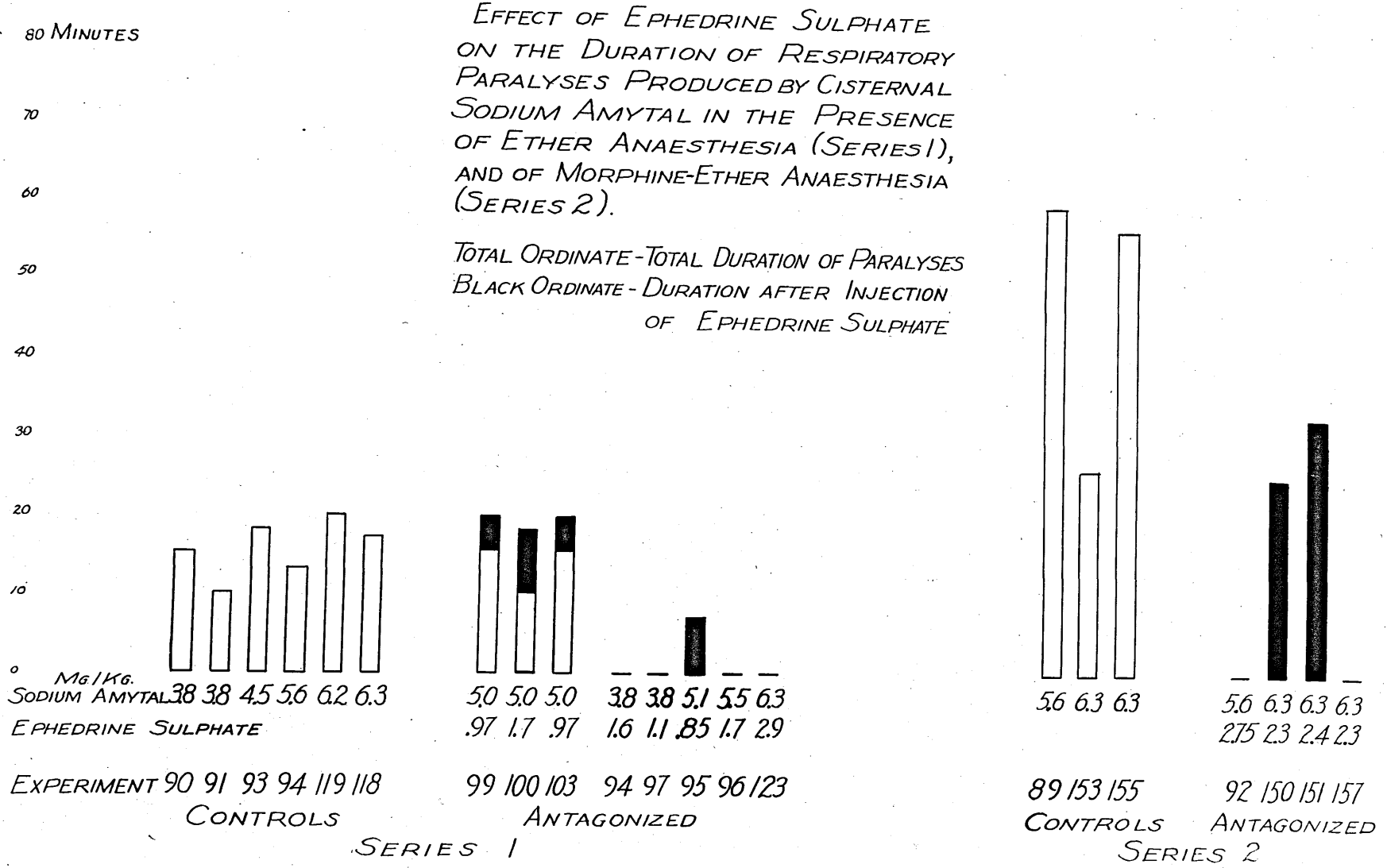
Only two control experiments, numbers 118 and 119, are presented where the dose of cisternal sodium amytal falls in the 6.3 mg. per kg. range. Respiratory paralyses lasting 17 and 20 minutes respectively were obtained. With morphine-sodium amytal anaesthesia no paralyses shorter than 45 minutes were obtained.

When in the presence of ether, ephedrine sulphate was introduced into the cistern in doses of 0.95, 1.7, and 0.95 mg. per kg. respectively after paralyses produced by sodium amytal in doses of 5 mg. per kg. in each case (experiments 99,100, and 103) total durations of 20, 18, and 20 minutes respectively were produced. Recovery after the injection of the analeptic was obtained in 4,9, and 4 minutes respectively. Unfortunately no experiments are presented in the morphine-sodium amytal series using cisternal sodium amytal in the 5 mg. per kg. range. However, with smaller

Figure 3

Effect of Ephedrine Sulphate on the Duration of Respiratory Paralyses Produced by Cisternal Sodium Amytal in the Presence of Ether Anaesthesia (Series 1), and of Morphine-Ether Anaesthesia (Series 2).

Total Ordinate - Total Duration of Paralyses
Black Ordinate - Duration after Injection of Ephedrine Sulphate



doses of sodium amytal, 4.6 mg. per kg., and ephedrine sulphate in larger doses 2.3 mg.per kg. cisternally (experiments 78 and 80) total durations of 21 and 40 minutes respectively were produced,the recovery after the injection of the analeptic requiring 8 and 16 minutes respectively.

In this, the ether series, only one experiment is presented using cisternal sodium amytal in the 6.3 mg. per kg. range. In this experiment, number 123, respiratory paralysis failed to supervene when ephedrine sulphate 2.9 mg. per kg. was given simultaneously with the cisternal paralyzant. In experiment 95 using 5.1 mg. per kg. of sodium amytal simultaneously with 0.85 mg. per kg. of ephedrine sulphate, both cisternally, respiration was paralyzed 7 minutes. In experiment 96 employing 5.5 mg. per kg. sodium amytal and 1.7 mg. per kg. ephedrine sulphate cisternally no paralysis resulted.

In comparison with the results just described the results obtained in the series using morphine-sodium amytal anaesthesia include those obtained in experiments 138,144,145, and 148 in which doses of sodium amytal of 6.4,6.3,6.3, and 6.3 mg. per kg. respectively were administered simultaneously with ephedrine sulphate in doses of 2.2,2,2,and 1.8 mg. per kg. respectively by the cisternal route. Respiratory paralyses of 0,8,0, and 8 minutes respectively were obtained. These durations are striking-

ly short in view of the profundity of the preliminary anaesthesia which in its own right conduced in control experiments to respiratory paralyses lasting at least 45 minutes. The results indicate the analeptic potency of ephedrine in the most difficult circumstances.

When morphine 4 mg. per kg. preceded the ether as in experiments 89,153, and 155,cisternal sodium amytal in doses of 5.6,6.3, and 6.4 mg. per kg. respectively provoked respiratory paralyses of 60,26, and 57 minutes respectively. These durations compare in length with those obtained with morphine-sodium amytal anaesthesia and lead one to suspect that morphine plays an important role in the sensitization of the respiratory center to depression by cisternally administered paralyzants. Experiments 118 and 119 in which ether alone preceded the cisternal sodium amytal in the same dosage range ,yielded respiratory paralyses of 17 and 20 minutes respectively, a fact which strengthens the suspicion just alluded to.

In the morphine-ether anaesthesia series are four experiments, numbers 92,150,151, and 157, in which 5.6,6.3, 6.3, and 6.3 mg. per kg. of sodium amytal respectively were introduced cisternally simultaneously with ephedrine sulphate in doses of 2.7,2.3,2.4 ,and 2.3 mg. per kg. respectively. The durations of paralysis were respectively 0,25,33 and 0 minutes. Only two comparable experiments, numbers 123 and 95 ,are available where ether alone was used. In experiment 123 the duration of paralysis was 0

minutes with 6.3 mg. per kg. of sodium amytal simultaneously injected with ephedrine 2.9 mg. per kg. In the other, number 95, 5.1 mg. per kg. of sodium amytal cisternally injected simultaneously with ephedrine sulphate 0.85 mg. per kg. led to a paralysis of 0 minutes. These data are probably not too equivocal to point to the role of morphine as synergizing and possibly potentiating the respiratory depressant properties of sodium amytal cisternally injected.

Intravenous ephedrine was not used in this series because even in the controls, except in the additional presence of morphine, the duration of respiratory paralysis after cisternal sodium amytal was too short. This fact also gave rise to the necessity of administering the analeptic simultaneously with the depressant.

The pulse after cisternal sodium amytal in the presence of ether is not so pronouncedly decreased in frequency as it is in the presence of morphine-sodium amytal. This fact also obtains in the case of the experiments involving morphine-ether anaesthesia. Occasionally the pulse frequency is increased. The blood pressure as judged by femoral palpation is not much changed. Both observations are in harmony with the results obtained in the acute experiments where tracings were made. The decrease is possibly due to depression of the cardio-accelerator center whereas the increase is possibly due to preferen-

tial depression of the vagus center.

In all the experiments, with the exception of number 91, in this series the conjunctival reflex was abolished. The return was in all cases within 12 to 15 minutes except where preliminary morphine was used. Furthermore, the pupillary reflex was just as constantly abolished and almost as speedily restored.

Unless morphine was present in addition to ether the forelimb extensor reflex persisted after cisternal sodium amytal. This result differs sharply from those obtained in the presence of morphine-sodium amytal.

The cisternal injection of sodium amytal in the presence of ether gave rise to anaesthesia lasting no longer than 30 minutes until the return of the ability to walk . After the injection of cisternal ephedrine the animal recovered even more speedily. It was routine practise to discontinue ether after the injection of the cisternal depressant.

The fatalities in the ether and morphine-ether series were as follows:

Ether anaesthesia--controls-- 1 in six experiments

Ether anaesthesia--sequential ephedrine--
2 in three experiments

Ether anaesthesia--ephedrine simultaneously --
0 in four experiments

Morphine-ether anaesthesia--controls--
1 in three experiments

Morphine-ether anaesthesia--ephedrine simultaneously-
1 in four experiments

Legend to accompany condensed protocols on opposite page

Exp.	Time of administration and dose of atropine	Time of starting ether anaesthesia	Time of initial injection (cisternal)
90	9:06 A.M. 1 mg.	9:15 A.M.	9:45 A.M.
91	3:46 P.M. 1 mg.	4:50 P.M.	5:10 P.M.
93	11:38 A.M. 1 mg.	11:50 A.M.	12:22 P.M.
94	1:54 P.M. 1 mg.	2:10 P.M.	2:48 P.M.
118	4:30 P.M. 1 mg.	4:50 P.M.	5:07 P.M.
119	8:43 A.M. 1 mg.	8:50 A.M.	9:02 A.M.
99	10:00 A.M. 1 mg.	11:25 A.M.	11:52 A.M.
100	8:16 A.M. 1 mg.	8:40 A.M.	9:52 A.M.
103	10:20 A.M. 1 mg.	10:40 A.M.	11:52 A.M.
94a	9:08 A.M. 1 mg.	9:17 A.M.	9:40 A.M.
95	2:23 P.M. 1 mg.	3:00 P.M.	3:35 P.M.
96	5:32 P.M. 1 mg.	5:38 P.M.	6:20 P.M.
97	8:32 A.M. 1 mg.	8:40 A.M.	9:02 A.M.
89	2:35 P.M. 1 mg. (2:35 P.M. morph 4 mg./kg.)	2:45 P.M.	3:10 P.M.
153	2:07 P.M. 1 mg. (2:06 P.M. morph. 4 mg./kg.)	2:20 P.M.	2:39 P.M.
155	no atropine (9:40 A.M. morph. 4 mg./kg.)	9:50 A.M.	10:35 A.M.
92	3:06 P.M. 1 mg. (3:12 P.M. morph. 4 mg./kg.)	3:50 P.M.	4:12 P.M.
150	10:20 A.M. 1 mg. (10:08 A.M. morph. 2 mg./kg.)	10:22 A.M.	10:40 A.M.
151	no atropine (2:40 P.M. morph. 2 mg./kg.)	3:00 P.M.	3:26 P.M.
157	2:26 P.M. 1 mg. (2:20 P.M. morph. 2 mg./kg.)	2:25 P.M.	2:53 P.M.

Table 3.

CISTERNAL SODIUM AMYTAL

	ETHER ANAESTHESIA CONTROLS							CIST. EPH. SUL.				MIXED EPH. SUL.						MORPHINE ETHER ANAESTHESIA. CONTROLS				CIST. EPH. SUL.			
EXPERIMENT	90	91	93	94	118	119		99	100	103		94	95	96	97	123		89	153	155		92	150	151	157
DATE	1/19/33	1/19/33	1/21/33	1/28/33	5/12/33	5/13/33		3/4/33	3/4/33	3/18/33		2/4/33	2/4/33	2/9/33	2/18/33	5/27/33		11/8/33	8/7/33	8/9/33		1/20/33	8/4/33	8/4/33	8/10/33
DOG NUMBER	43	38	43	42	47	48		II 42	III	III		43	44	42	43	47		42	59	58		42	58	55	59
WEIGHT AND SEX	13.2F	13.5F	13.2F	9F	8.7M	16M		9F	20.1	20.1		13.2F	11.9F	9F	13.2	8.7M		9F	13.2F	15.5M		9F	15.5M	14.6M	13.2F
MG/KG PARALYZANT	3.8	3.8	4.5	5.6	6.3	6.2		5	5	5		3.8	5.1	5.5	3.8	6.3		5.6	6.3	6.3		5.6	6.3	6.3	6.3
MG/KG ANTAGONIST								.95	1.7	.95		1.6	.85	1.7	1.1	2.9						2.75	2.3	2.4	2.3
TIME INJECTION PAR.	9:45	5:10	12:22	2:48	5:07	9:02		11:52	9:52	11:52		9:40	3:35	6:20	9:02	9:35		3:10	2:39	2:53		4:12	10:40	3:26	3:30
TIME INJECTION ANT.								12:08	10:02	12:08		9:40	3:35	6:20	9:02	9:35						4:12	10:40	3:26	3:30
TIME RETURN RESP.	10:00	5:20	12:40	3:01	5:24	9:22		12:12	10:10	12:12		9:40	3:42	6:20	9:02	9:35		4:10	3:05	3:50		4:12	11:05	3:59	3:30
DURATION RESP. PARALYSIS	15	10	18	13	17	20		20	18	20		0	7	0	0	0		60	26	57		0	25	33	0
DURATION AFTER ANT.								4	8	4		0	7	0	0	0						0	25	33	0
PUPILLARY RESPONSE TO PARALYSIS	A	N.A.	A	A	A	A		A				A	A	A	A	A		A	A	A		A	A	A	A
CONJUNC. REFLEX TO PAR.	A	N.A.	N.A.	A	A	A		A				A	A	A	A	A		A	A	A		A	A	A	A
FORELIMB REFLEX RESPONSE TO PAR.		N.A	A	NA	A	A		A					A	NA				NA	NA			A	A	NA	A
NORMAL PULSE	200	200	160	160	216	208		176				170	160	140	196	220		210	160	160				164	200
PULSE AFTER PAR.	192	200	160	176	160	208		228				240	180	208	196	240		200	200	160				176	200
PULSE AFTER ANT.												240	180	208	260	240						280	200	176	200
TIME RETURN CONJ. REFLEX	10:00		12:30	3:13	5:22	9:14						9:40	4:10	6:30		9:46		3:40	3:08	3:12		5:00	10:54	3:45	3:40
TIME RETURN PUPILLAR. REFLEX				3:05	5:27	10:30									9:20					3:52			11.25	4:20	
TIME RETURN FORELIMB REFLEX			12:30	NA	5:23	9:50						9:46	4:06	NA				NA	NA	3:15		5:14	11.30		
TIME RETURN CONSCIOUSNESS	10:15	5:50	1:00	4:00	5:27	10:00						10:00		6:40	9:25	10:10		4:50	7:00	6:50		5:40	2:00	5:20	
NATURE RESTORED RESP.	R	16 R	R	20 R	20 R	32 R						52 R	20 R	20 R	40 R	GOOD		16	GOOD	GOOD		28 R	30 R	28 R	PANT
DURATION PRORATED	25	16	28	14	17	20												67	26	57					
FATE OF ANIMAL	RE.	RE.	RE.	RE.	RE	DEAD		DEAD	DEAD	RE.		RE	RE.	RE.	RE.	RE		RE	RE	DEAD		RE	RE	DEAD	RE
NOTATION	WALK 10:30	WALK 6:00	WALK 1:30		WALK 5:30							WALK 10:00			WALK 9:25	WALK 10:20			WALK 9:00				WALK 4:00	WALK 7:00	

* A-ABOLISHED, NA-NOT ABOLISHED, R-REGULAR

VII. PHARMACODYNAMIC REACTIONS OF THE LOCAL ANAESTHETICS IN THE SENSE OF ANTAGONISM AND SYNERGISM

1. Literature

The role of novocaine and of other local anaesthetics in the crises of spinal anaesthesia have already been mentioned. Despite the disconcerting incidence of these mishaps, the mechanisms involved in the crises remain the subject of much controversy. This account will concern itself with the antagonistic and synergistic phenomena relating to these drugs rather than with their involvement in spinal accidents.

Novocaine (procaine hydrochloride) is an official drug of the para amino benzoic acid group; chemically it is para-amino-benzoyl diethylaminoethanol. It differs chiefly from cocaine in properties, in its resistance to boiling, its inability to penetrate mucous surfaces, its failure to produce habituation, and its problematical lower toxicity.

Eggleston and Hatcher (71) believe that novocaine is detoxicated by the liver with more promptness than cocaine. It is well known that it does not lead to cumulative action and that it is possible to introduce prodigious doses in animals if they are administered slowly. The investigators just cited emphasized that its slighter toxicity in comparison with cocaine is only a relative matter dependent upon the mode of exhibition. Both drugs are general protoplasmic poisons by virtue of actions which no

one has as yet had the temerity to describe.

Isenberger (52) observed that, in spite of preliminary barbiturate medication, novocaine intravenously administered to dogs in repeated doses of 200 mg. in 20% solution produces a characteristic drop in blood pressure. Furthermore he found that, after preliminary sodium amytal, novocaine slowly administered in 1% solution or in doses just mentioned failed to produce convulsions. Equally important are his observations that the fall of blood pressure after novocaine closely paralleled and coincided with respiratory depression. If the depression progressed to complete paralysis he found that the only necessary adjunct to circulatory competency was adequate artificial respiration. He pointed out the earlier abolition of thoracic breathing followed by diaphragmatic arrest following the lumbar subarachnoid injection of novocaine. Likewise, he found sodium amytal effective in controlling the convulsive seizures of novocaine after they had developed. His views regarding the untoward results with novocaine in spinal anaesthesia coincide with those of Seevers and Waters (27). They insist upon the respiratory character of the spinal anaesthetic crises, and in so doing are almost certainly correct.

Earlier, Hofvendahl (72) remarked the utility of the barbiturates in combating local anaesthetic poisoning. She successfully used veronal sodium in cocain poisoning. The

utility of phenobarbital in this same regard was also attested by Guttman (73).

Tatum and others (74) believe that the site of the action of novocaine as a convulsant is cerebral. Hence they used narcotics such as the barbiturates and paraldehyde to combat novocaine convulsions. On the contrary Morita (75) found that the tolerance of rabbits to cocaine intoxication was not importantly improved by the extirpation of the hemispheres. Knoefel,Herwick, and Loevenhart (76) found amytal protective against local anaesthetics whereas magnesium is synergistic with these drugs in their depressant phases. Whatever the mechanism of the action , it is almost a truism to state that sodium amytal is the best drug to control the convulsions from drugs so diverse in character as cocaine, picrotoxin, and strychnine.

A curious antagonism between cocaine and bulbocapnine was reported by Buchmann and Richter (77) who reversed bulbocapnine catatonia in monkeys with cocaine. Their results present an interesting possibility for the treatment of narcolepsy.

Neither the hypothetical antagonism between ephedrine and novocaine or between sulphocyanide and novocaine has interested workers to the point of serious attention . In fact the trend of the studies of the antagonism in the first pair has been directed at the effects upon blood pressure. Hamet (78) described an antagonism between ephedrine and novocaine with respect to the action of

the former upon blood pressure.

In this study experimental evidence has gradually accumulated which seems to disclose,at least in isolated cases,an interesting synergism between ephedrine and novocaine against the barbiturates with respect to the effects of the latter on consciousness,in addition to a frank outspoken antagonism between them in the case of the respiratory paralyses produced by novocaine cisternally injected.

2. Pharmacodynamic behaviour of novocaine and of ephedrine when introduced into the great cistern of the dog. Experimental results

The experimental procedure is identical with that used in the series where sodium amytal was injected in the cistern. Only plain ether and morphine-sodium amytal anaesthesia were used. The sutopsy findings described in the sodium amytal series hold true in this series. There is no reasonable chemical excuse for the interaction of novocaine and ephedrine even when injected simultaneously dissolved in the same aliquot of cisternal fluid.

Group A. Results with morphine-sodium amytal anaesthesia.

In this group morphine, 4 mg. per kg., was injected subcutaneously followed by sodium amytal 30 mg. per kg. , intravenously after the development of morphine action.

The fatalities are listed in the following table:

Controls-	survived 5	Dead 1
Intravenous ephedrine-	survived 2	dead 1
Cisternal ephedrine sequentially	survived 6	dead 1
Cisternal ephedrine simultaneously	survived 4	dead 0

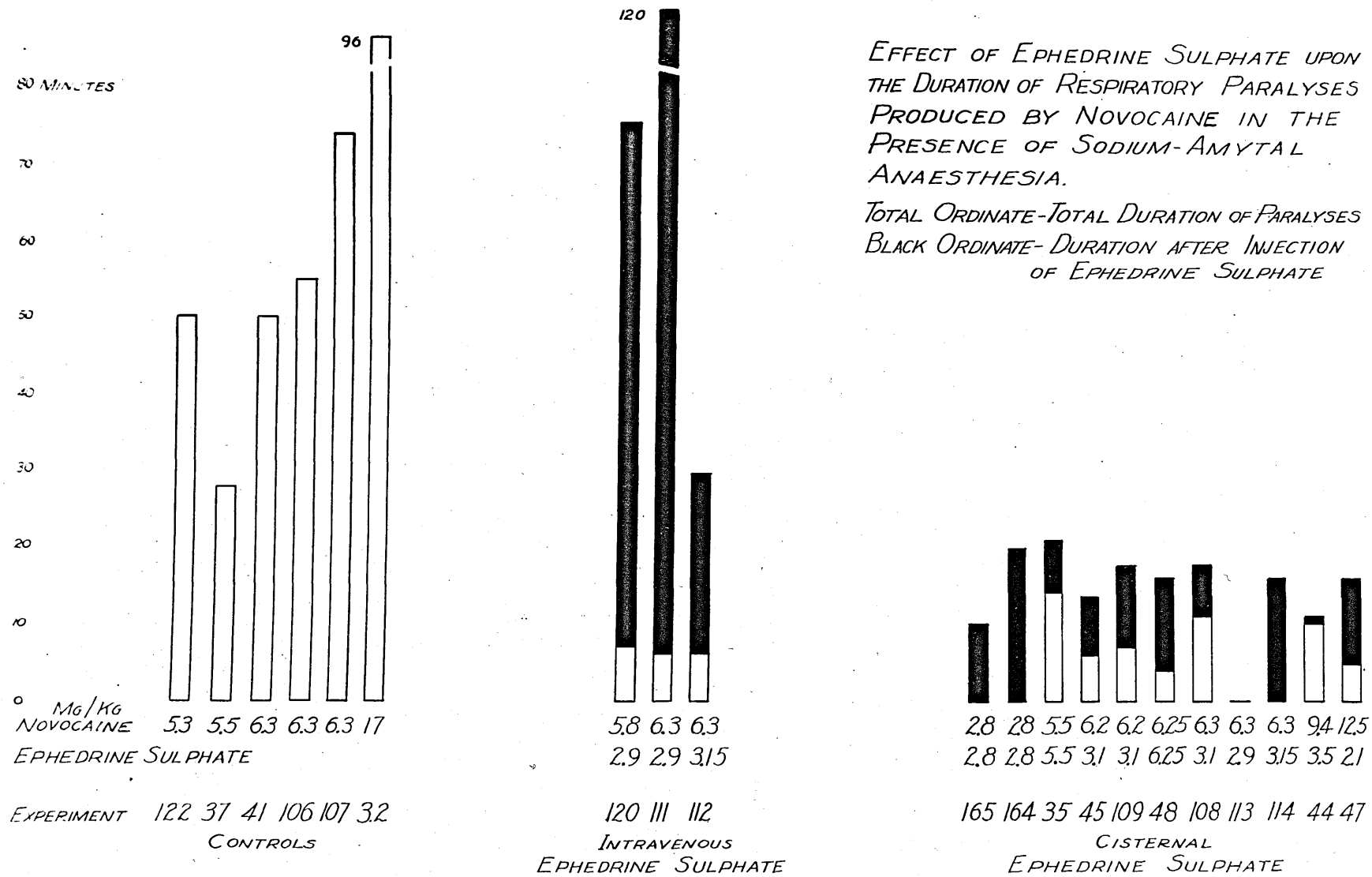
The recoveries in the control group seem more certain than in the series using cisternal sodium amytal. The series is far too short to produce satisfying conclusions but one would like to believe that the results grow out of a slowly developing antagonism between novocaine and sodium amytal which finds its expression in the mitigation of the post experimental depression. The antagonism is well known but its application to the problem of drugs introduced into the subarachnoid by Cotui (36) and ourselves is new. An uncritical interpretation of the antagonism has caused many anaesthetists to avoid preliminary barbiturate medication before lumbar anaesthesia because they feared that the barbiturate would annul the action of the regional anaesthetic. Their concern would better have been directed at the possibility of a strong depressive synergism with the relatively massive doses of the local anaesthetic confined within the narrow limiting confines of the neuraxis. The antagonism is probably limited to the stimulant aspects of the local anaesthetic action and not to its depressant aspects.

The duration of respiratory paralyses in experiments 41, 106, 107 using doses of 6.3, 6.3 and 6.3 mg. per kg. of cisternal novocaine after morphine-sodium amytal anaesthesia was found to be 50, 55, and 74 minutes respectively. In experiments 37 and 122 after 5.5 and 5.3 mg. per kg. of cisternal novocaine durations of 28 and 50 minutes respectively were obtained.

In experiments 111, 112 and 120 using intravenous ephedrine sulphate in doses of 2.9, 3.15,and 2.9 mg. per kg. respectively after paralyses from cisternal novocaine in doses of 6.3, 6.3, and 5.8 mg. per kg. respectively, respiratory paralysis lasted 120, 30, and 76 minutes respectively. The durations after the injection of the analeptic were 114, 24, and 69 minutes respectively. If anything,these durations are more prolonged than those of the controls.

When ephedrine sulphate was administered cisternally its analeptic potency was unmasked. In experiments 45, 48, 108, and 109 cisternal doses of 6.2, 6.3, 6.3, and 6.2 mg. per kg. respectively,antagonized by cisternal doses of ephedrine of 3.1, 6.25, 3.1, and 3.1 mg. per kg. respectively,yielded paralyses of 14, 16, 18, and 18 minutes respectively. Even in experiment 44 in which 9.4 mg. per kg. of cisternal novocaine was antagonized by 3.5 mg. per kg. of cisternal ephedrine sulphate paralysis lasted only 11 minutes.

Figure 4



EFFECT OF EPHEDRINE SULPHATE UPON THE DURATION OF RESPIRATORY PARALYSES PRODUCED BY NOVOCAINE IN THE PRESENCE OF SODIUM-AMYTAL ANAESTHESIA.

TOTAL ORDINATE-TOTAL DURATION OF PARALYSES
BLACK ORDINATE- DURATION AFTER INJECTION OF EPHEDRINE SULPHATE

In three experiments, numbers 113, 114, and 172, cisternal doses of 6.3, 6.3, and 6.3 mg. per kg. were antagonized by the simultaneous cisternal injection of 2.8 mg. of ephedrine sulphate in each case. The durations of paralysis were respectively 0, 16, and 4 minutes. Analepsis by ephedrine is strikingly demonstrated in this series.

Four experiments, numbers 164, 165, 166, and 169 portray the antagonism of ephedrine sulphate in doses of 2.8 mg. per kg. to novocaine in doses of 2.8 mg. per kg., both cisternally. These experiments yielded respiratory paralyses lasting 20, 10, 6, and 4 minutes after the simultaneous administration of the drugs. The results of the experiments are not shown graphically. The choice of dosage of novocaine depended upon the exigencies of experimental procedure quite foreign to the purposes of the other experiments in this group. These experiments were designed to test a hypothetical synergism between ephedrine and novocaine. They will later be analyzed.

The conjunctival reflex is abolished by novocaine in a range of doses from 2.8 mg. per kg. to 17 mg. per kg. Likewise, the pupillary reflex is abolished by the same doses of the same drug. The same is true for the forelimb extensor reflex. The return of all these reflexes was apparently hastened by ephedrine either cisternally or intravenously.

The pulse rate after cisternal novocaine is decreased.

Legend to accompany condensed protocols on opposite page

Exp.	Time of administration and dose of morph. in mg./kg.	Time of administration and dose of sodium amytal in mg./kg.	Time initial injection
32	9:45 A.M. 4	11:00 A.M. 30	10:19 A.M.
37	11:20 A.M. 2	11:25 A.M. 30	12:32 P.M.
41	11:15 A.M. 4	11:25 A.M. 32	2:50 P.M.
106	4:00 P.M. 4	4:16 P.M. 30	5:00 P.M.
107	8:45 A.M. 4	9:00 A.M. 30	9:20 A.M.
122	8:55 A.M. 4	9:05 A.M. 30	9:27 A.M.
111	8:36 A.M. 4	8:45 A.M. 30	8:55 A.M.
112	4:20 P.M. 4	4:30 P.M. 30	4:45 P.M.
120	9:54 A.M. 4	10:07 A.M. 30	10:14 A.M.
35	12:23 P.M. 2	12:26 P.M. 30	1:10 P.M.
44	3:17 P.M. 4	3:30 P.M. 30	4:35 P.M.
45	4:30 P.M. 4	4:39 P.M. 30	4:45 P.M.
47	10:15 A.M. 4	10:27 A.M. 35	10:40 A.M.
48	4:10 P.M. 4	4:20 P.M. 30	4:42 P.M.
108	4:29 P.M. 4	4:40 P.M. 30	5:05 P.M.
109	8:39 A.M. 4	8:47 A.M. 30	9:00 A.M.
113	9:06 A.M. 4	9:18 A.M. 30	9:37 A.M.
114	3:44 P.M. 4	3:56 P.M. 30	4:20 P.M.
164	11:42 A.M. 4	11:54 A.M. 30	12:12 P.M.
165	9:18 A.M. 4	9:42 A.M. 30	10:02 A.M.
172	4:14 P.M. 4	4:23 P.M. 30	4:44 P.M.
169	10:54 A.M. 4	11:08 A.M. 30	11:33 A.M.
173	11:01 A.M. 4	11:13 A.M. 30	12:10 P.M.

Table 4.

Morphine Sodium Amytal Anaesthesia — Cisternal Novocaine

	Controls						Int. Eph. Sul.			Cisternal Eph. Sul							Eph., Nov Mixed				Seq. Extra			
Experiment	32	37	41	106	107	122	111	112	120	35	44	45	47	48	108	109	113	114	164	165	173	169	172	166
Date	7/28/32	8/9/32	8/30/32	4/7/33	4/8/33	5/24/33	4/15/33	4/21/33	5/13/33	8/3/32	9/22/32	9/28/32	9/24/32	9/27/32	4/13/33	4/14/33	4/22/33	4/28/33	5/10/33	5/29/33	9/23/33	9/9/33	9/22/33	9/23/33
Dog Number	21	24	28	47	48	45	47	48	46	24	29	28	18	24	47	48	47	48	64	63	64	62	62	64
Weight and Sex	12M	9F	8F	8.7F	16M	19F	8.7F	16M	8.7F	9F	8.5M	8F	12M	16F	8.7M	16M	8.7M	16M	11.6F	14.6M	11.6F	9.1M	9.1M	11.6F
Mg/Kg. Paralyzant	17	5.5	6.3	6.3	6.3	5.3	6.3	6.3	5.8	5.5	9.4	6.2	12.5	6.25	6.3	6.2	6.3	6.3	2.8	2.8	6.3	2.8	2.8	
Mg./Kg. Antagonist							2.9	3.15	2.9	5.5	3.5	3.1	2.1	6.25	3.1	3.1	2.9	3.15	2.8	2.8	2.8	2.8	2.8	2.8
Time Injection Par.	10:19	12:32	2:30	5:00	9:20	9:27	8:55	4:45	10:14	1:10	4:45	4:45	10:40	4:42	5:05	9:00	9:37	4:20	12:12	10:02	12:10	11:33	4:44	
Time Injection Ant.							9:01	4:51	10:22	1:25	4:55	4:51	10:45	4:46	5:16	9:07	9:37	4:20	12:12	10:02	12:36	11:33	4:44	11:33
Time Return Resp.	11:55	1:00	3:40	5:55	10:34	10:17	10:35	5:15	11:30	1:32	4:56	4:59	10:56	4:58	5:23	9:18	No Par.	4:36	12:32	10:12	12:48	11:39	4:47	
Duration Respiratory Paralysis	96	28	50	55	74	50	120	30	76	22	11	14	16	16	18	18	No Par.	16	20	10	38	6	13	
Duration After Ant.							114	24	69	7	1	8	11	12	7	11	No Par.	16	20	10	12	6	13	
Pupillary Response to Paralysis	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A		A	A	
Conjunc. Reflex to Paralyzant	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	N.A.	N.A.	A	N.A.		N.A.	A	
Forelimb Reflex Response to Paralyzant				A	A	N.A.		A			A					A	N.A.		A	N.A.		N.A.	N.A.	N.A.
Normal Pulse	160	150		164	136	100	192	160	132	150	68	88	114	80	150	100	160	140	180	88		78	106	
Pulse after Par.	112	108		160	90	120	162	156	120						110	128								
Pulse after Ant.							220	200	240	132	200	240	270	200	210	212	210	230	200	200		200		
Time Return Conj. Reflex		1:05	3:50	6:06	10:37	10:12	9:21	4:56	11:16	1:45	5:00	5:04	11:15	4:57	5:30	9:19	N.A.	N.A.	12:25	10:10		N.A.	4:52	
Time Return Pupill. Reflex				6:20	10:37		9:39								5:55			5:07						
Time Return Forelimb Reflex				6:00		N.A.		5:25	12:30						5:45	9:56	N.A.	N.A.	2:00	N.A.				NA
Time Return Conscious.	In Night	6:00	8:00	7:00	12:00	In Night	11:20	6:00	—	3:00	Next Morn	6:00	12:00	6:00	6:15	10:30	10:15	5:15	2:10	10:35		5:30	5:00	5:21
Nature Restored Resp.	P	14	G	16 G	16 G	G	G	16 G	18 G	32 R	14 R	G	16 R	36 G	16 R	16 R	G	16 G	G	24 G	G	G	G	G
Duration Prorated	33	32	50	55	74	54	114	30	—	—	—	14	—	16	18	18	0	16	—	—	—	—	—	—
Fate of Animal	D	Re	Re	Re	Re	Re	Re	Re	D	Re	Re	Re	Re	D	Re	Re	Re	Re	Re	Re	Re	Re	Re	Re
Notation										Walk 5:30								Walk 5:30	Walk 8:00	Walk 11:00				No Novo Cain

Notes: A - Abolished, N.A. - Not Abolished, P - Poor, G - Good, R - Regular, Re - Recovered
D - Died, Seq - Sequential

There is probably little effect from cisternal novocaine upon the vasomotor center in the doses routinely used in our experiments for the abolition of breathing. However, when the asphyxia accompanying respiratory paralysis impinges upon the vasomotor center there is a sharp decrease in irritability made manifest by a fall in blood pressure. Hill and MacDonald (79) prefer an explanation involving the depression of an adrenaline secreting mechanism but the asphyxial explanation seems straightforward.

Group B. Results obtained in the presence of ether.

The durations of the controls in which novocaine was injected during light ether anaesthesia were little shorter than the durations of the paralyses when ephedrine was injected after or with the depressant. The ether controls were much shorter than the controls secured with morphine sodium amytal anaesthesia. To support these conclusions the following experiments are adduced.

In experiments 116 and 117 durations of 0 and 27 minutes respectively were obtained in the paralyses eventuating from cisternal novocaine in doses in the 6.3 mg. per kg. range.

Cisternal novocaine was found to decrease the fast pulse caused by the ether anaesthesia. If ephedrine was administered,then the pulse rate remained uniformly high.

The conjunctival reflex and the pupillary reflex were constantly abolished by cisternal novocaine. The forelimb

extensor reflex is apparently not so constantly abolished. The return of the conjunctival generally required from 40 to 50 minutes whereas the pupillary reflex lagged far behind this time in restoration. The forelimb reflex returned very speedily.

Consciousness returned promptly after cisternal novocaine. The duration of true narcosis after doses in the 5 to 6.2 mg. per kg. range lasted about 20 minutes. This fact may be related to the complete recovery of all animals in this group.

Our observations with dogs do not agree with those of Soupault (80) with respect to the abolition of consciousness in man after cisternal novocaine. He reported the persistence of consciousness during respiratory paralysis in man after doses of 100 mg. novocaine and doses of 50 mg. of chloralose cisternally. One is astonished by the temerity of a worker who introduced depressants into the human cistern before the acquisition of experimental data on animals.

Legend to accompany condensed protocols on opposite page

Exp.	Time of administration of and dose of atropine sul.	Time of beginning ether anaesthesia	Time of initial injection (cisternal)
101	9:00 A.M. 1 mg.	9:10 A.M.	9:30 A.M.
104	4:19 P.M. 1 mg.	4:20 P.M.	4:51 P.M.
116	9:36 A.M. 1 mg.	9:44 A.M.	9:52 A.M.
117	10:30 A.M. 1 mg.	10:40 A.M.	10:53 A.M.
102	4:08 P.M. 1 mg.	4:20 P.M.	4:34 P.M.
110	3:16 P.M. 1 mg.	3:21 P.M.	3:35 P.M.
154	2:10 P.M. 1 mg. 2:09 P.M. morphine, 2 mg./kg.	2:25 P.M.	2:44 P.M.

Table 5

	Ether Anaesthesia Controls					Cisternal Novocaine Cist. Eph. Sul.		
Experiment	101	104	116	117		102	110	154
Date	3/10/33	3/24/33	5/6/33	5/6/33		3/17/33	4/14/33	8/8/33
Dog Number	45	46	47	48		45	46	60
Weight and Sex	20.1F	8.7F	8.7	16M		20.1F	8.7F	10.9M
Mg/Kg Paralyzant	5	5.7	6.3	6.25		5	4.9	6.2
Mg/Kg Antagonist						1.2	2.8	2.3
Time Injection Par	9:30	4:51	9:52	10:53		4:34	3:35	2:44
Time Injection Ant.						4:34	3:35	2:44
Time Return Resp.	10:12	5:05	9:52	11:20		5:00	3:49	2:44
Duration Respiratory Paralysis	42	14	0	27		26	14	0
Duration After Ant						26	14	0
Pupillary Response to Paralysis	A	A	A	A		A	A	A
Conjunc. Reflex to Paralyzant	A	A	NA	A		A	A	A
Forelimb Reflex Response to Paralyzant	NA	A	NA	A		NA		A
Normal Pulse	144	186	252	232			200	180
Pulse after Par.	208	180	216	220		240	220	200
Pulse after Ant.						240	220	200
Time Return Conj. Reflex		5:10		11:15		5:02	3:46	3:12
Time Return Pupillar Reflex								
Time Return Forelimb Reflex	NA	5:25	NA	11:20		5:10		
Time Return Consciousness	10:30	5:30	10:00	11:30		5.20	5:10	3:00
Nature Restored Respiration	16 Good	28 Poor	32 Reg.	18 Reg.		28 Good	20 Reg.	56 Reg.
Duration Prorated	52	15	0	27				
Fate of Animal	Rec.	Rec.	Rec.	Rec.		Rec.	Rec.	Rec.
Notation	Walk 10:30	Walk 5:40	Walk 10:20	Walk 11:40			Walk 5:10	Walk 3:40

* A-Abolished, NA-Not Abolished

VIII. PHARMACODYNAMIC REACTIONS OF CISTERNAL PICROTOXIN

1. Literature

Sufficient mention has been made of the pertinent published observations of the pharmacodynamic properties of picrotoxin.

2. Experimental Results obtained with Picrotoxin in reversing depressed states produced by cisternal Sodium Amytal

The recovery of experimental animals after picrotoxin is extremely problematical. This series of experiments suffers from this difficulty in that it has been impossible to obtain drastic control experiments.

Six experiments are presented representing doses of picrotoxin from 0.023 to 1.7 mg. per kg. There were three deaths and three survivals. The dose of 1.7 mg. per kg. is manifestly too large but it was given before any experimental criterion of the proper dose of cisternal picrotoxin was available. The experiment employing cisternal picrotoxin in dose of 0.032 mg. per kg. after sodium amytal in dose of 5.3 mg. per kg.,cisternally,resulted in death from pulmonary involvement whereas an experiment employing 0.033 mg. per kg. of picrotoxin and 6.2 mg. per kg. of sodium amytal, both cisternally, led to recovery.

The animal which received 1.7 mg. per kg. of cisternal picrotoxin exhibited after the return of spontaneous breathing a most violent type of breathing. The action of the picrotoxin was slow to assert itself in the face of the

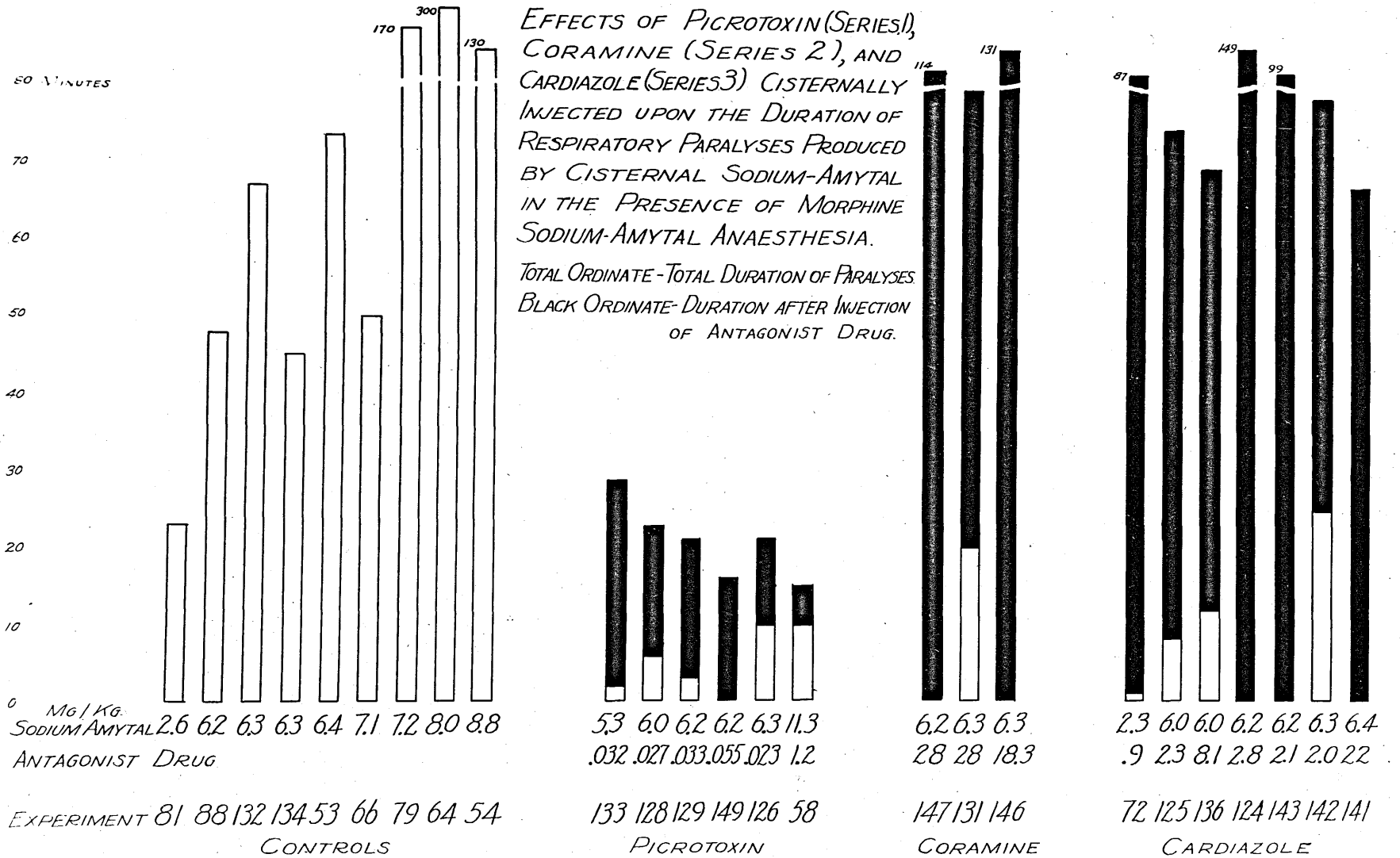

EFFECTS OF PICROTOXIN (SERIES 1), CORAMINE (SERIES 2), AND CARDIAZOLE (SERIES 3) CISTERNALLY INJECTED UPON THE DURATION OF RESPIRATORY PARALYSES PRODUCED BY CISTERNAL SODIUM-AMYTAL IN THE PRESENCE OF MORPHINE SODIUM-AMYTAL ANAESTHESIA.
TOTAL ORDINATE - TOTAL DURATION OF PARALYSES.
BLACK ORDINATE - DURATION AFTER INJECTION OF ANTAGONIST DRUG.
MINUTES
0
10
20
30
40
50
60
70
80
170
300
130
114
131
87
149
99
MG / KG.
SODIUM AMYTAL 2.6 6.2 6.3 6.3 6.4 7.1 7.2 8.0 8.8
ANTAGONIST DRUG
5.3 6.0 6.2 6.2 6.3 11.3
.032 .027 .033 .055 .023 1.2
6.2 6.3 6.3
28 28 18.3
2.3 6.0 6.0 6.2 6.2 6.3 6.4
.9 2.3 8.1 2.8 2.1 2.0 22
EXPERIMENT 81 88 132 134 53 66 79 64 54
CONTROLS
133 128 129 149 126 58
PICROTOXIN
147 131 146
CORAMINE
72 125 136 124 143 142 141
CARDIAZOLE

Figure 5

large dose of sodium amytal (12 mg. per kg.) but the lag was more probably associated with the poor diffusion of the picrotoxin than with impotency of analepsis. The restored breathing consisted of alternate periods of apnea and of hyperpnea lasting about 15 seconds. During apnea the animal was drowsy and during hyperpnea, very alert. There was evidence of strong clonus of the limbs with twitching of the facial muscles. In addition, there was twitching of the neck muscles and occasional strong claw extension. We assume that the mode of dissolving the picrotoxin in 10% aqueous alcohol played no part in the train of events.

The mode of death seems clear in its relation to the casualties earlier experienced. The jerky hyperpnea of most alarming proportions could not possibly have failed to produce some trauma to the delicate pulmonary apparatus. Later, after the picrotoxin effect had waned, the animal was confronted with the necessity of disposing of 12 mg. per kg. of cisternal sodium amytal after the preliminary morphine-sodium amytal anaesthesia. The dose of picrotoxin was certainly momentarily capable of annulling the effect of the sodium amytal but its action was over too soon to forestall the profound depression from the summated doses of the barbiturate. The momentary character of the efficacy of the picrotoxin is evidenced by the absence of convulsions.

The death of dog # 57 in experiment 149 which received 6.3 mg. of cisternal sodium amytal per kg. and 0.023 mg. of cisternal picrotoxin in the presence of morphine-sodium amytal anaesthesia falls into a different category. Although the picrotoxin was adequate to restore respiration it was not able to restore a truly competent respiration. As long as five hours after the return of spontaneous breathing, elicited by the denial of artificial respiration, respiratory excursions were but feeble and non-assertive. Despite the injection of ephedrine the animal died an acute respiratory death.

No animal receiving more than 0.033 mg. per kg. of cisternal picrotoxin recovered. The results are not included to lead to conclusions as to the potency of picrotoxin in barbiturate intoxication but rather as a record for dosage of cisternal picrotoxin, because as far as we know there has as yet no dose of cisternal picrotoxin been described in the literature.

One animal exhibited after cisternal picrotoxin violent intestinal activity not accompanied by evacuation. In two other cases profuse salivation occurred. The doses were in the 0.033 mg. per kg. range. The inconstancy of appearance of this action is probably due to central depression of the salivatory mechanism in the cases where it failed to appear. Camp (81) has been able to demonstrate that cardiazole can stimulate the salivatory centers if

the depth of anaesthesia is not great.

In all cases picrotoxin cisternally slowed the heart. The injection of 1 mg. of atropine intravenously effected a reversal of this action which was probably due to central vagus stimulation. The slowing in all cases was additional to the slowing produced by cisternal sodium amytal.

Cisternal picrotoxin in all the doses used restored almost immediately the conjunctival and pupillary reflexes abolished by cisternal sodium amytal. Herein picrotoxin differs from ephedrine because with the latter the return of the pupillary reflex is long deferred. This observation is in harmony with the observations of Chen (82) who described the strong and lasting ephedrine mydriasis which in our experiments deferred so long the return of the pupillary reflex.

Cisternal picrotoxin restored respiration abolished by cisternal sodium amytal about as effectively as did ephedrine and in doses about 1/80 as large. The breathing restored by picrotoxin was not as well co-ordinated as was that restored by ephedrine. Furthermore,with picrotoxin the convulsive limits were more closely approached than with ephedrine, a drug which in our experiments did not show the slightest indication of convulsive action. In addition the analepsis of picrotoxin was accompanied by cardiac depression while that of ephedrine takes place in the presence of a profound circulatory improvement.

IX. PHARMACODYNAMIC REACTIONS OF CISTERNAL CORAMINE

1. Discussion of Published Observations of the Actions of Coramine

Coramine was described by Killian (83) as pyridine carboxylic acid diethylamide. Hence it is a dialkylated amide of nicotinic acid, quite soluble in water and almost certainly a true chemical compound and not a mixture. It is advertised as a respiratory and cardio-vascular analeptic which according to Gremels (84) produces elevation of the blood pressure providing there is competency of the vasomotor center.

That coramine is able to break through the narcosis of avertin is attested by many experimentalists and clinicians. Killian (83) has adduced sufficient clinical evidence to make this conclusion inescapable. Moreover, Killian envisaged coramine as categorically analeptic to depressions whatever their causes. This contention is strengthened by the observations of Braams(85) who reported experiments finding coramine superior to cardiazole in stimulating depressed respiration.

Tartler's experiments (62) also indicated the superiority of coramine over cardiazole in analeptic value because the action of the former is asserted before the convulsive limits are reached whereas potent doses of the latter approach that limit. This worker found that coramine antagonizes small and synergizes large doses of medinal. We

suspect similar reaction of coramine with sodium amytal.

That coramine mitigates the depression of cortical depressants such as paraldehyde and avertin,whereas it synergizes those of the brain stem narcotics such as barbiturates and chloral,was observed by Moritsch (61) who also found that ephetonin (synthetic optically inactive ephedrine) synergizes brain-stem narcotics and is actually a depressant in its own right for decerebrated rabbits. Both ephetonin and coramine he found stimulant to the vasomotor center. Heppner (86) reported the ability of coramine to break through pernocton-ether anaesthesia of rabbits and Zunz (87) asserted that it stimulates the respiratory centers of animals with denervated carotid sinuses. In his studies of the labyrinthine and other postural reflexes of rabbits Kohlhoff(88) described the antagonism of coramine to respiratory depressants as limited to action against chloral and paraldehyde.

The manufacturers of coramine, Ciba and Co., have recently marketed a double salt of coramine called calciocoramine in which two molecules of coramine are united with one of calcium sulphocyanide. Such a compound might integrate the hypothetical analeptic properties of the sulphocyanide ion with the authenticated properties of coramine. Uhlmann (89) found this new drug to be a respiratory,cardiac, vasomotor, and secretory stimulant with anti-inflammatory properties.

Niedermoser (90) used coramine prophylactically to

facilitate the adjustment of the respiration during the narcotization of maniacal patients. He emphasized the inability of the drug to reverse the narcosis in any true sense and claimed its efficacy was existent both with pernocton and with somnifen. He found it superior to lobeline to which it is related chemically and recommended the use of doses of 250 mg.

Maloney and Tatum (91) observed the superiority of coramine over cardiazole in reversing the depression of certain narcotics and the total inadequacy of both in barbiturate depressions. In view of the fact that the barbiturates are solids of small chemical lability and greatly resistant to detoxication as a consequence of their stability ,there is small wonder that analeptics can at best break through their actions in only the most fleeting sense. In comparison ,drugs like paraldehyde possess a most effective reaction to detoxication and are volatile liquids.

2. Experimental Results with Coramine

Coramine was injected simultaneously with sodium-amytal in the cisterns of dogs anaesthetized with morphine 2 mg. per kg. and sodium amytal 30 mg. per kg. The dose of sodium amytal ,cisternally ,with which coramine was caused to contend was uniformly 6.3 mg. per kg. The dose of coramine ranged from 18.2 to 28 mg. per kg.

There can be no possible chemical reason for the reaction of coramine with sodium amytal at the temperature of

the body. Although the small quantity of lactic acid contained in the coramine solution in the ampoules must affect the pH of the sodium amytal solutions the change is too small to produce significant changes in solubility of the barbiturate. It was necessary to reject one c.c. of cisternal fluid and to supplant it with 1 c.c. of the coramine solution because our supply of coramine was in ampoule form.

Our feeling that the danger of convulsions from coramine is remote was confirmed in this group. Since mixed drugs were administered we are unable to state definitely how coramine affects the circulation but we submit the provisional assertion that cisternally it slows the heart less readily than does cardiazole.

Assuming that the doses of cisternal sodium amytal were adequate to abolish the conjunctival reflex (certainly not a gratuitous assumption) coramine has about the same potency in restoring it as has cardiazole.

The unsuitability of coramine for abbreviating the respiratory paralysis produced by cisternal sodium amytal is attested by the graphic comparison of the protocols in Figure 5 . Apparently coramine actually serves to prolong the duration of such paralysis. Its potency in reestablishing abolished reflexes is of a similar inferior order.

Our experiments with coramine are limited in number because of the unpromising nature of its action and be-

cause we are reserving this drug for a future study in a more fundamental sense. The cisternal avenue of exhibition will be used.

X. PHARMACODYNAMIC REACTIONS OF CISTERNAL CARDIAZOLE

1. Published Observations on the Pharmacodynamic Reactions of Cardiazole

The analeptic phases of the actions of cardiazole will be discussed in this section because despite its comparative youth there has sprung up since the publication of the first paper describing its action by Schmidt, Hildebrandt and others (92) in 1925,a truly voluminous literature.

Cardiazole, which is marketed in the United States as "Metrazole" and which is produced by the chemical reaction of hydrazoic acid with cyclohexanone is probably a true chemical compound corresponding to the technical name, pentamethylene tetrazole. It is resistant to boiling and is quite soluble in water, a fact which, in one sense, makes it definitely superior to camphor.

The consensus of German opinion is that it is a medullary stimulant. The original workers (92) asserted that it is quickly absorbed and not cumulative in action; that its absorption is so great that subcutaneous doses are about as efficacious as intravenous; and that its efficacy after both modes of exhibition is of the same order and in the same dosage potency. They reported stimulation of the hearts of frogs, rats,and rabbits both in normal and depressed states and the intermediation of cortical action in the case of its antagonism to morphine depression.

On the contrary Stross (93) found that cardiazole action

is not exerted so markedly on the normal heart but rather upon the heart depressed by chloroform. Its stimulant action, he believed,was, exerted through an increase of blood pressure not manifested after decapitation of the experimental animal, the frog, and also by a lasting vagus action. The cardiac accelerator mechanism was unaffected. Asher (94) reported that in rabbits cardiazole is a cardio-respiratory analeptic but he also reported the production of convulsions by doses of cardiazole much smaller than those of coramine effective in the same stimulant sense.

Camp (81) described the parasympathetic action of cardiazole, a phenomenon which we too have remarked. That it stimulates the depressed respiration, he denied. Its central action on the salivatory apparatus was not obtained in our experiments but Camp has already given sufficient reason for the failure of the action in terms of central depression due to anaesthesia.

Barker and Levine (95) reported the inefficacy of cardiazole to stimulate the cardio-respiratory systems of cats depressed by hemorrhage, quinidine,and mineral acid.

That cardiazole is effective in reversing avertin narcosis is clear,but Janossy (31) pointed out that its effectiveness in stimulating respiration depressed by the same drug is problematical. The sense of our experiments is that its use to combat respiratory failure from depressants is probably quite unwise.

Ruef (96), after long clinical investigation, reported the improvement of blood pressure even in moribund cases with the development of a digitalis pulse after long administration. Buding (97) would definitely place cardiazole in the picrotoxin rather than in the camphor group. In his experiments he was able to mitigate both with cardiazole and picrotoxin the depression produced by caffein, a depression which Tartler (63) had earlier described as produced in rats.

The usefulness of cardiazole in improving the circulation was reported by Gremels (84), who found its greatest utility in depressions associated with depressed vasomotor tone. Burgi and Gordonoff (98) found digitalis additive to cardiazole, providing the digitalis preparations were free from digitoxin, a condition not easily achieved in view of the capricious pharmaceutical chemistry of digitalis.

Maloney and Tatum (99) found cardiazole distinctly inferior to coramine in antagonizing barbiturate depression. David and Vareed (100) reported that cardiazole produces a transient stimulation of the depressed heart and respiration after barbiturate medication, but they pointed out that the effective dose is near the convulsive dose and that the effect upon animals is not dependable, particularly in certain species. They could obtain predictable results with cats, in which animals Watt (101) found that the effect of car-

diazole elicited vomiting in doses near the convulsant dose and that the action in therapeutic doses consisted of stimulation of the respiration and of actual depression of the isolated heart. Against chloroform depression they found cardiazole useless in eliciting cardiac improvement.

2. Experimental Results with Cisternal Cardiazole

Since the results with cardiazole have been very discouraging of any promise for analeptic action in the respiratory depressions produced by cisternal sodium amytal , only six experiments are presented. The results are shown graphically in Figure 5 .

Only morphine-sodium amytal anaesthesia was used. The cisternal medication consisted of sodium amytal in doses of 2.3 to 6.5 mg. per kg. mixed with cardiazole in doses of 0.9 to 2.2 mg. per kg. There is small possibility of chemical reaction between the cardiazole and the sodium amytal.

The doses of cardiazole were observed to produce striking functional modification and were for this reason considered adequate to produce any analeptic action the drug may possess. So potent were they in impairing the circulation that ephedrine therapy was necessary in most of the cases observed. Despite their untoward action on the circulation there were no fatalities in the cardiazole series.

The most outstanding feature of cardiazole action after cisternal exhibition was the profound slowing of the

pulse and the speedy re-establishment of the corneal reflex. The slowing effect corresponds nicely with the published observations of Camp (81), who found cardiazole strongly stimulant to parasympathetic structures. Our results further agree with Camp's in the failure of the stimulation of the salivatory apparatus during deep anaesthesia. The parasympathetic action of cardiazole was further evident in our experiments by the easy and speedy constriction of the pupil dilated by cisternal sodium amytal.

An analysis of the data on respiration indicates that cisternal cardiazole probably prolongs rather than abbreviates the respiratory paralysis produced by cisternal sodium amytal.

The powerful action of picrotoxin in producing strong intestinal movements was found lacking in cardiazole when injected cisternally. Making due allowance for the slow diffusion of picrotoxin and the fast diffusion of cardiazole, we are led to conclude that the two drugs have much in common but that cardiazole is much inferior in activity. This is likewise true with respect to the duration of narcosis, a phenomenon which we believe was actually prolonged by cisternal cardiazole.

XI. PHARMACODYNAMIC REACTIONS OF SODIUM THIOCYANATE

1. Published Observations of the Actions of Sodium Thiocyanate

The only possible sanction for an attempt to demonstrate an antagonism to barbiturates by sodium thiocyanate is the work of Wilder D. Bancroft and his associates (102). Their experimental work is based upon the assumption that reversible deviation from a normally dispersed condition of the colloids of nervous protoplasm constitutes the sole effective mechanism of stimulation and depression of nervous structures.

The working hypothesis is obviously a repetition of the theory of Claude Bernard (103) and other investigators. Bancroft and Richter (104) adduced experimental evidence gained with yeast plants wherein the organisms were narcotized with amyl alcohol and later freed from narcosis by washing and centrifugalization. The plants were capable, after being freed from the narcotic, of causing alcoholic fermentation and of growth. When narcotized, Brownian movement was at low ebb in the organisms, but after washing it returned with its original intensity. These experiments Bancroft and Richter called a great triumph for the theory of Bernard.

Henderson and Lucas (105) objected vigorously to the synonomous usage of the terms "anaesthesia" and "narcosis" by the Bancroft group. They considered his generalization

too sweeping particularly in view of the fact that few animals were used and that time for recovery from earlier medication was not always permitted before the performance of experiments. The reported improvement in breathing they believed could be explained by sensory stimulation.

The most explicit necessity of the Bancroft theory is the insistence upon the role played by the proteins and especially by the albuminous proteins of the protoplasmic colloids of the nervous tissue. The lipoids are caused to assume a much less important role than they play in the Meyer-Overton theory. The latter theory has been characterized by Bancroft as a theory of transport and absorption rather than as a theory of narcotic action. The lipoids are reserved in the Bancroft theory to explain phenomena not explicable in terms of the protein colloidal aggregates. In view of the fact that for alkaline albumin the peptization by ions is achieved in the following order $CNS > I > Br > NO_3 > Cl > C_2H_3O_2$ of decreasing potency, sodium sulphocyanide (thiocyanate) with its relatively harmless sodium ion becomes the therapeutic agent par excellence for dispersing reversibly agglomerated nervous colloids. In addition the dispersing power must be considered in relation to the ionic environment in which the narcotic coagulation has taken place.

The sodium ion although it is inferior to caesium, rubidium and potassium as peptizing agent is used because

the other ions are cardiac poisons. Multivalent cations are also more serviceable as peptizing agents but they are also protein precipitants.

Since there is no reason to suspect that ingestion of thiocyanates might lead to cyanide intoxication the most damaging bar to thiocyanate therapy is removed. Bodansky (106) assigned to thiocyanate the mechanism of detoxication of cyanide.

Bancroft (102) described the awakening of a rabbit from sodium amytal sleep by the injection of 1 c.c. of 10% sodium thiocyanate solution. He believed that it would be proved superior to ephedrine and caffeine and also that it would be entirely free from harmful side-actions. Its chief therapeutic use has been in the reduction of hypertension and it has been known to produce maniacal episodes.

Bancroft considers doses of 450 mg. per kg. harmless for rabbits. One wonders what effects such doses might have upon proteinaceous systems other than the nervous structures. No doubt the albumin content of such extra-nervous structures is often higher than the content of nervous protoplasm. We have found that the exhibition of thiocyanate leads to severe gastro-intestinal upsets and possibly to trophic changes in the maxillae.

The colloidal theory of anaesthesia of this modern school has been broadened to include drug addiction, anaphylaxis, shock, and the psychoses and it has enlisted the

co-operation of psychiatrists. Under the conditions specified by the theory, Lang and Paterson (107) have attempted to classify psychoses in terms of dispersion and agglomeration. Thus catatonia became, in their thinking, a dispersed phenomenon while epilepsy became a coagulated phenomenon. Bancroft calls ephedrine a dispersing agent for albuminous systems in the alkaline range and as such it should be the treatment for epilepsy.

The drug bulbocapnine produces typical catatonia in experimental animals. In terms of the Bancroft theory it must be a dispersing agent. Bancroft induced bulbocapnine (108) into animals experiencing amytal narcosis, a typical agglomeration narcosis, without effect.

The use of thiocyanate in psychosis led Bancroft to recommend the thiocyanate marketed by a specific manufacturer. The recommendation elicited a not unmerited rebuke in the Journal of the American Medical Association (109).

In spite of the unquestionably over-sanguine statements of the Bancroft group it must in all fairness be remembered that these workers were responsible for the rejuvenation of much pharmacologic thinking with respect to the causation of narcosis.

2. Experimental Results with Cisternal Sodium Amytal and Cisternal Sodium Thiocyanate

This series of experiments does not include controls obtained on the same animal but a proper comparison was

furnished by the multiplicity of controls secured in other groups of experiments. The fragmentary character of this series grew out of our unwillingness to invoke in experimental animals the post-experimental lethargy and diarrhea which we have observed in some of our animals after massive thiocyanate therapy, particularly when the drug produced such discouraging results as an analeptic in barbiturate depression.

It is believed that the five experiments presented indicate the inability of thiocyanate to abbreviate respiratory paralyses after cisternal sodium amytal. In each case about 6 mg. per kg. of sodium amytal were injected cisternally which in each case produced respiratory paralysis.

In Experiment 156 after the production of respiratory paralysis by 6 mg. per kg. of sodium amytal cisternally, 40 mg. per kg. of sodium thiocyanate was injected in the saphenous vein. This animal never recovered the spontaneous ability to breathe in spite of ephedrine medication.

In experiment 158 after the production of respiratory paralysis by 6.0 mg. per kg. of cisternal sodium amytal followed by 6.3 mg. per kg. of thiocyanate, spontaneous respiration returned 80 minutes after its onset and 73 minutes after the injection of the thiocyanate.

In experiments 160,161, and 162, employing 6.3 mg. per kg. of cisternal sodium amytal followed by 12.6,12.6, and

25.2 mg. per kg. respectively of sodium thiocyanate, total durations of respiratory paralysis of 43,35, and 90 minutes respectively were observed. The duration after the proposed analeptic medication were 29, 31, and 83 minutes respectively.

One property of sodium thiocyanate which seems to give some promise is its ability to reinstitute the conjunctival reflex very speedily. About 15 minutes after the abolition of the reflex by sodium amytal it was again functional when cisternal sodium thiocyanate was injected.

How much of the effect of sodium thiocyanate is dependent upon the alkalinity of its aqueous solutions we have not investigated. Sodium citrate produces strong stimulation of respiration as is attested by Tatum (110). Its aqueous solutions are quite alkaline. There has been recently in this locality a belief that the intravenous injection of strong acids also produces strong stimulation of of the respiratory center asphyxiated by CO or by natural gas. In a couple of experiments which are mentioned only incidentally we were unable to detect any shortening of barbiturate narcosis by the injection of 1 to 2 c.c. of 10% HCl intravenously and quickly.

After cisternal sodium thiocyanate administered to dogs experiencing respiratory paralysis after the cisternal injection of sodium amytal there is little change in pulse rate or in blood pressure as detected by palpation.

3. Experimental Results with Cisternal Sodium Thiocyanate and Cisternal Novocaine

This series is the earliest in the study and contains the results of experiments in which both dosage and functional modification were unknown quantities. Some of the experiments were obtained with broken doses of the drugs. Apparently the injection of broken doses of novocaine cisternally leads to the possibility of administering quantities of drugs in the aggregate without respiratory paralysis which if added at once would produce profound paralysis. A possible explanation of this fact lies in the assumption that the speed and intensity of fixation of the drug by the nervous tissue lies in the concentration gradient obtaining between the cisternal fluid and the nervous tissue to which it has access. The nicety of experimentation has been appreciably lost by the necessity in the earlier experiments of giving broken doses. To mark the time and the duration of respiratory paralysis in experiments employing broken doses of novocaine the doses are summated and recorded as of the time of last injection.

A comparison of duration of paralysis in the control experiments and in the experiments using cisternal thiocyanate after the onset of paralysis suggests an antagonism between the two drugs. The longest duration was 112 minutes obtained with 33 mg. per kg. of body weight of novocaine antagonized by 50 mg. per kg. of sodium thiocyanate. The

novocaine was injected cisternally and the thiocyanate partially cisternally and partially intravenously. As a result of this practice which was also followed in other experiments in this series it has been impossible to make a graphic analysis of the protocols in this series. In the tabular analysis the author has attempted to estimate proper expression of the data. Hence the tabulations for this group contain arbitrary and not necessarily true recorded time episodes for the injection of the antagonist, sodium thiocyanate. An accurate summary of the actual time and manner of exhibition of the drug is contained in the following table.

Exp. 29	Initial inj.	NaSCN	5:50 P.M.	cistern	8.3	mg./kg.
	second "	"	6:05 P.M.	vein	17.0 "	"
Exp. 31	Only one avenue--cistern					
Exp. 32	Initial inj.	NaSCN	12:10 P.M.	cistern	16	mg./kg.
	second "	"	12:20 P.M.	"	8 "	"
	third "	"	1 :08 P.M.	vein	333 "	"
Exp. 33	Only one avenue--cistern					
Exp. 34	Only one avenue--cistern					
Exp. 38	Initial inj.	NaSCN	12:32 P.M.	cistern	6	mg./kg.
	second "	"	12:37 P.M.	"	6 "	"
	third "	"	1:08 P.M.	"	12 "	"
Exp. 39	Initial inj.	NaSCN	3:33 P.M.	"	6 "	"
	second "	"	3:40 P.M.	"	6 "	"
Exp. 39 a	Only one avenue of exhibition--cistern					

An analysis of the data in the experiments suitable for our purpose numbers 31,33,34, and 39-a in which cisternal doses of novocaine of 13.3,16.6,8.8, and 23.5 mg. per kg. were antagonized by cisternal doses of sodium thiocyanate of 13.3, 29, 17.6, and 35.1 mg. per kg. respectively gives total durations of 15,112,63, and 23 minutes respectively. The durations after the injection of the thiocyanate were respectively 5, 20, 55, and 20 minutes. These durations are somewhat shorter than those obtained in control experiments in other series employing,it is true, different doses but smaller doses. These experiments indicate if not an antagonism between thiocyanate and novocaine, at least, certainly, no synergism as was obtained with cardiazole.

Unfortunately, the recovery from paralysis presumably brought about by thiocyanate is offset by the post-experimental lethargy and gastro-intestinal irritations which the drug produces. In addition, thiocyanate was observed to produce spastic seizures of a clonic type. In experiment 42 it was found that the clonic seizures were not produced by novocaine but rather by thiocyanate. The dog in this experiment received only thiocyanate in the cistern in dose of 24 mg. per kg.

That sodium thiocyanate is reactive chemically with novocaine (procaine hydrochloride) in aqueous solution is quite apparent. When cisternal fluid containing dissolved

Legend to accompany condensed protocols on opposite page

Exp.	Time of administration and dose of morph. in mg./kg.		Time of administration and dose of sodium amytal in mg./kg.		Time of initial injection (cisternal)
131	9:34 A.M.	4	9:40 A.M.	30	9:55 A.M.
146	10:12 A.M.	4	10:30 A.M.	30	10:44 A.M.
147	9:24 A.M.	4	9:40 A.M	30	10:06 A.M.
58	4:10 P.M.	4	4:40 P.M.	30	5:00 P.M.
126	9:51 A.M.	4	10:10 A.M.	30	10:39 A.M.
128	4:02 P.M.	4	4:12 P.M.	30	4:23 P.M.
129	9:44 A.M.	4	9:52 A.M.	30	10:14 A.M.
133	11:20 A.M.	4	11:23 A.M.	30	11:51 A.M.
149	10:43 A.M.	4	11:01 A.M.	30	11:51 A.M.
72	9:16 A.M.	4	9:39 A.M.	25	10:26 A.M.
124	2:57 P.M.	4	3:12 P.M.	30	3:21 P.M.
125	10:25 A.M.	4	10:38 A.M.	30	10:52 A.M.
136	9:15 A.M.	4	9:26 A.M.	30	9:40 A.M.
141	9:55 A.M.	4	10:15 A.M.	30	10:48 A.M.
142	9:00 A.M.	4	9:15 A.M.	30	9:26 A.M.
143	9:50 A.M.	4	10:04 A.M.	30	11:01 A.M.
29	4:10 P.M.	4	4:20 P.M.	35	5:40 P.M.
31	9:25 A.M.	4	9:35 A.M.	30	12:25 P.M.
32	9:45 A.M.	4	9:55 A.M.	30	12:00 M.
33	9:37 A.M.	4	10:00 A.M.	30	10:10 A.M.
34	12:00 M.	4	12:15 P.M.	30	4:54 P.M.
38	11:35 A.M.	4	11:40 A.M.	30	12:09 P.M.
39	3:00 P.M.	4	3:15 P.M. (barbital)	100	3:25 P.M.
39a	10:05 A.M.	4	10:10 A.M.	30	11:22 A.M.

	Morphine - Sodium Amytal Anaesthesia Coramine Picrotoxin										Cisternal Sodium Amytal Cardiazole							Cisternal Novocaine NaSCN							
Experiment	131	146	147		58	126	128	129	133	149	72	124	125	136	141	142	143	29	31	32	33	34	38	39	39a
Date	6/5/33	7/24/33	7/25/33		10/25/33	6/2/33	6/7/33	6/8/33	6/13/33	7/31/33	3/32	6/1/33	6/2/33	6/30/33	7/8/33	7/15/33	7/17/33	7/25/32	7/27/32	7/28/32	7/29/32	7/30/32	8/10/32	8/10/32	8/11/32
Dog Number	49	56	57		29	51	50	49	45	57	33	49	50	53	52	54	55	18	20	21	22	23	20	26	23
Weight and Sex	89F	136M	9MM		9M	128M	10.9F	8.9F	19F	9M	1F	8.9F	10.9F	12.3M	11.4M	12.3F	14.6M	12M	15M	12M	12M	8.5M	15M	17F	8.5M
Mg/Kg Paralyzant	6.3	6.3	6.2		11.3	6.3	6.0	6.2	5.3	6.2	3	6.2	6	6	6.4	6.3	6.2	12.5	13.3	33.2	16.6	8.8	6.6	5.9	23.5
Mg/Kg Antagonist	2.8	18.3	2.8		1.2	.023	.027	.033	.032	.055	9	2.8	2.3	8.1	2.2	2	2.1	25	133	50	29	176	13.3	198	35.1
Time Injection Par.	9:55	10:44	10:06		5:00	10:39	4:23	10:14	11:51	11:51	0:26	3:21	10:52	9:40	10:48	9:26	11:01	5:40	12:25	12:00	10:10	4:54	12:09	3:25	11:22
Time Injection Ant.	10:15	10:44	10:06		5:10	10:49	4:29	10:17	11:53	11:51	0:34	3:27	11:00	9:52	10:48	9:50	11:01	5:50	12:35	1:08	10:27	5:02	12:37	3:40	11:25
Time Return Resp.	11:15	12:55	12:00		5:15	11:00	4:46	10:35	12:20	12:07	:52	5:50	12:07	10:50	11:55	10:45	12:40	6:08	12:40	1:52	10:52	5:57	12:40	3:55½	11:45
Duration Resp. Paralysis	80	131	114		15	21	23	21	29	16	36	149	75	70	67	79	99	28	15	112	42	63	21	30	23
Duration after Ant.	60	131	114		5	11	17	18	27	16	37	143	67	58	67	54	99	18	5	20	15	65	3	15½	20
Pupillary Response to Paralysis	A	A	A		A	A	A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Conjunc. Reflex to Paralyzant	A	A	A		A	A	A		A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Forelimb Reflex Response to Paralyzant	A	A	A		A	A	A		A	A	A	NA	A	A	A	A	A	A	A	A	A	A	A	A	A
Normal Pulse	162	148	132			133	144	136	160	116	42	150	132	152	112	130	152	80	120	160	150	132	152		140
Pulse after Par.	128	124	102			120	116	132	128	100	40	144	116	102	88	100	132								
Pulse after Ant.	168	100	102			148	118	80	112	100	30	96	100	100	88	96	132	96							
Time Return Conj. Reflex	10:35	11:40	10:33			11:10	4:49	10:26		2:12	:41	3:52	11:20	10:52	11:15	10:02	—	6:10							
Time Return Pupillar Reflex							4:49			2:12															
Time Return Forelimb Reflex			10:44			11:15	5:00	10:34		2:45	0:40	4:03		10:35		10:36	11:54								
Time Return Consciousness	In Night	In Night	In Night		5:15	12:00	In Night	6:30		6:00	ight	Night	Night	Night	Night	Night	Night	Night							
Nature Restored Resp.	15 Poor	10	12 Good			28	84 Poor	12 Err.	18 Reg.	6 Poor	16 oor	16 Good	Poor	Poor	16 Poor	Poor	Poor	9 Reg	16 Poor	6 Poor	10 Good	16 Good	16 Good	14 Good	24 Good
Duration Prorated	80	131	114			21	24	21		16															
Fate of Animal	Re.	Re	Re.		Death	Re.	Re	Re.	Death	Death	Re	Re.	Re.	Re.	Re.	Re.	Re.	Re.	Re.	Death	Death	Re	Re.	Re.	Death
Notation					Congested Lungs						old dog													Barbital	
																								Awaes	

A - Abolished , NA - Not Abolished , Reg - Regular , R Recovered

novocaine was mixed with sodium thiocyanate there was observed the precipitation of what was presumably the free procaine base. It was always possible to dissolve the precipitated base,which formed at the zone of contact of thiocyanate crystals with the cisternal fluid containing dissolved novocaine,in excess of cisternal fluid.

XII. COMPARATIVE EXPERIMENTAL RESULTS

1. Comparison of the Efficacy of Novocaine and Sodium Amytal in the Production of Respiratory Paralysis in the Presence of Morphine-Sodium Amytal Anaesthesia

In four control experiments, numbers 53,88,132, and 134 involving cisternal doses of sodium amytal of 6.4, 6.2,6.3,and 6.3 mg. per kg. respectively,respiratory paralyses of 74,48,67, and 45 minutes respectively resulted. The average duration of paralysis is 58 minutes. In three control experiments, numbers 41,106, and 107,employing cisternal novocaine in doses of 6.3 mg. per kg.,respiratory paralyses of 50,55, and 74 minutes respectively resulted. The average duration is 59.6 minutes. Even in spite of the well authenticated antagonism existing between novocaine and sodium amytal there is little difference in time of duration between the two categories described.

Five experiments, numbers 49,138,144,145, and 148,employing cisternal sodium amytal in doses of 6.7, 6.4, 6.3 6.3 and 6.2 mg. per kg. followed or accompanied by cisternal ephedrine sulphate in doses of 2.7, 2.2, 2.0, 2.0, and 1.8 mg. per kg. respectively,yielded respiratory paralyses of 24, 0, 8, 0, and 13 minutes respectively. The durations after the injection of the ephedrine were 16, 0, 8, 0, and 13 minutes respectively. The average duration (total) was 9 minutes. The average duration after ephedrine was 7.4 minutes. Six experiments, numbers 45, 48, 108, 109, 113,

and 114 , employing doses of cisternal novocaine of 6.2, 6.2, 6.3, 6.2, 6.3, and 6.3 mg. per kg. respectively followed by cisternal doses of ephedrine sulphate of 3.1, 6.25, 3.1, 3.1, 2.9, and 3.1 mg. per kg. yielded respiratory paralyses lasting in the total 14, 16, 18, 18, 0, and 16 minutes respectively. The average duration is 13.7 minutes. The average duration after ephedrine is 10.3 minutes. If there are any significant conclusions manifested by these data, they are that novocaine is about as efficacious as sodium amytal in producing respiratory paralysis and that ephedrine antagonizes cisternal novocaine about as effectively as it does cisternal sodium amytal.

With maximum dosage the efficacy of novocaine to produce respiratory paralysis is apparently smaller than that of sodium amytal, providing that three experiments can validate the assumption. Control experiment, number 32, involving 17 mg. per kg. of cisternal novocaine caused a respiratory paralysis of 74 minutes whereas a sodium amytal experiment employing 8.8 mg. per kg. (number 54) caused a paralysis of 130 minutes. A similar control experiment, number 64, employing 8.[illegible] mg. per kg. of cisternal sodium amytal yielded a paralysis of 300 minutes. The animal receiving 8.8 mg. per kg. recovered while the one receiving 8 mg. per kg. succumbed.

With intravenous ephedrine sulphate as the analeptic the antagonism to cisternal novocaine is apparently great-

er than the antagonism to cisternal sodium amytal. In experiments 121, 130, 134, and 139 paralyses of 22, 210, 45, and 42 minutes respectively were produced by doses of 6.3, 6.0, 6.3, and 6.0 mg. per kg. respectively after medication with ephedrine sulphate in doses of 2.9, 1.8, 1.7, and 1.6 mg. per kg. respectively. These figures represent total durations. The durations after the injection of the analeptic were respectively 1, 195, 3, and 5 minutes. We are not forgetting that the injections of the analeptic were made quite late in the experiments. In the novocaine series are two experiments, numbers 111 and 112, employing cisternal doses of novocaine of 6.3 mg. per kg. followed by doses of ephedrine of 2.9 and 3.15 mg. per kg. which yielded total paralyses of 120 and 30 minutes. The intervals after the ephedrine were 114 and 30 minutes. These experiments are difficult of analysis but indicate an inferior type of antagonism of ephedrine intravenously. The potency against novocaine is apparently greater than that against sodium amytal.

The proration of the experimental results to some definite standard is, of course, a highly speculative procedure. In our tabulated protocols, Table 2, a column of prorated values is included in which the durations of respiratory paralysis are prorated to a hypothetical duration which would have been attained with 6.3 mg. per kg. if such a linear relation obtains.

When 8 control experiments employing cisternal sodium amytal are prorated to 6.3 mg. per kg. of the drug, assuming the linear relation of duration of paralysis to dosage, an average duration of 61 minutes is obtained. Similarly, proration of the durations in the novocaine experiments to 6.3 mg. per kg. of drug yields an average duration of 51 minutes. The results are not at great variance with the results already analyzed.

2. Results in the Presence of Ether Anaesthesia

The proration of six control experiments with ether as the anaesthetic and with sodium amytal in the prorated dose of 6.3 mg. per kg. (cisternally) yields an average duration of respiratory paralysis of 20.3 minutes. Four novocaine experiments with the same anaesthetic and similarly prorated yield an average duration of 15.7 minutes.

3. Conclusion Derived from this Section

The sense of these prorated results is that the paralysis from novocaine is less profound than that from sodium amytal under ether and sodium amytal anaesthesia. It must not be forgotten that variability in animals together with variability in experimental conditions may have been responsible for the results obtained in the highly speculative type of analysis just employed. If the proration does possess merit it indicates that the choice of dosage based upon body weight may not be inferior to the choice recommended by Cotui(23).

XIII. EXPERIMENTAL RESULTS OBTAINED ON THE SAME ANIMAL

In this series are collected the data obtained on the same animals. Such data constitute control results in the most absolute sense. Unfortunately, it was not always possible to achieve recovery after the production of the depressions necessary to the experimental procedure. Figure 6 gives graphic representation to the protocols. The legend for this figure is so extensive that it can not be reproduced contiguously to the figure. The tabulated protocols which follow will serve as legend for the figure.

1. Dog # 42 9 kg. female	Total duration	After analeptic
Exp. 89 morphine-ether anaesthesia 5.5 mg. per kg. sodium amytal in cistern	60 min	--
Exp. 92 morphine-ether anaesthesia 5.5 mg. per kg. sodium amytal mixed with 2.25 mg. per kg. ephedrine sul. cistern	0 min.	0 min.
Exp. 96 ether anaesthesia- 5.5 mg. per kg. sodium amytal mixed with 1.7 mg. per kg. ephedrine--cistern	0 min.	0 min.
Exp. 99 ether anaesthesia-5.5 mg. per kg. sodium amytal followed by 5.5 mg. per kg. ephedrine--cistern	20 min.	16 min.

These experiments indicate the ability of ephedrine to abbreviate the respiratory paralysis caused by cisternal sodium amytal. The prolonged duration of the control experiment hints at the ability of morphine to potentiate the depression of the cisternal sodium amytal.

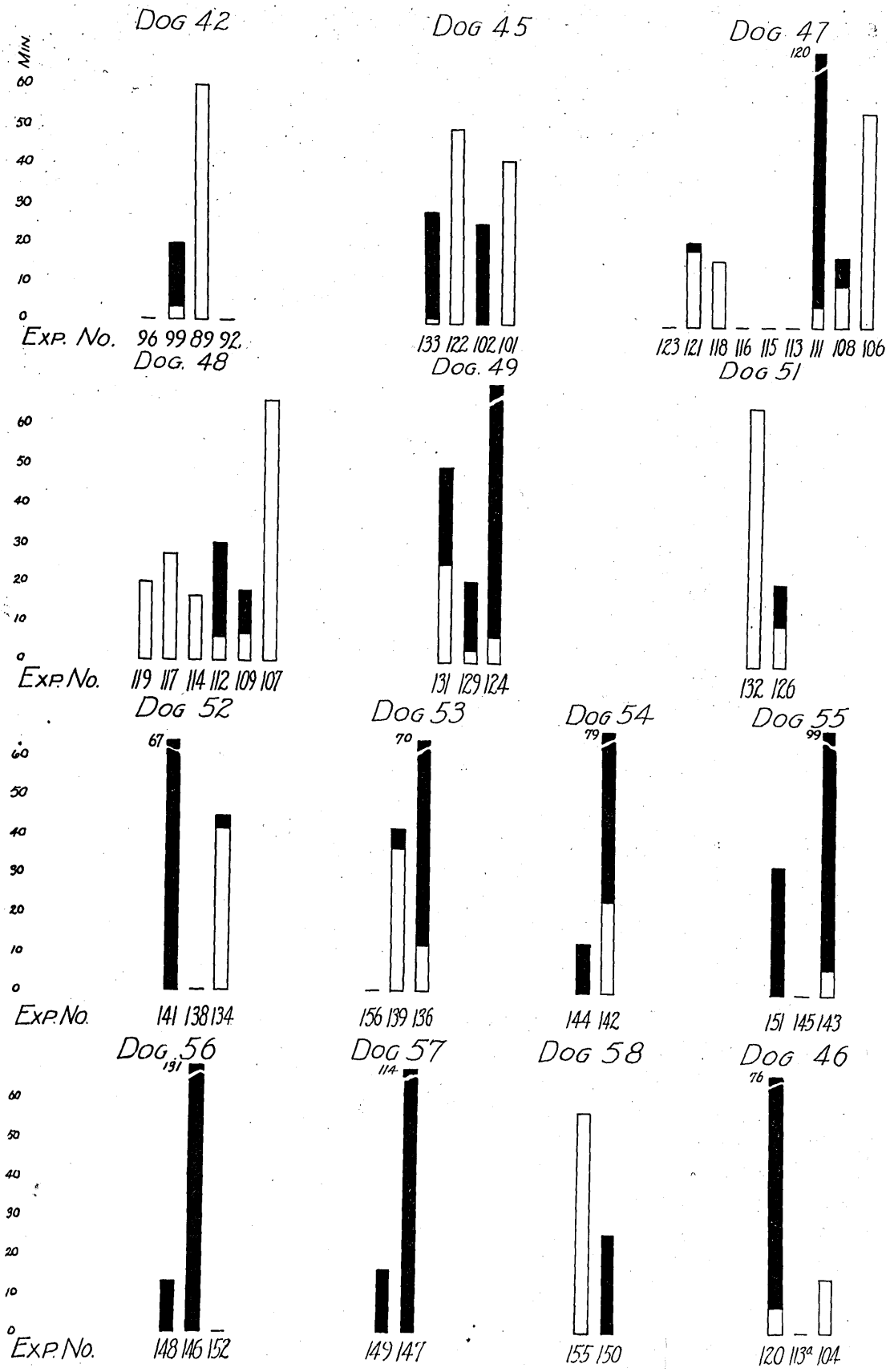

Dog 42
Min.
60
50
40
30
20
10
0
Exp. No. 96 99 89 92.
Dog 45
133 122 102 101
Dog 47
120
123 121 118 116 115 113 111 108 106
Dog. 48
60
50
40
30
20
10
0
Exp. No. 119 117 114 112 109 107
Dog. 49
131 129 124
Dog 51
132. 126
Dog 52
67
60
50
40
30
20
10
0
Exp. No. 141 138 134
Dog 53
70
156 139 136
Dog 54
79
144 142
Dog 55
99
151 145 143
Dog 56
131
60
50
40
30
20
10
0
Exp. No. 148 146 152
Dog 57
114
149 147
Dog 58
155 150
Dog 46
76
120 113a 104

Figure 6

2. Dog # 45 19 kg. female		Total duration	After analeptic
Exp. 133	morphine 4 mg. per kg. sodium amytal 30 mg. per kg. anaesthesia. 5.3 mg. per kg. sodium amytal followed by picrotoxin 0.031 mg. per kg.--cistern	29 min.	27 min.
Exp. 122	same anaes. as above-5.3 mg. per kg. novocaine--control	50 min.	--
Exp. 102	ether-atropine 1mg. anaesthesia- 5.3 mg. per kg. novocaine mixed with 1.31 mg. per kg. ephedrine--cistern	26 min.	26 min.
Exp. 101	atropine 1 mg.-ether anaesthesia--5.3 mg. per kg. novocaine--cistern--control	42 min.	--

These experiments indicate the sensitization of the centers to depression from novocaine by the preliminary use of morphine and sodium amytal for anaesthesia. Also they indicate the potency of ephedrine in combating the depressant effects of novocaine. Picrotoxin was given too late to lead to conclusions.

3. Dog # 46 8.7 kg. female			
Exp. 120	morphine 4 mg./kg. and sodium amytal 30 mg./kg. anaesthesia--5.7 mg./kg. novocaine followed by 2.8 mg./kg. ephedrine in vein	75 min.	69 min.
Exp. 113a	same anaes. as above-4 mg. per kg. morphine sulphate in cistern	0 min.	--
Exp. 104	atropine 1 mg. ether anaesthesia--5.7 mg. per kg. cisternal novocaine	14 min.	--

These experiments indicate the role morphine plays in sensitizing the centers to depression. Note the great-

er duration of paralysis after morphine-sodium amytal anaesthesia even with intervention with ephedrine than the duration in the presence of ether with no intervention.

4. Dog # 47 8.7 kg. male		Total duration	After analeptic
Exp. 123	ether anaesthesia-6.3 mg./kg. sodium amytal mixed with 2.9 mg. per kg. ephedrine-cistern	0 min.	0 min.
Exp. 121	morphine 4mg./kg. sodium amytal 30 mg./kg. anaes.-6.3 mg./kg. sodium amytal mixed with 2.9 mg./kg. ephed.-cistern	22 min.	2 min.
Exp. 118	ether anaesthesia--6.3 mg./kg. sodium amytal cistern control	17 min.	--
Exp. 116	atropine 1 mg. ether anaes. 6.3 mg./kg. novocaine cistern control	0 min.	---
Exp. 115	anaes. same as Exp. 121-- 2.9 mg./kg. ephedrine cistern	-----	-----
Exp. 113	anaes. same as Exp. 121,6.3 mg. per kg. novocaine mixed with 2.9 mg. per kg. ephedrine cistern	0 min.	0 min.
Exp. 111	anaes. same as exp. 121-- 6.3 mg./kg. novocaine cistern followed by 2.9 mg./kg. ephedrine in vein	120 min.	114 min.
Exp. 109	anaes. same as Exp. 121-- 6.3 mg. per kg. novocaine followed by 2.9 mg. per kg. ephedrine in cistern	18 min.	7 min.
Exp. 106	anaes. same as Exp. 121,6.3 mg. per kg. novocaine in cistern control	55 min.	---

These experiments indicate the greater potency of sodium amytal in producing respiratory depression than that of novocaine. The analeptic properties of ephedrine against respiratory depression produced by either is also clear.

Furthermore, the greater potency of ephedrine when it is mixed with the depressant than when it follows the depressant seems clear. No experiment designed as a control for cisternal sodium amytal is presented but one experiment in which the analeptic was given late serves as a control. This experiment shows the greater ease of producing depressions with cisternal sodium amytal when a pre-existing systemic morphine amytal depression exists than that when only an ether depression exists. We should say that such a result is predictable in terms of our earlier analyses.

The sensitization of the center to sodium amytal depression by preliminary morphine-sodium amytal has its counterpart in the depression of the center produced by novocaine cisternally. The comparative results embodied in the foregoing tabulations strongly indicate this fact.

Finally, the inferior potency of intravenous ephedrine when compared with cisternal is clearly shown by our well controlled data of the foregoing group.

5. Dog # 48	16 kg. male	Total duration	After analeptic
Exp. 119	atropine 1 mg. ether anaes. 6.25 mg./kg. sodium amytal cistern control	20 min.	-----
Exp. 117	atropine 1 mg. ether anaes. 6.25 mg./kg. novocaine cistern--control	27 min.	-----
Exp. 114	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes.- 6.25 mg./kg. novocaine mixed with 3.12 mg./kg. ephedrine sul. cisternal	16 min.	16 min.

5. concluded		Total Duration	After Analeptic
Exp. 112	same anaes. as exp. 114 6.25 mg./kg. novocaine cisternal followed by 3.12 mg./kg. ephedrine in vein	30 min.	24 min.
Exp. 109	same anaes. as exp. 114 6.25 mg./kg. cisternal novocaine followed by 3.12 mg. cisternal ephedrine sul. per kg.	18 min.	11 min.
Exp. 107	same anaes. as exp. 114 6.25 mg./kg. novocaine control cisternal	67 min.	-----

These results again indicate the part played by preliminary morphine-sodium amytal depression in establishing respiratory paralysis after cisternal novocaine. Nowhere else in our results is the superiority of cisternal ephedrine over intravenous ephedrine so clearly shown.

6. Dog # 49 8.9 kg. female			
Exp. 131	morphine sul. 4 mg./kg. sodium amytal 30 mg./kg. anaes.--6.3 mg./kg. cisternal sodium amytal followed by 28 mg./kg. cisternal coramine	50 min.	25 min.
Exp. 129	same anaes. as Exp. 131 6.3 mg./kg. cisternal sodium amytal followed by 0.033 mg./kg.cisternal picrotoxin	21 min.	18 min.
Exp. 124	same anaes. as Exp. 131 6.3 mg./kg. cisternal sodium amytal followed by 2.8 mg./kg cisternal cardiazole	139 min.	132 min.

These experiments show the superior potency of picrotoxin to that of either coramine or cardiazole in abbreviating the respiratory paralyses of cisternal sodium

amytal. The potency of both coramine and cardiazole is practically nil. Perhaps they actually synergize the effects of the cisternally exhibited depressant.

7. Dog # 51 12.8 kg. male		Total duration	After analeptic
Exp. 132	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. cisternal control 6.2 mg./kg. sodium amytal	67 min.	---
Exp. 126	same anaes. as Exp. 132 6.25 mg./kg. sodium amytal followed by 0.023 mg. per kg. cistern picrotoxin	21 min.	11 min.

These experiments indicate very strongly the analeptic potency of picrotoxin against the respiratory depression of cisternal sodium amytal.

8. Dog #52 11.4 kg. male			
Exp. 141	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. 6.4 mg./kg. sodium amytal mixed with 2.2 mg. per kg. cardiazole cistern	67 min.	67 min.
Exp. 138	same anaes. as foregoing 6.4 mg./kg. sodium amytal mixed with 2.2 mg./kg. ephedrine sul. cistern	0 min.	0 min.
Exp. 134	same anaes. as foregoing 6.4 mg./kg. sodium amytal in cistern followed by 2.2 mg./kg. ephed. sul. in vein	45 min.	3 min.

The last experiment was designed as a control but the condition of the animal necessitated the late administration of ephedrine by vein. It can serve as a control. These results bring out the superiority of ephedrine over cardiazole as an analeptic for respiratory depressions

produced by depressant drugs. Quite possibly cardiazole intensifies the depression.

9. Dog # 53 12.3 kg. male		Total duration	After analeptic
Exp. 156	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. 6 mg./kg. sodium amytal cisternal followed by 40 mg./kg. NaSCN in vein	never could breathe	
Exp. 139	same anaes as Exp. 156 6 mg./kg. sodium amytal in cistern followed by 1.6 mg./kg. ephed.sul. vein	42 min.	5 min.
Exp. 136	same anaes. as Exp. 156 6 mg./kg. sodium amytal in cistern followed by 8.1 mg./kg. cardiazole in cistern	70 min.	58 min.

The sense of these results is that cardiazole does not materially shorten the respiratory paralysis produced by cisternal sodium amytal. Even intravenous ephedrine, which we have shown to be poorly efficacious, is superior to cisternal cardiazole. There also exists the suspicion that cardiazole actually deepens the depression.

10. Dog # 54 12.3 kg. female			
Exp. 144	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. 6.3 mg./kg. sodium amytal mixed with 2.0 mg./kg., ephedrine in cistern	13 min.	13 min.
Exp. 142	same anaes. as foregoing 6.3 mg.per kg. sodium amytal mixed with 2 mg. per kg. cardiazole-cistern	79 min.	55 min.

These results are indicative of the superiority of ephedrine over cardiazole as a respiratory analeptic.

The suspicion still exists that cardiazole actually deepens the respiratory depression from sodium amytal.

		Total duration	After analeptic
11. Dog # 55	14.6 kg. male		
Exp. 151	morphine 2 mg./kg. ether anaes.--6.3 mg./kg. sodium amytal mixed with 2.0 mg./kg. ephedrine in cistern	33 min	33 min.
Exp. 145	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes.- 6.3 mg./kg. sodium amytal mixed with 2.0 mg./kg. of ephed. sul. in cistern	0 min.	0 min.
Exp. 143	same anaes. as Exp. 145 6.3 mg./kg. sodium amytal mixed with 2.0 mg./kg. cardiazole cistern	99 min.	92 min.

This series yields a longer duration after morphine ether anaesthesia than after morphine-sodium amytal anaesthesia in the presence of similar medication. This constitutes a dilemma which we shall not attempt to explain because there is no explanation at hand. The result with cardiazole is in harmony with our earlier findings that cardiazole does not assist in the abbreviation of respiratory depressions resulting from cisternal sodium amytal.

12. Dog # 56	13.6 kg. male*		
Exp. 148	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. 6.3 mg./kg. cisternal sodium amytal mixed with 1.9 mg./kg. ephedrine sul.	13 min.	13 min.
Exp. 146	same anaes. as foregoing 6.3 mg./kg. sodium amytal mixed with 19 mg./kg. coramine cisternally	131 min.	131 min.

The duration of respiratory paralysis after coramine

* Experiment # 152 was rejected

is ten times as long as the duration after ephedrine with the dosage of ephedrine one tenth as large as the dose of coramine. Results like these cause us to suspect that coramine also seems to deepen the depression of the respiration caused by cisternal barbiturate.

13. Dog # 57	9 kg. male	Total duration	After analeptic
Exp. 149	morphine 4 mg./kg. sodium amytal 30 mg./kg. anaes. 6.2 mg./kg. sodium amytal mixed with 0.055 mg./kg. picrotoxin in cistern	16 min.	16 min.
Exp. 147	same anaes. as foregoing 6.2 mg./kg. sodium amytal mixed with 27 mg./kg. coramine in cistern	114 min.	114 min.

Picrotoxin is manifestly a better analeptic than coramine which seems in this dosage and in the light of earlier results actually to potentiate the depression of cisternal sodium amytal.

14. Dog # 58	15.5 kg. male		
Exp. 155	morphine 2 mg./kg. ether anaes.-6.3 mg./kg. sodium amytal in cistern-control	57 min.	----
Exp. 150	same anaes. as foregoing 6.3 mg./kg. sodium amytal mixed with 2.3 mg./kg. ephedrine sulphate cisternal	25 min.	25 min.

Ephedrine is shown by these results to be antagonistic to the cisternal sodium amytal used to produce respiratory paralysis in the face of morphine-ether anaesthesia.

XIV. ACUTE EXPERIMENTS

1. Experiment # 10 April 23 1932 Dog # 5 12.5 kg. male

This experiment depicts the failure of respiration after subarachnoid novocaine at the lumbar level and its spontaneous return after a preliminary inadequate attempt to breathe. Only that portion of the tracing (Figure 7) showing the last two events is reproduced because the tracing is too lengthy for complete reproduction.

Anaesthesia was invoked by subcutaneous morphine sulphate, 4 mg./kg., and intravenous sodium amytal, 30 mg. per kg. The conjunctival reflex persisted after anaesthesia.

Novocaine in 5 % solution was introduced into the lumbar subarachnoid in a dose of 3.6 c.c. at 2:41 P.M. and a dose of 2.4 c.c. at 3:38 P.M. Respiratory paralysis unlike the characteristic paralysis after lumbar novocaine which first involves the intercostals and then the phrenics set in at 3:53 P.M. Accompanying it the initial carotid blood pressure of 108 m.m. of mercury fell to a level little above the zero mark without any preliminary asphyxial rise. Artificial respiration restored the blood pressure to 70 m.m. of mercury.

Subarachnoid NaSCN in 1 c.c. doses of 5% solution was injected into the subarachnoid lumbar space at 4:23 P.M., 4:24 P.M., 4:26 P.M., 4:30 P.M., and 4:36 P.M. The in-

jections were followed by slight increases in blood pressure preceded by small preliminary decreases. Pulse frequency was not materially modified. Intravenous NaSCN, 10 c.c. of 5% solution, was injected at 4:48 P.M. and 1 gm. of the same drug in 5 c.c. of saline at 4:59 P.M.

The lumbar subarachnoid method of exhibition involving as it does the necessity of diffusion to the central structures before the manifestation of the desired respiratory paralytic action, is manifestly unsuited to test in a quantitative sense either the ability to produce such paralysis or the ability to mitigate its severity. Cisternal exhibition produces immediate clear-cut quantitatively measurable results.

In the tracing (Figure 7) are shown three significant events. These events occurred very late in the experiment after the animal had been experiencing respiratory paralysis for at least two hours. At 5:45 P.M.(#32) artificial respiration was denied the animal to test its ability to breathe. There was a small fall in blood pressure which after a short plateau became very profound in spite of the return of a species of inadequate breathing. At 5:47 (#33) artificial respiration was supplied after which the blood pressure arose to a height fully 30 m.m. in excess of the levelled pressure prior to the denial of artificial respiration. At 5:50 P.M. the denial of artificial respiration provoked the return of spontaneous breathing

fully adequate for life (# 34).

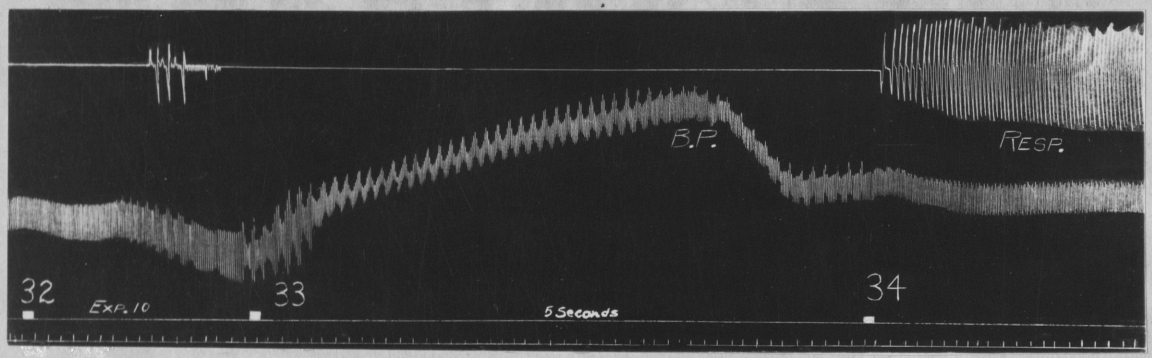


Figure 7 32. denial of artificial respiration 5:45 P.M., 33. reinstitution of artificial respiration 5:46 P.M., 34. denial of artificial respiration 5:50 P.M.

That the vasomotor tone was decreased by the lumbar injection of novocaine is apparent but it is equally apparent that there was a residue of functional adequacy in the vasomotor apparatus. However, it must be remembered that the blood pressure had previously experienced a gradual decline which appeared in those portions of the tracing which we were forced to delete. We believe that such a gradual decline always conduces to anoxaemic changes in the central structures in a cyclic sense because it is the consequence of gradual respiratory inadequacy, an inadequacy which seemed in this experiment to elude our observation. Much of the vasomotor impairment was probably the effect of intercostal insufficiency.

Whether the medullary factor in the respiratory paralysis obtained or whether NaSCN produced an analeptic effect on respiration depressed by novocaine cannot be answered by this type of experiment.

At 6:30 P.M. tremors involving the forelimbs and the neck were observed. They were easily abolished with ether in small quantity.

That the sub-dural space was entered and that the drug penetrated into the subarachnoid was evidenced by the early loss of tone of the anal sphincter after the injection of novocaine.

The animal was deliberately sacrificed at 7:00 P.M. after the maintenance for one hour of adequate respiration.

2. Experiment 27 July 23 1932 Dog # 16 male 10 kg.

Preliminary anaesthesia was induced by subcutaneous morphine sulphate, 4 mg./kg. at 2:00 P.M. and intravenous sodium amytal, 30 mg./kg. at 2:20 P.M. The spinal needle was introduced into the lumbar subarachnoid at 3:50 P.M.

The tracing is reproduced to show the gradual fall of blood pressure which accompanies the abolition of intercostal and,later,diaphragmatic breathing. (Figure 8) The tracing has been assembled in sections to give a serial picture of events.

At 4:28 P.M. (# 4) the decrease in respiratory frequency was compensated by an increase in amplitude probably sufficient to maintain the functional competency of the vasomotor system. After the onset of profound novocaine action the respiratory frequency again increased and the amplitude gradually decreased until extinction.

As might be expected there was no asphyxial rise in blood pressure when diaphragmatic breathing ceased because the vasomotor apparatus had already become gradually depressed by the anoxaemia consequent to the decreased respiratory minute-volume. The existence of the anoxaemia was evident from inspection of the cyanotic tongue periphery. The legend accompanying figure 8 supplies the events necessary to the interpretation of this experiment.

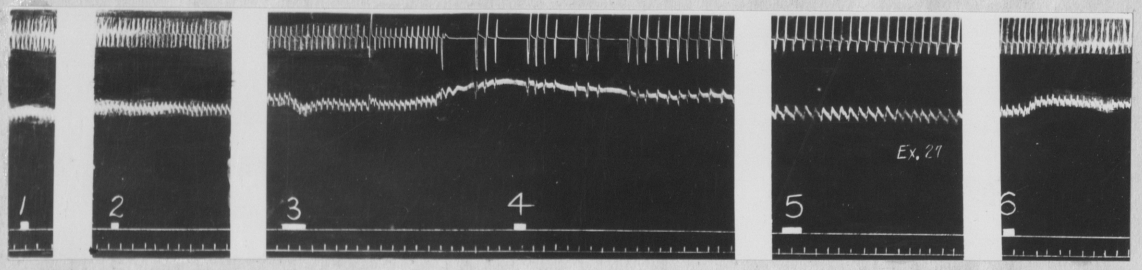
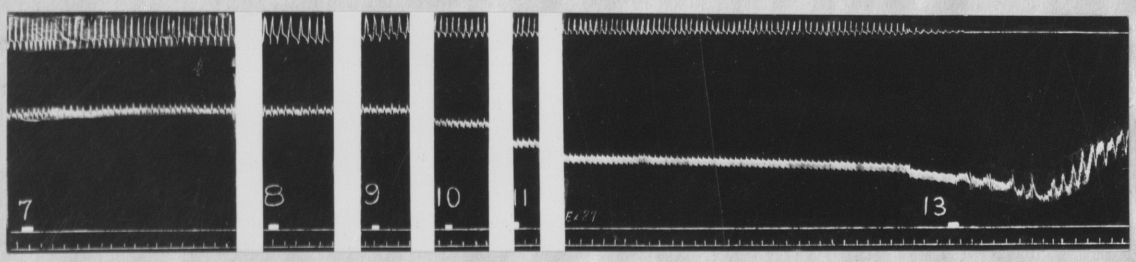


Figure 8 (1) 4:10 P.M. 2 c.c. 5% novocaine in subarach. (2) 4:14 P.M. 1 c.c. 5% novocaine in subarach. (3) 4:25 P.M. 2 c.c. 5% novocaine in subarach. (4) 4:28 P.M. removal of support from under belly (5) 4:36 P.M. 1 c.c. of 5% novocaine in subarach. (6) 4:38 P.M. replaced support under belly.



(7) 4:40 P.M. intercostal paralysis (8) 4:51 P.M. 1 c.c. 5% novocaine in subarach. (9) 4:56 P.M. 2 c.c. 5% novocaine in subarachnoid (10) 5:07 P.M. 2 c.c. of novocaine-5% in subarachnoid (11) 5:17 P.M. 2 c.c. 5% novocaine in subarach. (13) 5:32 total abolition of respiration

Shortly after # 13 artificial respiration was supplied and there was an immediate restoration of blood

pressure, inferior to be sure to normal, but not at all inadequate for life.

At 5:40 P.M. and at 5:50 P.M. 500 mg. of NaSCN respectively dissolved in about 7 c.c. of saline at each injection were introduced into the lumbar subarachnoid. At 6:23 P.M. 1000 mg. of the same drug dissolved in 7 c.c. of saline solution were introduced into the subarachnoid. At 6:27 P.M. spontaneous diaphragmatic breathing returned but artificial respiration was necessary to sustain life.

The animal died at 6:37 from combined circulatory and respiratory collapse which artificial respiration was unable to circumvent.

That the subarachnoid was entered was evidenced by the hind-limb jerk when the needle was introduced and by the ability to remove spinal fluid. However, this experiment, experiment # 10 and others not reported in this thesis convinced us of the capriciousness of lumbar puncture in the dog unless preceded by laminectomy. Furthermore, the total inadequacy of methods using divided doses of drugs for the production of measurable results was apparent.

3. Experiment 98 Feb. 25 1933 Dog # 33 female 8 kg.

Anaesthesia was induced at 7:40 P.M. by ether inhalation preceded by morphine sulphate subcutaneously, 4 mg. per kg. and atropine sulphate, 1 mg. subcutaneously. The tracing is unfortunately unsuitable for reproduction.

Sodium amytal was introduced into the cistern in the following broken doses: 9:45 P.M., 17.5 mg.; 9:47 P.M., 17.5 mg.; and 10:00 P.M., 35 mg. The first injection was followed by a slight rise in femoral blood pressure and a great decrease in respiratory amplitude. Respiration nearly ceased. However, within one minute respiration improved. Following the first slight rise there was, as respiration failed, a large asphyxial rise in blood pressure.

At 10:00 P.M. 35 mg. of sodium amytal were injected into the cistern and respiration still persisted. At this time the animal had received 60 mg. of sodium amytal, or 7 mg. per kg., a summated dose which in one injection cisternally has always produced respiratory paralysis. After the injection at 10:00 P.M. the expiratory phase was greatly enhanced and with the enhancement came a decrease of blood pressure from 150 m.m. to 90 m.m. of mercury. When the blood pressure had fallen to a compensated level the inspiratory phase of respiration returned after its temporary depletion.

The cisternal injection of 25 mg. of sodium amytal at 10:15 P.M. was followed by respiratory paralysis in about one minute with an attendant further decrease in blood pressure. In spite of a manifestly heavy etherization, blood pressure was slightly restored by artificial respiration.

The pulse frequency increased after the first injection

from 126 to 176 as a consequence, possibly, of central vagus depression or cardio-accelerator stimulation.

The improvement of respiration after the first injection of sodium amytal was probably due to the routine discontinuance of ether after the injection. The return of heavy etherization later in the experiment was followed by a pronounced decrease in blood pressure.

This experiment indicates the inadequacy of broken doses of depressants to produce pronounced effects when cisternally injected, even when the summated doses reach adequate levels for single injections.

This animal was purposely sacrificed at 10:30 P.M. It had previously experienced cistern taps but traumatic damage to the central structures was not disclosed by autopsy.

4. Experiment 99 March 4 1933 Dog # 42 female 9 kg.

Preliminary anaesthesia was induced by ether inhalation at 10:18 A.M. after 1 mg. atropine sulphate subcutaneously at 10:10 A.M. After the introduction into the cistern of sodium amytal, ether was discontinued. Early in the experiment the ether depression was carried to great depth.

The stabilized femoral blood pressure was 134 m.m. of mercury and the pulse frequency 168 per minute. In the early moments of etherization it was 210 per minute.

At 11:50 A.M. 50 mg. of sodium amytal were introduced into the cistern. In spite of the satisfactory injection,

paralysis of respiration failed to set in immediately. With the hope of preventing paralysis ephedrine sulphate, 50 mg. was injected into the cistern at 11:54 A.M. The tracing figure 9 betokens the approach of the paralysis before it was possible to introduce the ephedrine. To explain the fact that paralysis did occur after the injection of ephedrine one might invoke the explanations suggested by Wright (13) and Schmidt (14) who interpreted the respiratory depressant effects of ephedrine in terms of circulatory changes. The former ascribed the effects to the washing out of carbon dioxide from the central areas; the latter ascribed the effects to reflexes mediated by the carotid sinus. We have discussed these phenomena elsewhere at greater length. It is also quite possible that the analeptic effects of ephedrine are not easily expressed in the presence of deep ether. We have already demonstrated that deep ether inhibits the characteristic pressor effects of ephedrine.

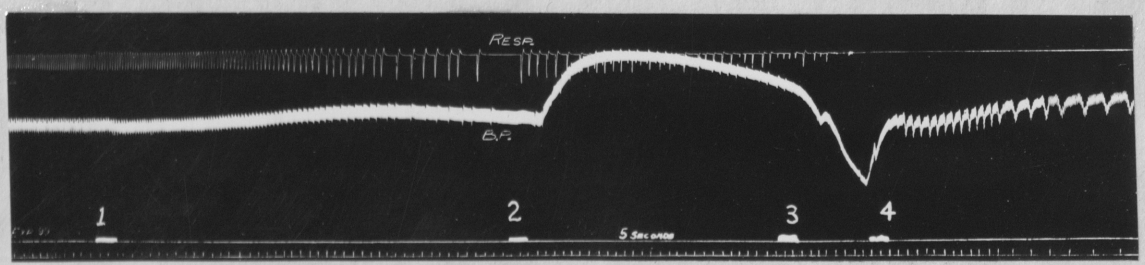


Figure 9 (1) 11:50 A.M. 50 mg. sodium amytal in cistern, (2) 11:54 A.M. 50 mg. ephedrine sulphate in cistern, (3) 11:59 A.M. adjustment of artificial respiration (4) 12:00 P.M. artificial respiration

The injection of ephedrine precluded the observation

of changes in vasomotor tone after the injection but before the injection of the ephedrine the respiratory changes produced by cisternal sodium amytal were accompanied by little if any impairment of vasomotor tone, a fact clearly demonstrated by the prompt asphyxial rise in blood pressure when respiration began to fail.

It has already been pointed out that the denial of artificial respiration for a period of one minute probably suffices to elicit spontaneous breathing provided the paralyzed structures have emerged adequately from depression. In this experiment the denial of artificial respiration for periods of one minute always produced a fall in blood pressure as a consequence, probably, of central anoxaemia. The asphyxial effects upon centers appear to fall, then, into two categories; those effects which are of short duration and which lead to asphyxial rise in blood pressure and those effects which are of longer duration and which lead only to a fall of blood pressure. The ease with which artificial respiration restores blood pressure after the termination of the periods of abeyance of artificial respiration argues, we believe, very strongly for the existence of very little impairment of vasomotor function by the cisternal injection of sodium amytal in reasonable doses.

Pulse frequency was increased about 9 per minute by the cisternal injection of sodium amytal, a phenomenon which

in this case can be explained by the difficulty of diffusion of the drug in the already traumatized cistern. We refer to the changes caused by excessive fibrotic responses by the limiting walls of the cistern rather than to consequential damage to the nervous structures. The animal had already experienced multiple taps.

The duration of respiratory paralysis until 12:40 P.M. is longer than the characteristic duration. Possibly the duration would have been shorter but experimental difficulties precluded the employment of the abeyance period in time to ascertain if the duration were a short one.

The animal was purposely killed with ether at the termination of the experiment and revealed no trauma to the nervous structures at autopsy.

5. Experiment 100 March 4 1933 Dog 45 Female 20.1 kg.

Ether anaesthesia was induced by inhalation at 8:40 A.M. after preliminary atropine sulphate, 1 mg. subcutaneously at 8:16 A.M. During etherization the blood pressure was 192 m.m. of mercury and the pulse frequency 200 per minute.

After the injection of 100 mg. of sodium amytal into the cistern at 9:52 A.M. respiration faded out in three minutes. The consequences of depression were manifested in gradually decreasing amplitude rather than in change in frequency. Both thoracic and diaphragmatic breathing stopped simultaneously. Concomitant with the abolition of

respiration was a prompt rise in blood pressure which persisted until respiration was definitely abolished, after which the blood pressure sharply decreased. At 9:55 A.M. artificial respiration was brought into play but the blood pressure did not reach its former height. If this were the only record available one might be led to suspect that vasomotor depression alone was responsible for the lowered blood pressure. However, since ether was suspended when sodium amytal was injected into the cistern the fall in blood pressure may have possibly been caused by the withdrawal of ether. After the cisternal injection of the sodium amytal the pulse frequency dropped to 185 per min. an effect more probably caused by the withdrawal of ether than to the effect of the barbiturate or most probably to the combined set of conditions.

After the injection of ephedrine sulphate, 35 mg., cisternally the blood pressure climbed to the 200 m.m. level and the pulse frequency to more than 200 per minute. These responses conduce strongly to the belief that both the vasomotor and the cardio-accelerator mechanisms were not significantly depressed or if they were that they were easily amenable to analepsis.

The deprivation of artificial respiration at 10:07 A.M. for a period of 40 seconds led to the return of spontaneous breathing after a total elapsed time of 15 minutes and 5 minutes after the exhibition of ephedrine. The durations

are in good accord with the results of other experiments.

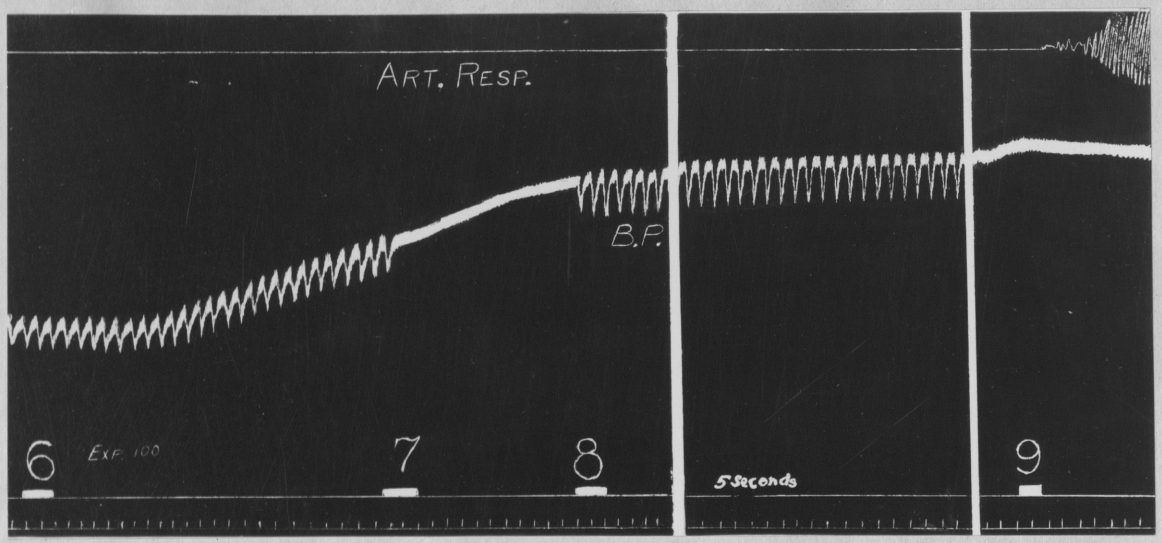


Figure 10 (6) 10:03 A.M. ephedrine sulphate, 35 mg., in cistern (7) 10:05 A.M. artificial respiration off (8) 10:06 A.M. artificial respiration on (9) artificial respiration off-breathed before lapse of 1 minute.

Since it was desired to save the animal the experiment was terminated at 10:20 A.M. and the femoral breach repaired. The animal made an eventless recovery and was used for subsequent experiments.

The results of this experiment point to the greater resistance to depression of the vasomotor center than that of either the respiratory or cardio-accelerator centers. All these centers react easily to ephedrine but the vasomotor centers most easily. That artificial respiration is capable of supporting the blood pressure during respiratory paralysis caused by cisternal sodium amytal would seem clear. This observation is in harmony with those of Isenberger (52) and of Seevers and Waters (27) who found oxygen-want the most devastating factor in the

crises arising in spinal anaesthesia.

6. Experiment 103 Mar. 18 1933 Dog 45a Female 20.1 kg.

Ether anaesthesia was induced by inhalation after the subcutaneous injection of 1 mg. atropine sulphate at 10:20 A.M. The animal was anaesthetized to the condition of sluggish conjunctival reflexes by 10: 45 A.M. Blood pressure under ether was stabilized at 130 m.m. of mercury.

The injection of 100 mg. of sodium amytal into the cistern at 11:52 produced respiratory paralysis in 55 seconds. Paralysis was preceded by diminution of both amplitude and frequency and the abolition of breathing was unaccompanied by an asphyxial rise in blood pressure.

After the cisternal injection ether was discontinued but the cisternal barbiturate produced an adequate narcosis. Even after the discontinuance of ether the blood pressure failed to return to its initial level in spite of adequate artificial respiration. The pulse frequency decreased from 200 to 180 per minute. Apparently a mild degree of vasomotor depression prevailed as well as an impairment of cardio-accelerator irritability.

The cisternal injection of 20 mg. of ephedrine sulphate at 12:08 P.M. was followed by an increase of blood pressure to 220 m.m. of mercury within four minutes. The prompt appearance of ephedrine action conduces strongly to the belief that at least a part of the effects of ephedrine are neurotropically rather than musculotropically produced.

The vasomotor response to ephedrine suggests strongly the existence of much residual central irritability.

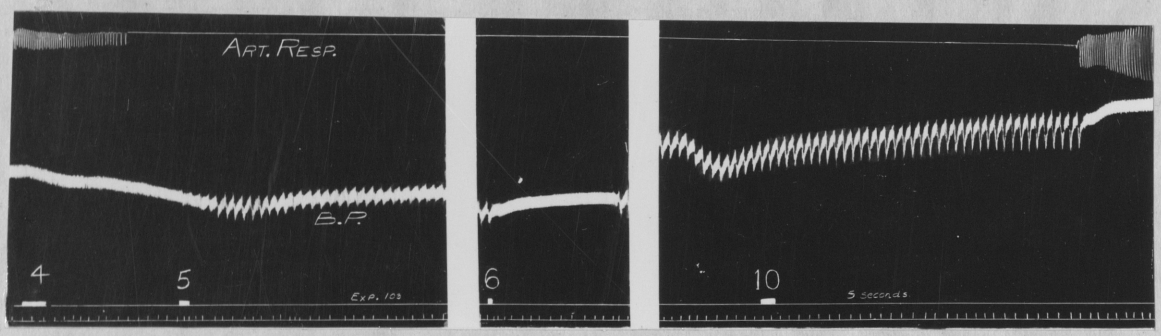


Figure 11 (4) 11:52 A.M. 105 mg. sodium amytal in cistern (5) 11:53 A.M. artificial respiration on (6) 11:59 A.M. (10) 20 mg. cisternal ephedrine sulphate

These results seem to be in harmony with our belief that neither the vasomotor nor the cardio-accelerator mechanism are as profoundly modified by cisternal depressants as is the respiratory center.

Spontaneous breathing returned at 12:12 P.M. while the animal was being respired. This result strengthens our conviction that the denial of artificial respiration for one minute intervals is sufficiently long to test the return of irritability to the respiratory center or centers.

As in the case of other experiments employing the cisternal exhibition of depressants the onset of respiratory paralysis was rapid and its degree profound. The results point sharply to the central nature of the paralysis. Either the respiratory center or the phrenic nuclei or both are probably involved in the depression.

The elevated blood pressure was well maintained until 12:44 P.M. at which time the experiment was terminated after the repair of the femoral breach. The animal was returned to its cage for further use but,unfortunately,succumbed during the night. At autopsy there was disclosed a wide-spread purulent broncho-pneumonia with hemothorax.

7. Experiment 105 Dog 45 male 20.1 kg. Mar. 25,1933

Ether anaesthesia was induced at 10:00 A.M. after preliminary atropine sulphate 1 mg. subcutaneously at 9:55 A.M. Blood pressure was 150 m.m. of mercury and pulse frequency was 210 per minute after stabilization of the anaesthesia. The respiration was 60 per minute and regular, rhythmical, and fairly deep.

Ephedrine sulphate was introduced into the cistern in doses of 15 mg. in 2 c.c. of cisternal fluid at each dose at 10:58 A.M., 11:12 A.M, 11:22 A.M., and 11:27 A.M. During the period of ephedrine exhibition there was no pressor effect, a fact which grows out of the deepness of the etherization.

At 11:30 A.M. the discontinuance of ether was followed by a substantial increase in blood pressure, an effect which we do not support with a reproduction of the tracing because of limitation of space.

After the removal of deep ether when an adequate blood pressure had been secured, novocaine, 100 mg., was injected into the cistern. The vehicle of exhibition was

2 c.c. of aspirated cisternal fluid. Fifty seconds after the injection of novocaine at 12:04½ P.M. there was complete cessation of respiration. Its abolition was preceded by a gradual decrease in amplitude of the respiratory excursions with no change in frequency. Concomitant with and after the depression of respiration there was a sharp increase in blood pressure accompanied by a drop in pulse frequency, a fact conducing strongly to the belief that the vasomotor apparatus is capable of withstanding the effects of depressants injected cisternally.

Artificial respiration instituted at 12:06 P.M. produced a level of blood pressure even higher than that attained during light ether.

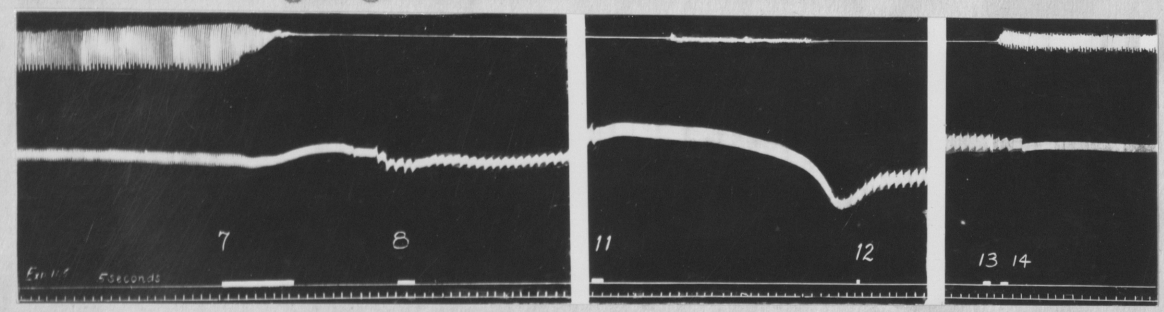


Figure 12 (7) 12:04½ P.M. 100 mg. novocaine cisternally (8) 12:06 P.M. artificial respiration (11) 12:15½ P.M. denial of artificial respiration (12) artificial respiration restored (13) 12:31½ P.M. stopped drum; spontaneous breathing returned at 12:32 P.M. in the face of artificial respiration (14) 12:32 P.M. spontaneous breathing

---

Feeble diaphragmatic movements appeared at 12:16 P.M. but they were not adequate for the preservation of life. Artificial respiration was again invoked and discontinued at 12:19 P.M. because the animal breathed in the presence

of the artificial respiration. Because this effort to breathe was also an abortive one, the animal was again respired artificially until 12:32 P.M. when adequate spontaneous breathing appeared, despite artificial ventilation. The short duration of respiratory paralysis, 11 minutes, suggests that ephedrine behaves prophylactically against novocaine depressions produced cisternally.

After repair of the femoral breach the animal was returned to its cage. Return to consciousness was exceedingly rapid and recovery was complete. The animal regained the ability to walk at 1:30 P.M.

8. Experiment 121, May 20 1933 Dog 47 male 8.7 kg.

Preliminary anaesthesia was produced by morphine sulphate, 4 mg. per kg. subcutaneously, at 9:05 A.M. followed by sodium amytal, 30 mg. per kg.,intravenously, at 9:16 A.M. Following anaesthesia, blood pressure was stabilized at 120 m.m. of mercury with a pulse frequency of 182 per minute.

At 10:37 A.M. sodium amytal, 55 mg., was injected into the cistern in a 2 c.c. aliquot of cisternal fluid. Within 50 seconds breathing was abolished. Coincident with the paralysis blood pressure fell 30 m.m. of mercury and pulse frequency fell from 182 to 132 per minute. There was no preliminary asphyxial rise. Apparently the summated doses of systemic and cisternal sodium amytal consituted a depressant threat to the irritability of the vasomotor

centers.

During the periods when artificial respiration was denied, the blood pressure fell to even lower levels but the re-institution of artificial assistance sufficed to restore it to its former comparatively low level.

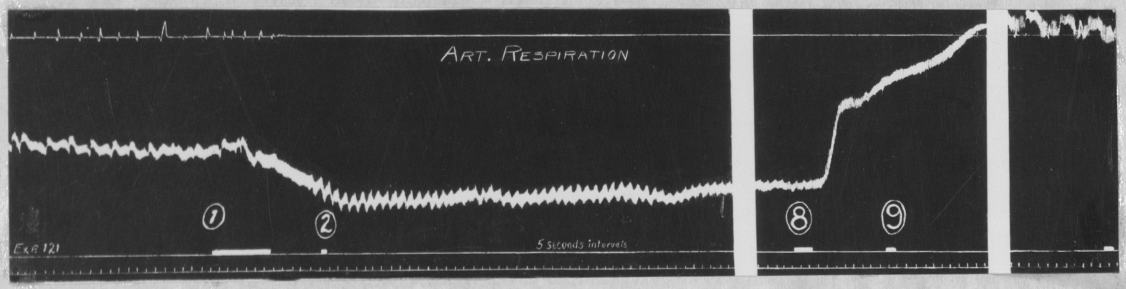


Figure 13 (1) 10:37 A.M. 55 mg. sodium amytal in cistern (2) 10:38 A.M. artificial respiration on (8) 10:58 A.M. ephedrine sulphate, 25 mg., in cistern (9) 10:59 A.M. artificial respiration off.

The injection of 25 mg. of ephedrine sulphate into the cistern at 10:58 A.M. was followed by an enormous increase in blood pressure and by the return of the spontaneous ability to breathe, in 2 minutes. Coincident with these physiological changes was an increase in pulse frequency from about 128 per minute to 180 per minute.

The total duration of respiratory paralysis was in this experiment only 23 minutes and its duration after ephedrine only 2 minutes. These figures harmonize with those earlier obtained for novocaine followed by ephedrine.

This animal made an eventless recovery after the repair to the femoral breach.

An analysis of the results of this experiment con-

duce very pointedly to the view that either the tone of the vasomotor apparatus is little impaired in a fundamental sense or that the analeptic properties of ephedrine with respect to this apparatus are as great as or greater than those with respect to the respiration.

9. Experiment 173, Sept. 23 1933, Dog 64 female 11.6 kg.

Anaesthesia was induced by subcutaneous morphine sulphate, 4 mg. per kg., at 11:01 A.M. followed by sodium amytal, 30 mg. per kg. intravenously, at 11:13 A.M. Blood pressure was stabilized at 106 m.m. of mercury with pulse frequency of 134 per minute. The heart-beat was regular and forceful.

At 12:10 P.M. novocaine, 6.3 mg. per kg., dissolved in 3 c.c. of cisternal fluid, was injected into the cistern. Respiration was abolished within one and one half minutes after the injection. Immediately after the injection the blood pressure arose to 134 m.m. of mercury. After the rise,the blood pressure began to fall at 12:11 P.M. and in 1 minute reached the 60 m.m. level from which it was quickly restored to 135 m.m. of mercury by the aid of artificial respiration. The pulse frequency increased to 160 per minute but it attained a count of 200 per minute during the short asphyxial rise. The increase in pulse frequency is not characteristic for this type of exhibition of novocaine.

The adequacy of the circulatory system was not main-

tained because at 12:30 P.M. the blood pressure had fallen to 62 m.m. of mercury at which low level it remained until the injection of ephedrine, 2.8 mg. per kg., into the cistern. The response to ephedrine was slowly manifested but it was asserted by a level of blood pressure of 128 m.m. of mercury at 12:45 P.M.

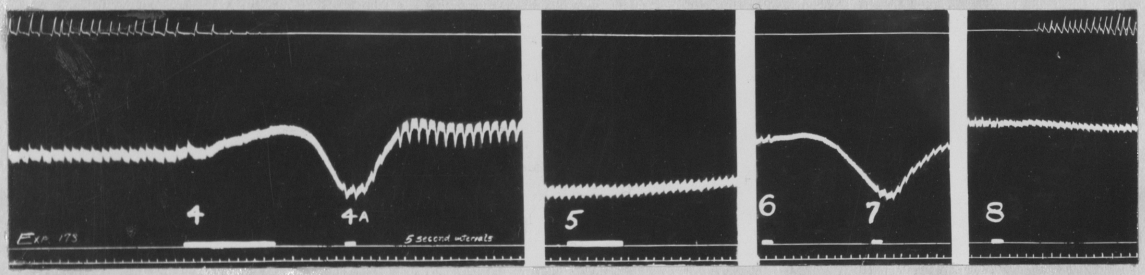


Figure 14 (4) 12:10 P.M. cisternal novocaine, 73 mg. (4a) artificial respiration on 12:12 P.M. (5) 12:36 P.M., ephedrine sulphate cisternally, 33 mg. (6) 12:44 P.M. artificial respiration off(7) 12:45½ P.M. artificial respiration on (8) artificial respiration off; return of adequate spontaneous respiration.

The denial of artificial respiration at 12:44 failed to elicit spontaneous breathing and provoked a sharp fall in blood pressure. A subsequent denial at 12:48 elicited adequate spontaneous breathing in 30 seconds.

The total duration of respiratory paralysis was 38 minutes and its duration after ephedrine was 12 minutes. These durations are long compared with other similar experiments.

This experiment,like other similar experiments, indicates the far-reaching effects of asphyxia on centers whose irritability has been impaired by depressants. That this is true is evidenced by the absence of any asphyxial rise

in blood pressure when artificial respiration was denied after the complete development of the effect of cisternal novocaine.

At 12:50 the experiment was terminated and the femoral breach repaired. Consciousness returned at 2:00 P.M. The animal made an eventless recovery.

XV. A POSSIBLE SYNERGISM BETWEEN EPHEDRINE AND NOVOCAINE

The study of respiratory paralysis produced by cisternal novocaine and the abbreviation of that paralysis led, in incidental fashion, to the conviction that there is, in addition to the antagonism between ephedrine and novocaine, a synergism between these drugs which finds expression in the reversal of sodium amytal anaesthesia even when the anaesthesia is fortified by preliminary morphine action. The conviction would be stronger if the qualitative observations supporting it were buttressed by convincing quantitative evidence. The qualitative evidence consists of the exceptionally good psychic orientation and integration of dogs awakened from morphine-sodium amytal anaesthesia by the cisternal injection of ephedrine and novocaine combined. The purposive behaviour of these dogs was in every case much superior to that of dogs awakened by cisternal ephedrine alone after the same anaesthesia.

The quantitative measurements of the phenomena produced results which were not only equivocal but even damaging to the opinion provoked by the qualitative observations. In the table which follows shortly, the essential data from eleven experiments are adduced. In these experiments the dose of novocaine was in each case 2.8 mg. per kg. In the experiments leading to the impressive qualitative observations the dose was generally at least twice this dose. These latter experiments were not projected

to study the return of consciousness but rather for the specific purpose of measuring analepsis of respiration. The data derived from this group of experiments are not considered meritorious of critical analysis in a quantitative sense.

Duration of Anaesthesia after the Cisternal Injection of Ephedrine Sulphate and Novocaine Combined.

Exp. Number	Time from onset of anaesthesia to consciousness	Time from injection of analeptic to consciousness	Dose Novocaine mg./kg.	Dose Ephedrine in mg./kg.
Dog 62				
167	229 minutes	----	control	control
169	70 "	70 minutes	2.8	2.8
171	94 "	77 "	--	2.8
172	58 "	37 "	6.3	2.8
Dog 63				
168	420 "	----	control	control
163	26 "	9 "	--	2.8
165	53	43 "	2.8	2.8
Dog 64				
170	145 "	----	control	control
166	25 "	5 "	--	2.8
164	136 "	118 "	2.8	2.8

The sense of these data is that ephedrine alone is responsible for the speed of recovery from the barbiturate narcosis.

The study of possible synergism between novocaine and ephedrine is being reserved until we shall have gained sufficient skill in the interpretation of the data derived from the observation of changes produced in the labyrinthine reflexes to justify their employment. We are convinced that the observation of these reflexes furnishes the most impressive approach to an analysis of the prob-

lem of the reversal of anaesthesia.

It is not improbable that some local anaesthetic possessing marked cortical action is more suitable for combination with ephedrine to produce the reversal of barbiturate anaesthesia. Perhaps some quinoline derivative such as nupercaine will be found to have the proper delirifacient properties combined with a resistance to detoxication. Cocaine would offer the proper degree of cortical stimulation but it is probably as easily detoxicated as novocaine.

XVI. SUMMARY AND ACKNOWLEDGMENT

The expedient of describing this study in separate chapters has obviated the necessity of a lengthy summary. However, it would seem desirable to reiterate in condensed form the purposes of this study and to describe compactly the measure of success in their achievement.

The most fundamental proposition tested in this study is the question of the antagonism between ephedrine and sodium amytal. The existence of this antagonism has been assumed by certain investigators without the preliminary acquisition of impressive data and has been obscured by others who studied the activity of ephedrine as an antidote to barbiturate poisoning. That the antagonism exists , particularly in the case of respiratory depression produced by sodium amytal, has been demonstrated in this study.

The equally important antagonism between ephedrine and novocaine has likewise been demonstrated by our experiments. Its existence has not been seriously questioned but its physiological interpretation has , we believe, been misdirected. Respiratory analepsis by ephedrine, in cases of grave depression produced by the cisternal injection of novocaine, seems to deserve strong emphasis.

Concomitant with the study of drug antagonism there has been sought an estimate of the utility of cisternal exhibition of drugs for the express purpose of pharmacodynamic experimentation. The conviction that this utility exists has

steadily grown.

Although this study has dealt more fully with the analeptic properties of ephedrine, it has also attempted,in a briefer sense, to demonstrate any analeptic properties of coramine, cardiazole, picrotoxin, and sodium thiocyanate. Only picrotoxin seems to possess any usefulness when cisternally injected.

The use of dogs rather than rabbits, although the former are quite expensive, has seemed to lead nearer to the pharmacodynamic construction of meaning which must be sought in evaluating the reactions of drugs destined for human administration.

Throughout the investigation the writer has worked under the most favorable conditions of guidance and co-operation. To Dr. R. M. Isenberger and to Dr. O. O. Stoland the writer expresses his gratitude for unfailing kindness and unstinted patience. To Mr. M. C. Carroll, of the Department of Pharmacology, the writer owes a vast debt of gratitude, both for hearty co-operation and for the added benefit of Mr. Carroll 's broad experience in animal experimentation.

XVII. CONCLUSIONS

1. The cisternal exhibition of drugs constitutes an excellent method for the study of pharmacodynamics.

2. Ephedrine sulphate, especially when cisternally injected, exerts an antagonism to the depressant actions of sodium amytal and of novocaine, when the latter are cisternally administered.

3. The respiratory analeptic properties of ephedrine sulphate are superior to those of picrotoxin in that they are manifested without the accompanying danger of convulsions.

4. The respiratory depressant properties of cisternally injected sodium amytal and novocaine are enhanced by preliminary morphine or sodium amytal medication or by a combination of both.

5. Depressions adequately profound to terminate breathing do not nullify completely the intrinsic irritability of the vasomotor apparatus even when the depressants, sodium amytal and novocaine, come into close contact with its central regulators after cisternal injection.

6. Neither coramine nor cardiazole, in the doses used, when cisternally injected, are capable of abbreviating respiratory paralyses produced by the cisternal injection of sodium amytal. Indeed, they may actually prolong the duration of such paralyses.

7. Sodium thiocyanate has not proved either safe or effective as an antagonist to sodium amytal.

8. The central neurotropic phase of ephedrine's pressor action has been demonstrated.

9. Adequate artificial respiration alone seems essential to the maintenance of life during respiratory paralyses produced by the cisternal injection of sodium amytal or of novocaine.

10. A dose of 6.3 mg. per kg. of sodium amytal or of novocaine is safely adequate to arrest respiration in dogs when the drugs are cisternally injected. A dose of ephedrine sulphate of 2.8 mg. per kg. is effective as an antagonistic stimulant and is not at all hazardous.

11. The repeated periodic cisternal injection of drugs in dogs is a feasible procedure accompanied by slight danger of meningeal infection.

12. The cisternal injection of ephedrine in the event of grave barbiturate poisoning merits thoughtful consideration because that mode of exhibition offers quick access to vital centers even after both circulation and respiration have become profoundly depressed.

Bibliography

1. Sollmann, Torald — A Manual of Pharmacology, third edition, W.B. Saunders Philadelphia 1930

2. Bastedo, Walter A. — Materia Medica, Pharmacology, Therapeutics and Prescription Writing, W.B. Saunders, Philadelphia 1932

3. Dorland, W.A.N. — The American Illustrated Medical Dictionary, W.B.Saunders,Philadelphia, 1927

4. Webster, Noah — Webster's New International Dictionary of the English Language, G.& C Merriam, Springfield, Mass., 1925

5. Magnus, R. — Die Körperstellung, J. Springer, Berlin, 1924

6. Eddy, N.B. — Studies on Hypnotics of the Barbituric Acid Series, J. Pharmacol. 33, 43-68 (1928)

7. LeRiche, R. — De Quelques Faits utiles a connaitre pour la pratique de L'anaesthésie Rachidienne, Presse med. 15, 1-3 (1928)

8. Gesell, R. — The Chemical Regulation of Respiration, Physiol. Rev. 5, p.551(1925)

9. Haldane,J.S. and Priestley, J.C. — The Regulation of the Lung Ventilation, J. Physiol. 32, 225-266(1905)

10. Warburg, O. — Über die Oxydationen in Lebenden Zellen nach Versuchen am Seeigelei, Z. Physiol.Chem. 16,305-340 (1910)

11. Loeb,J. and Wasteneys, H. — Is Narcosis due to Asphyxia? J.Biol. Chem. 14, 517-529 (1913)

12. Winterstein, H. — Der Einfluss der Narkose auf den Gaswechsel des Frosch Rückenmarks, Biochem. Z. 61, 81-101 (1914)

13. Schmidt, C.F. — The Action of Adrenalin on the Respiratory Center with Remarks upon the Treatment of Severe Depression, J.Pharmacol.35,297-311 (1929)

14. Wright, S. — Action of Adrenalin and Related Substances on Respiration, J. Physiol. 69,493-499 (1930)

15. Weed, L. H. — The Cerebrospinal Fluid, Physiol. Rev.2, 171-203 (1922)

16. Weed, L. H. — Studies on Cerebrospinal Fluid, J. Med. Research 31, 21-119(1914)

17. Frazier,C. and Peet, M. M. — Factors of Influence in the Origin and Circulation of the Cerebrospinal Fluid, Am.J. Physiol. 25, 268-282 (1914)

18. Cotui, F. W. and Standard, S. — Experimental Studies on Subarachnoid Anaesthesia I. Paralysis of Vital Medullary Centers, Surg., Gynecol.,Obstet.55,290-297(1932)

19. Riquier, C.C. and Ferraro, A. — The Circulation of the Cerebrospinal fluid from the Standpoint of Intraventricular and Intraspinal Therapy, J. Ment. and Nerv. Dis. 64, 561-580 (1926)

20. Flexner, L. B. Clark, J. H. and Weed, L. H. — The Elasticity of the Dural Sac, Am. J. Physiol. 101, p.292 (1932)

21. Cushing, H. — Third Circulation and its Channels, Lancet 2, 851-857 (1925)

22. Dandy, W. and Blackfan, K. — An Experimental and Clinical Study of Internal Hydrocephalus, J. Am. Med. Assoc. 61, 2216-2217 (1913)

23. Cotui, F. W. — The Intracisternal Minimum Lethal Dose of Procaine Hydrochloride in Dogs, J. Pharmacol. 48, 223-228 (1933)

24. Jonnesco, T. — Remarks on General Spinal Anaesthesia, Brit. Med. J. 2, 1396-1401 (1909)

25. Bower, J. O., Clark, J. Waggoner, G., and Burns, J. C. — Spinal Anaesthesia-A Summary of Clinical and Experimental Investigations with Practical Deductions, Surg., Gynecol., Obstet. 54, 882-897 (1932)

26. Ferguson, L. K. and North, J. P. — Observations on Experimental Spinal Anaesthesia, Surg. Gynecol. Obstet. 54, 621-634(1932)

27. Seevers, M. H. and Waters, R. M. — Respiratory and Circulatory Changes during Spinal Anaesthesia, J. Am. Med. Assoc. 99,961-968 (1932)

28. Koster, H. and Kasman, L. P. — Spinal Anaesthesia for the Head, Neck, and Thorax, Surg. Gynecol. Obstet. 49, 617-630 (1929)

29. Westenhofer, M. — Zur Geschichte der Okzipitalinzision and Punktion, Munch. Med. Wochschr. 71, p.1687 (1924)

30. Camus, J. — Paralysie Experimentale des Centres Respiratoires, Comptes rend. soc. biol. 74, 761-764 (1913)

31. Janossy, J. — Über die Wirkung des intrazisternose verabreichter Lobelins, Med. Klin. 21, 1009-1010(1925)

32. Jonnesco, T. and Jiano, A. — L'Anaesthésie générale par injection intrarachidienne-II Congress de la Societe Inter. de Chirurgie Brit. Med. J. 2, 1396-1401 (1919)

33. Bloch, R., Camus, J. and Hertz, A. — Rachistovainisation et Rachisyncainisation experimentales; leurs accidents, les moyens d'y remedies, Comptes rend. soc.biol. 85, 297-299 (1921)

34. Camus, J. — Paralysie Experimentale des Centres respiratoires, Comptes rend. soc. biol. 74,761-764(1913)

35. Vehrs, G. R. — Heart Beat and Respiration in Total Novocaine Anaesthesia, Northwest Medicine 30, 256-260 and 322-330 (1931)

36. Cotui, F. W. — The Effect of different Narcotics and Narcotic Combinations on the Minimum Lethal Dose of Procaine Hydrochloride Cisternally, J. Pharmacol 48, 228-233 (1933)

37. Plaut, F. — Zur Zisternpunktion beim Kaninchen, Klin. Wochschr. 8, p. 976 (1929)

38. Bastedo, W. A. — Materia Medica, Pharmacology, Therapeutics and Prescription Writing, p. 432, W.B.Saunders, Philadelphia (1932)

39. Schoen, R. — Beiträge zur Pharmakologie der Korperstellung und der Labyrinthreflexe, Arch. exp. Path. Pharmakol. 113, 275-304 (1926)

40. Keeser, J. — Beitrag zur pharmakologischen Wirkung der Barbitursäurederivate, Pernocton und Somnifen; Schmerz, Narkose, Anaesthesie 2, 260-265 (1929)

41. Rising, M. Shroyer, J.H. and Stieglitz, J. — Chemical Studies of the Mechanism of the Hypnosis induced by the Hypnotics. I. The Synthesis of Colored Derivatives of Phenobarbital, J. Am. Chem. Soc. 55, 2817-2820 (1933)

42. Leulier, A. and Postic, F. — Influence de la Nitration et de l'amination sur les proprietes physiques de la methyl phenyl malonyl urea (rutonal) et de l'ethyl phenyl malonyl urea (gardenal) ou luminal, Comptes rend. soc. biol. 26, 1476-1478 (1931)

43. Page, I. H. — Isoamyl ethyl barbituric acid; an anaesthetic without influence on blood sugar regulation. J. Lab. Clin. Med. 9, 194-196 (1923)

44. Johnson, C.A., Luckhardt, A.M., and Lighthill, J. — Control of Barbital Anaesthesia and Poisoning by Diuresis, J. Am. Med. Assoc. 95, p. 576 (1930)

45. Gower, W. E. and Tatum, A. L. — Diuresis and Individual Tolerance in Experimental Barbital Poisoning, J.Pharmacol. 37, 481-492 (1929)

46. Marx, Hellmut — The Effect of Isoamylethyl Barbit-Uric Acid on the Excretion of Water, J. Pharmacol. 41,483-490(1931)

47. Eddy, N. B. — The Excretion of Diethyl Barbituric Acid on the Excretion of Water, J. Pharmacol. 37,273-282 (1929)

48. Gower, W. E. and Van de Erne, J. — Recovery from Experimental Barbital Poisoning under Various Types of Fluid Administration J. Pharmacol.48, 141-147 (1933)

49. Munch, J. — Bioassays, a Handbook of Quantitative Pharmacology, Williams and Wilkins, Baltimore (1931)

50. Koppen, M. — Pikrotoxin und Coriamyrtin als Kollapsmittel, Arch. exp. Path. u. Pharmacol. 29, 327-352 (1892)

51. Maloney, A. H. Fitch,R.H. and Tatum, A.L. — Picrotoxin as an Antidote in Acute Poisoning by the Shorter Acting Barbiturates, J. Pharmacol. 41, 465-482 (1931)

52. Isenberger, R.M. — Pharmacological Action of Sodium Amytal, Am.J. Surg. N.S. 9, 35-54, (1930)

53. Bloch, R. Camus, J. and Hertz, A. — Rachistovainisation et Rachisyncainization experimentales; leurs accidents, les moyens d'y remedier, Comptes rend. soc. biol. 85, 297-299 (1921)

54. Airila, Y. — Über die Einwirkung die verschiedenen Erregungsmittel der Grosshirnrinde auf den Chloralhydratschlaf, Arch. Intern. Pharmacodynamie 23, 453 (1913)

55. Morita, S. — Die Einwirkung zentraler Erregungsmittel auf den Chloralschlaf, Arch. exp. Path. Pharmacol. 78,218 (1915)

56. Doyle, J. B.and Daniels, L. — Symptomatic Treatment for Narcolepsy, J. Am. Med. Assoc.96,p.1371(1931)

57. Ockerblad, N. F. and Dillon, T. G. — The Use of Ephedrine in Spinal Anaesthesia, J. Am.Med.Assoc. 88, 1135-1136 (1927)

58. Chen, K. K. - — Variations in Blood Pressures on Repeated Administration of l and dl Ephedrines, J. Pharmacol. 33, 219-235 (1928)

59. Calton, G. S. — Effect of Ephedrine upon Blood Lactic Acid and Respiratory Metabolism in Man. Proc. Soc. Exp. Biol. Med. 29, 854-856 (1932)

60. Raginsky, R. B. and Bourne, W. — The Action of Ephedrine in Avertin Anaesthesia, J. Pharmacol. 43,209-218 (1931)

61. Moritsch, P. — Über die Wirkung von Weckmitteln auf die Basisnarkose, Arch. exp. Path. Phar. 168, 248-273 (1932)

62. Collins, H. A. — Ephedrine in the Treatment of Narcolepsy, Ann. Intern. Med. 5,1289-1295 (1932)

63. Tartler, O. P. — Über den Antagonismus und Synergismus zwischen einiger Analepticis und Medinal, Arch. exp. Path. Pharmacol. 143, 1-14 (1929)

64. Merck and Co., — Merck's Index, Rahway, N. J. (1930)

65. Barbour, H. G. and Hjort, A. M. — The Action of Ethylene Diamine J. Lab. Clin. Med.5,3-15 (1920)

66. Hahn, H. and Taeger, H. — Methodisches zur Hautblasenerzeugung, Klin. Wochschr. 10, 489-491 (1931)

67. Zerfas, L.G. McCallum, J. T. Shonle, H. A. Swanson, E. C.,Scott J. P. and Clowes, G. H. A. — Induction of Anaesthesia in Man by Intravenous Injection of Sodium Iso-Amyl Ethyl Barbiturate, Proc. Soc. Exp.Biol. 26, 399, (1929)

68. Sisson, Septimus — The Anatomy of the Domestic Animals, W. B. Saunders, Philadelphia,(1927)

69. Pick, E. P. — Schlaf und Schlafzentrum, J. Springer Vienna (1927)

70. Tilney, F. and Riley, H. A. — The Form and Function of the Central Nervous System, Paul B. Hoeber, New York, (1923)

71. Hatcher, R. A. Eggleston, C. — Novocaine, J. Pharmacol. 8, 385-405 (1916)

72. Hofvendahl, A. — Die Bekämpfung der Cocainvergiftung in Tierversuch, Biochem. Z. 117, 55-66, (1921)

73. Guttmann, M. R. — Acute Cocaine Intoxication, Prophylaxis and Treatment with Phenobarbital, J. Am. Med. Assoc. 90, p.1753 (1928)

74. Tatum, A. L., Atkinson, A. J. and Collins, K.H. — Acute Cocaine Poisoning; its Prophylaxis and Treatment in Laboratory Animals, J. Pharmacol. 26, 325-335 (1925)

75. Morita, S. — Untersuchungen an groshirnlosen Kaninchen, Arch. exp. Path. Pharmacol. 78, 208-217 (1914)

76. Knowfel, P. K. Herwick, R.P. and Loevenhart, A.S. — Prevention of Acute Intoxication from Certain Local Anaesthetics, J. Pharmacol. 33, p.265 (1928)

77. Buchmann, E.T. and Richter, C.P. — Abolition of Bulbocapnine Catatonia by Cocaine, Arch. Neur. Psychiatry 29, 499-503 (1933)

78. Hamet, R. — Über den Antagonismus zwischen Kokain und Ephedrin, Arch. exp. Path. Pharmacol. 160, 1-8 (1931)

79. Hill, E.F. and MacDonald, A.D. — Observations on Experimental Spinal Anaesthesia, J. Pharmacol. 47, 151-162 (1933)

80. Soupault, R. — Dissociation des centres bulbaires par la novocaine chez l'homme, Presse Med. 31, p.379 (1923)

81. Camp, W.J.R. — The Pharmacology of Cardiazole, J. Pharmacol. 33, 81-92 (1928)

82. Chen, K.K. and Poth, E.J. — Ephedrine as a Mydriatic in Caucasians, Am. J. Med. Sciences 178, 203-209 (1929)

83. Killian, H. — Coramin als Antidot bei Vergiftungen durch Narcotica und Hypnotica, Klin. Wochschr. 12,192-197 (1933)

84. Gremels, H. — Über die Kreislaufwirkung einiger neuerer Analeptika, Arch. exp. Path. Pharmacol. 153,36-49 (1930)

85. Braams, G. — Wirkung des Coramins auf die Avertinnarkose des Kaninchens, Klin. Wochschr. 12,69-70 (1933)

86. Heppner, E. — Die willkürliche Unterbrechung der pernocton mit coramine, Arch. exp. Path. Pharmacol.79,2077-2078 (1932)

87. Zunz,E. and Tremonti, P. — Recherches sur l'action de la coramine et du pentamethylene tetrazole sur la respiration, Arch. Intern. Pharmacodynamie, 41,1-22 (1931)

88. Kohlhoff, H. — Experimentelle Untersuchungen uber Coramin, Arch.exp.Path.Pharmacol. 136, 331-348 (1928)

89. Uhlmann, Fr. — Über Calcio-coramin, Arch. exp. Path Pharmacol. 168, 515-520 (1932)

90.Niedermoser, F. — Kollapsprophylaxe mit Coramin bei Narkose, Munch.Med.Wochschr. 79, p. 520 (1932)

91. Maloney, A.H. and Tatum,A.L. — Cardiazole(metrazole, and Coramine as Cardio-respiratory Stimulants, Arch.Intern. Pharmacodynamie,42 200-211 (1932)

92. Schmidt,K.F. Hildebrand,F., and Krehl, U. — Über Cardiazol, ein in wasseriger Lösung subcutan injizierbares neues Analepticum, Klin. Wochschr. 4, 1678-1680 (1925)

93. Stross, W. — Untersuchungen über die Wirkungsweise einiger Analeptika, Arch. exp. Path. Pharmacol. 113, 275-304 (1926)

94. Asher, L. — Untersuchungen über Coramin und Cardiazole, Z. ges. exp. med. 102, 197-213 (1926)

95. Barker,M.H. and — Cardiazole-Some Experimental Effects

Levine, S.A. — of this Drug on the Cardio-respiratory Mechanism, Arch. Internal Med. 42, 14-22 (1928)

96. Ruef, H. — Über klinische Erfahrungen mit Cardiazol, Klin. Wochschr. 35, 1680-1681 (1925)

97. Buding, E. S. — Zur Systematik des Cardiazols, Arch. exp. Path. Pharmacol. 157, 143-148 (1930)

98. Burgi,E. and Gordonoff, T. — Über die kombierte Anwendung der Digitalis Preparäte mit den campherähnlich Substanzen, Coramin, Cardiazol, und Hexeton, Klin. Wochschr. 7, 2098-2099 (1928)

99. Maloney,A.H. and Tatum, A. L. — Cardiazole (Metrazole) and Coramine as Cardio-respiratory Stimulants, Arch. Int. Pharmacodynamie, 42, 200-211 (1932)

100. David,J.C. and Vareed, C. — Some Observations on the Pharmacology of Cardiazole, Indian J. Med. Sci. 16, 920-924 (1929)

101. Watt, J. M. — The Action of Cardiazole on the Cardiovascular System, J. Med. Assoc. S. Africa 4, 36-39 (1930)

102. Bancroft,W.D.and Rutzler, J. E. — The Colloid Chemistry of the Nervous Systems. I. Sodium Thiocyanate Therapy, J. Physical Chem. 35, 1185-1211 (1931)

103. Bernard, Claude — Lecons sur l'anaesthésie et sur l'asphyxie, J. B. Balliere, Paris, (1875)

104. Bancroft, W.D.and Richter, G. H. — Claude Bernard's Theory of Narcosis, Proc. Nat. Acad. Sci. 16, 573-577 (1930)

105. Henderson,V.E. and Lucas,G.H.W. — Claude Bernard's Theory of Narcosis, J. Pharmacol. 44, 253-267 (1932)

106. Bodansky, M. — The Conversion of Cyanide into Thiocyanate in Man and in Alkaline Solutions of Cystine, J. Pharmacol. 37, 463-474 (1929)

107. Lang, H.B. and Paterson, J.A. — A Preliminary Report on Functional Psychoses, Proc. Nat. Acad. Sci. 17, 597-601 (1931)

108. Bancroft, W. D. and Rutzler, J.W. — Reversible Coagulation in Living Tissue, Proc. Nat. Acad. Sci. VIII , 17, 597-601 (1931)

109. Editorial Staff J.Am. Med.Assoc. — Current Comment, J. Am. Med. Assoc. 99,p.2270 (1932)

110. Tatum, A. L. — Personal Comment