

SOME PHYSIOLOGICAL RESPONSES
OF DOGS TO ARECOLINE

Thesis for the Degree of M. S.
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Humberto Ruiz Urbina
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THESIS

This is to certify that the

thesis entitled

SOME PHYSIOLOGICAL RESPONSES OF DOGS
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presented by

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FOREWORD

In the course of his investigations concerning the action of a drug on the living organism, the initial efforts of the pharmacologist is usually confined to qualitative observations. It is only when the drug shows promise of becoming a pharmacodynamic tool of clinical or experimental value that the emphasis is extended further to include the much more difficult studies on quantitative effects. Oftentimes, such data become conclusive only when supplemented by results from data accumulated through clinical usage over extended periods of time.

Veterinary pharmacodynamic research has never been able to compete with allied activities in the human field. As a consequence it has become customary to borrow basic data when applicable. Furthermore, the decentralized nature of applied veterinary medicine makes it difficult to conduct adequate and proper clinical trials with drugs both new and old. As a consequence of these conditions, the status of drugs of purely veterinary interest continues to remain obscure. The alkaloid arecoline is a typical example of such an agent. A review of the literature indicates a disproportionately meager knowledge concerning the pharmacology of this drug particularly as it applies to the use of the compound in veterinary medicine. The drug is employed by veterinarians to accomplish the single objective of rapidly emptying the lower digestive tract, serving as a so-called rapid purgative principally in horses and for the mechanical removal of tapeworms in small

animals. That it fails of its purpose in many instances is common knowledge to every clinician that has ever used this drug. It was, therefore, not surprising that the appearance of arecoline in the form of nemural (Winthrop) was eagerly greeted by many practitioners and subjected to clinical trial with the variable results not unusual in this method of investigation. No results from organized investigation concerning nemural have ever come to the attention of the veterinary profession. The purpose of this effort is an attempt to shed further light on the action of arecoline in dogs and to compare this action with that of nemural.

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I REVIEW OF LITERATURE

Arecoline is a liquid alkaloid present in the fruit of *Areca catechu*, a tree that belongs to the family of palm indigenous to the tropical countries of the far East. Betel nut, the fruit of the *Areca* plant, was known to the Chinese for its properties as a taenicide as early as the sixth century (18). It has been also used by people of the Malaya area for many ages; the natives used to chew the powdered nut because it was thought to sweeten the breath and improve digestion.

In 1888, Jahns (23) succeeded in isolating several alkaloids from the fruit of the *Areca* palm. These alkaloids are: arecoline, 0.07 to 0.1 percent, along with traces of arecaidine, arecaine, choline and guvacine. Fluckinger (16) found that *Areca* seeds also contain about 15 percent of a vegetable tannin and about 14 percent fat.

Immediately after the isolation of arecoline, Marmé 1890 (32) investigated the actions of the pure alkaloid. He experimented with it in human subjects and in such animals as dogs, cats, rabbits, chickens, pigeons, etc. He compared the action of arecoline in these animals and also made a comparison with the action of pelletierine, which has a similar chemical constitution, as well as with the action of muscarine and pilocarpine.

Marmé showed that solutions as weak as 0.04 percent causes a burning sensation with hyperemia when applied to the

tongue, and if one drop of such a solution be placed in the eye, it causes miosis reducing the pupil after a few minutes to $1/3$ of the normal size. This miosis persists for about one hour and disappears completely after one to one and a half hours. With strong concentration (one percent) in the eyes of rabbits, he found that after one to two minutes, there occurred ptialism, temporary slowing of the heart and emptying of the bowels.

Working with frogs and using arecoline by subcutaneous injection, he observed changes in the heart beat and respiration. Doses of 3 to 5 mgm. injected subcutaneously in male frogs caused a gradual decrease in heart rate until the heart stopped in diastole. Respirations were irregular and dyspnoeic.

Moderate doses given by stomach tube caused in dogs and cats repeated emesis, then foamy stools followed by feces of soft consistency and finally liquid. In small doses, the results were continuous defecations only.

Working with arecoline intravenously on dogs, cats and rabbits, he found that the effect on vagus endings was similar to those of muscarine. With large doses in the same species under artificial respiration and with the heart exposed, he observed an initial transient stoppage of both ventricles. This was succeeded by weak contractions of the right ventricle while the left one remained in systolic arrest. As a result of these observations, Marmé states that the action of arecoline upon the musculature of the left ventricle is similar to that described by Kobert (26) after

large doses of muscarine.

Marme' also noted that arecoline like pelletierine develops paralytic effects upon the brain and causes, like pelletierine and also pilocarpine, an increase in spinal reflexes up to the degree of developing tetanus. He also states that arecoline after absorption acts similarly to muscarine and pilocarpine upon the glands. It increases the secretion of the salivary glands and spastic contractions of the gut, while it influences the sweat secretion much less than does pilocarpine.

Leepin 1891 (28) conducted experiments in dogs and cats and concludes that fairly large doses of arecoline when given to these animals causes an increase in the relative hemoglobin content of the blood due to the loss of water by way of the salivary glands and the gut. He also describes an increase in the movements of the gut after the oral administration of arecoline.

Frohner 1894 (17) reported clinical results from the use of arecoline on one cow and four horses. He concludes that arecoline produces effects upon the muscular and glandular structures of the gut as well as vagus and respiratory effects similar to pilocarpine and eserine. The respiratory effects were evident only with large doses. He compares the action of this alkaloid with that of others and concludes that arecoline hydrobromide is an excellent sialagogue much better than pilocarpine. It causes salivation after 5 minutes following subcutaneous injection which reaches a maximum in 1/2 hour and lasts for one hour. As a laxative, he

states it is superior to eserine and pilocarpine either alone or in combination but causes great dehydration.

Graefe 1894 (19) gives some clinical reports on the use of arecoline hydrobromide in intestinal disturbances of large domestic animals. When given subcutaneously (0.08 gm. in 10 cc. of distilled water) to horses, the symptoms were increased salivary secretion and increased expulsion of intestinal contents. The animals became restless and showed increased barborygmus and peristaltic movements of the gut; sweating was profuse. The surface of the body became warm, respiration increased, and pulse decreased. After one and one half hours, most of the symptoms observed were abating.

Lavagna 1895 (27) investigated the miotic action of arecoline hydrobromide by instillation into the normal human eye. One drop of one percent solution placed into the lower conjunctival sac causes a feeling of warmth locally followed by lacrimation and spasm of the eye lids. The local irritation lasts only one minute. It causes hyperemia and after two minutes is followed by diminution of the pupil size. He concluded that arecoline has a more marked effect on the pupil than pilocarpine, but somewhat less than physostigmine.

Plesch in 1895 (45) conducted experiments concerning the action of arecoline on dogs, white mice, and pigeons, in an attempt to show that this alkaloid belongs in the class with B-piperidin. He gave special attention to the saliva inciting action, the action on the respiratory nerves and

its narcotic and cramping actions.

Coenders 1904 (8) using arecoline hydrobromide in experiments on mice showed that the alkaloid salt has a definite stimulant action upon intestinal peristalsis and does not seem to have any cumulative effect. He also concludes that arecoline results in a temporary stimulation of the respiratory center with death usually being caused by paralysis of the heart.

Milks 1906 (36) experimented on several dogs to ascertain the effects of arecoline hydrobromide in different doses. On a fox terrier of 18 pounds, 1/2 gr. of arecoline hydrobromide injected subcutaneously resulted in the following symptoms: in three minutes, the dog was dull and weak. He was thrown into convulsions at each attempt to move. In a short time, he was quiet, lying upon his side; his breathing was irregular; the pupils were dilated; the bowels moved in fifteen minutes and again in one and a half hours.

Another dog weighing about 25 pounds received subcutaneously on four successive days doses of 1/20, 1/5, 1/10 and 1 grain. The dog was, apparently, as well as ever the day following the injection of the 1 grain dose. Three days later, 2 gr. were injected and were followed by toxic symptoms with blood appearing in the feces. After 6 days, the dog, apparently, recovered. Two weeks from the beginning of the experiments, 3 gr. were injected during the afternoon and the dog died the following forenoon.

He also experimented on several kittens and found that doses of 1/8 to 1/2 grain were toxic with the following

symptoms: passage of feces in about three minutes; signs of illusions; running about the cage with tail bristled and spitting at imaginary objects; pupils were dilated; lay upon its side in eight to ten minutes. Soon the respiration ceased but the heart did not stop until one or two minutes later.

To further study the cardiac effects, he performed experiments upon the horse and the frog. In the case of the former, intravenous injections were used and a blood pressure tracing made. In each case, a very rapid fall in blood pressure occurred. In the case of the frog, a minim of the solution was dropped upon the heart. It was found that a 1 percent solution would stop the heart within one beat and more permanently than stimulation of the vagus. Solutions of 0.1 percent acted nearly as strongly as the 1 percent.

He concluded that arecoline is a rapid intestinal evacuant, increasing both peristalsis and the secretion and that its action is accompanied by colic symptoms and profuse salivation. Also, its action upon the eye is twofold; locally being miotic and internally a mydriatic. The chief dangers in its use are its action upon the heart and respiration.

Fish 1907 (15) conducted experiments on five horses testing the action of arecoline hydrobromide upon the circulatory system. He obtained blood pressure tracings from horses under chloroform anesthesia following the intravenous and hypodermic injection of the drug. The doses used were 0.1 mg., 0.05 mg., 0.19 mg., 0.1 mg. and 0.1 mg.

respectively per kgm. of body weight. He concluded that in all five cases, there was a uniform lowering of blood pressure and slowing of the heart rate. Other symptoms seen were profuse salivation, increased sweating and in some cases increased venosity of the blood. Atropine sulfate in the same dose and administered in the same manner as arecoline hydrobromide counteracted its actions upon the circulatory system as shown by the more rapid beat of the heart and an increase in blood pressure.

Meier 1907 (33) working with frogs, turtles and rabbits reported the action of arecoline upon the heart, blood pressure and respiration. He concludes that when given in large doses this alkaloid causes paralysis preceded by convulsions, decreased heart rate and a fall in blood pressure. The drug may kill by stopping the heart but appears to be without influence upon respiration. He adds that atropine, to a certain degree, counteracts the action of arecoline, and that nicotine, pilocarpine and arecoline have the same type of action; nicotine acting more upon the central nervous system; pilocarpine upon the peripheral, with arecoline occupying a midway position.

Patz 1910 (43) using Magnus method (31) worked on isolated intestine of cats in order to study the action of arecoline on the automatic movements of the gut. He found that in the isolated gut, arecoline (1 to 80,000,000) increases rhythmic movements of the smooth muscle. This concentration caused little or no increase in tonus, but a dilution of 1 to 20,000,000 produces a maximum tonus increase.

Jackson 1914 (22) studied the action of certain drugs on the bronchioles and he states that if about one-eighth of a milligram of arecoline hydrobromide is injected intravenously into a cat or medium sized dog, a most profound bronchoconstriction is produced immediately. He also states that the action is very much more marked than that of pilocarpine and death might easily follow from the absolute failure of air to enter the lungs. Injection of epinephrine will promptly cause dilatation of the bronchioles when constricted by arecoline. Also a minute dose of atropine or hyoscine hydrobromide will cause relaxation and will prevent a later injection of arecoline in any sized dose from causing constriction. In comparing the action of arecoline and pilocarpine on the bronchioles, he concludes that with arecoline the constriction comes on quickly but tends to disappear early while with pilocarpine, the constriction comes on more slowly but tends to persist for a considerable time.

Hall and Shillinger 1923 (21) tested arecoline hydrobromide as an anthelmintic in dogs and birds. They gave the drug in tablets per os and hypodermically. The authors concluded that arecoline hydrobromide in therapeutic doses is an efficient anthelmintic and purgative. It will sometimes remove all the tapeworms from dogs and will do this in the majority of cases (4 out of 7 cases in experiments). In therapeutic doses, it will sometimes fail to remove any tapeworms from dogs, but this will happen, probably, in a

minority of cases (3 out of 7 cases in their experiments). In excessive doses (1.5 to 2 gr.), it may remove all the tapeworms present or as little as 37.5 percent; conceivably, it might fail to remove any under certain conditions. They also state that arecoline hydrobromide may sometimes fail in practice as well as in experiments. It causes depression, emesis and catharsis, but animals recover rather promptly from its effects.

Ross 1924 (47) conducted clinical experiments on dogs in an effort to demonstrate the possible value of arecoline hydrobromide as an anthelmintic. He observed the effect of arecoline given in watery solutions per os and states that arecoline administered by mouth in aqueous solution is effective in bringing about purgation in from twenty minutes to one hour, and does not appear to cause any untoward after effects. A dosage rate ranging from a minimum of 1/16 gr., in the case of dogs from 5 to 10 pounds in weight, up to a maximum of 1/2 gr. for dogs over 30 pounds appears to be quite safe. It was also found that in some cases, dogs showed a tendency to vomit soon after administration, but this was not general. He also states that due to the rapidity of the action of the drug and the cessation of this action after the passage of the stool, it would appear that little, if any, is absorbed, its action being due to direct stimulation of the nerve endings in the gut wall. This being the case, it was probable that the dilution in which arecoline is given might have a marked effect, apart from any variation in the dose, in causing more or less marked

increase of peristalsis, and so increasing or lessening the time taken to induce purgation. It is possible that beyond a certain dilution, no manifest reaction might be observed. Experiments on seven dogs showed the following results: dilution of 1 to 2000 does not appear to be effective in bringing about purgation rapidly; dilution 1 to 1000 produced purgation in from twenty to forty-five minutes. The production of vomition is not very definitely shown to depend on the dilution at which the drug is given, though it probably has some relation to it. One dog vomited in seven minutes when given a dilution of 1 to 2000, another dog after five minutes with a dilution of 1 to 1000; another dog vomited after nine minutes with a dilution of 1 to 1000 and after three minutes with dilution of 1 to 500 while another dog did not vomit even when given a dilution of 1 to 120.

Dale 1930 (9) performed some experiments on the rabbit heart before and after section of the A-V (atrio-ventricular) bundle. With the A-V bundle intact, injection of 0.001 mg. of arecoline is followed by a slowing of heart rate, accompanied by a diminution in the amplitude of the auricular and the ventricular contractions. After section of the A-V bundle, a dose of 0.01 mg. will inhibit the auricular contractions almost completely, while the ventricular rate is slightly diminished.

In experiments on cows, Amadon 1930 (3) observed that half-grain doses of arecoline used in the initial experiments caused complete depression of rumino-reticular movements for intervals ranging from forty to fifty minutes, with

no apparent improvement in motility succeeding this action. In further experiments with reduced doses of the drug, it was discovered that no depression appeared with administration of less than 1/4 gr. and that very pronounced stimulant action resulted from doses as small as 1/16 gr. and 1/8 gr. The improvement in the strength of the rumen and reticular contractions appeared in five to twelve minutes and persisted for one and one half hours. The reticulum was more strongly affected than the rumen.

Schwarte and Dukes 1931 (48) in a series of studies on the effect of drugs on the cardiovascular system of the pig showed that arecoline hydrobromide, in doses ranging from 1 to 5 mg. in four different animals produced in each instance a decided fall in blood pressure. This was accompanied by cardiac depression as shown by membrane manometer records. The fall in blood pressure varied from approximately 20 to 50 percent of normal. There was, however, only a slight correlation between the size of the dose and the magnitude of the fall in blood pressure. The action of arecoline on the pig is similar to its action on other animals. In doses of 4 to 5 mg. increased salivation and pronounced muscular tremors were observed.

Epstein 1932 (12) conducted experiments on the responses of the batrachian alimentary canal (*Xenopus laevis*, the South African clawed toad) to autonomic drug and showed that arecoline causes contraction of every portion of the alimentary canal of *X. laevis*, and that atropine can antagonize this effect. It was shown also that pilocarpine fails to

produce a definite measurable rise in tone of the ileum, but arecoline on the other hand was usually able to cause contraction of this structure. Arecoline thus appears to have a more powerful effect on motor parasympathetic nerve endings.

In a dissertation of Tierarztliche Hochschule in Berlin 1933 (51) concerning the action of arecoline base and of the hydrobromide on the isolated small intestine of dogs, changes in tone, pendulum motion, and volume are described. The drug shows prompt effects including an increased tone, greater amplitude of contractions and greater variations in intestinal volume with rhythm remaining practically unchanged. These effects were the results of pure local diffusion of the drug from the intestinal lumen and could be checked with atropine.

Kristinn Stefanson 1937 (50) studied the action of arecoline on the intestine of guinea pigs and concluded that arecoline increases peristalsis and tone of the small and large intestines, and restores to normal the decreased activity after morphine.

Kadonaga 1938 (24) reported that arecoline hydrochloride injected into the dorsal lymph sac of the frog caused paralysis sometimes preceded by convulsive attacks; the M.L.D. was 0.005 gm. per 10 gm. body weight. The drug inhibited the isolated frog's heart, decreased blood pressure in rabbits chiefly by slowing the heart, while large doses accelerated respiration.

Richter 1939 (46) concludes from his work on isolated

intestine of the guinea pig, that arecoline lowers irritability of the intestinal musculature resembling nicotine. Atropine counteracts the muscular action of arecoline.

Mentova 1940 (34) in a series of studies on the effects of parasympathetic drugs upon the coronary vessels reports that arecoline has a vaso-constrictor effect when given in large doses although it acts as a vaso-dilator in small doses. These experiments were performed on isolated rabbit hearts. The author concludes that the dilator effect is parasympathetic, as evidenced by its absence in the atropinized heart.

Oppenheimer and Mann 1941 (40) reported experiments studying the influence of cathartics on the activity of the small intestine. By means of balloons in thirty-wella loops they tested arecoline hydrobromide, administered by stomach tube to eight dogs in doses of 1/10 to 1/2 gr. (0.006 to 0.032 gm.). In all cases, tonus curves were marked and amplitude of segmenting contractions was increased. Although the increase in amplitude was sometimes more than threefold, the rate remained fixed (± 1 per minute) when compared with the control period. They comment that none of the agents studied changed the rate of contraction of the small intestine and also give other references concluding that in the intact small intestine, with nerve and blood supply intact, this rate is not easily altered.

Nemural*, marketed by the Winthrop Chemical Company in tablet of 18 mg. appeared in 1939** as a substitute for arecoline as a vermifugal agent against tapeworm in small animals. According to the laboratory data on this new compound obtained from the manufacturer, nemural tablets contain two ingredients, i. e., a double salt of spirocide (paroxyl) and arecoline in molecular proportions. Thus, the tablet contains 3.13 mg. of arsenic as spirocide and 6 mg. of arecoline. Fanslau (14) conducted clinical experiments on two different groups of cats using arecoline and nemural. He concluded that arecoline alone is a more drastic purgative than nemural. The alkaloid in a dosage of 6 mg. produced stools within 15 to 25 minutes after medication, but nemural (one tablet containing 12 mg. of paroxyl and 6 mg. of arecoline) produced purgative action somewhat later, 20 to 60 minutes, and was less severe than the reaction to arecoline alone.

Davidson (10) reports the use of nemural for a period of over one year in the treatment of tapeworms and as a purgative in small animals (cats and dogs) and gives some comments on indications for its use as well as some results of his clinical observations. He observed that best results are obtained when nemural is administered in a small gelatin capsule. Occasionally, vomiting occurs a short time

* Nemural is stated by Winthrop Chemical Company (New York) to be: 4-oxy-3-acetyl-amino-phenyl-arsonic acid N-diethyl-tetrahydro-pyridine-B-carbonic acid methyl ester.

** There is evidence that this compound was marketed by a German firm for some time prior to this date (41) in certain South American countries.

after the drug has been given. However, this symptom does not appear to disturb the patient, nor does it interfere with the action of the drug. The passage of mucus from the intestinal tract appears to be a good guide for indicating satisfactory action of the drug. He also observed that it is necessary to vary the dosage of nemural for use as a teniacide in dogs and cats (In his work he has used the drug in tablet form, each tablet containing 18 mg.). He adds that there is reason to believe that in some patients one tablet (18 mg.) would have been as efficacious as two. He has used a little as 1/3 tablet (2.25 mg.) and as much as 12 tablets (216 mg.) in other cases with good results and, apparently, no ill effects. He also noted that dogs seem to be inclined to drink more water than usual after nemural medication and recommends that it would be wise to regulate this intake, in order to avoid emesis caused by drinking too much water at one time. He finally concludes that nemural is not infallible in the treatment of teniasis or when used as a purgative in small animals; however, he believes that the drug has definite merit in small animal practice.

II EXPERIMENTAL PROCEDURE

A. Selection of Subjects. All dogs used in the experiments were purchased from a city dog pound. Every effort was made to control the incidence of distemper commonly affecting dogs from such a source. As soon as the animals arrived, the temperature was checked and those showing rise of temperature were given subcutaneously injection of anti-canine distemper serum at the rate of 1 cc. per pound body weight and repeated every eight days for at least three doses. In some instances, especially after experimental surgery, anti-canine distemper anti-bronchiosepticus-streptococcus-typhimurium serum (Homologous) was used. These animals were kept in cages and fed with commercial dog food.

B. Selection of Dosage. Table I gives the various therapeutic dosages of arecoline hydrobromide and nemural* as reported in the literature. It also includes the fatal dose of arecoline hydrobromide by different authors and practitioners. Partly on the basis of the dosages reported in Table I and partly on the basis of the amount of arecoline present in the recommended dose of nemural, it was decided to use arecoline hydrobromide at the rate of 3.2 mg. and 4.8 mg. per kgm. of body weight given as a solution by stomach tube. In order to have a comparison of both drugs under the same

* Nemural in fine powder was obtained through the courtesy of Winthrop Chemical Company (New York). The same drug in tablets was purchased from the same company. Arecoline hydrobromide in powder was supplied in part by courtesy of Merck Company (Rahway, New Jersey).

dosage rate, the dose of nemural was calculated on the basis of its arecoline content. According to the manufacturer, each gram of nemural powder contains 0.360 gm. of arecoline and 0.640 gm. of paroxyl. Each tablet of nemural containing 18 mg. of the above powder contains in each tablet arecoline base 6.48 mg. and paroxyl 11.52 mg. To calculate the quantity of arecoline as the hydrobromide represented in nemural, the following procedure was used:

Molecular weight of arecoline* 155.11

Molecular weight of arecoline hydrobromide** 236.12

$$236.12 \div 155.11 = 1.52 \text{ (Factor)}$$

One gram of nemural powder contains 0.360 gm. of arecoline base, therefore its equivalent to arecoline hydrobromide would be:

$$0.360 \times 1.52 = 0.547 \text{ gm.}$$

thus:

One gram of nemural powder is equivalent to 0.547 gm. of arecoline hydrobromide.

On the other hand, one tablet of nemural contains 6.48 mg. of arecoline base, therefore its equivalent to hydrobromide would be:

$$6.48 \times 1.52 = 9.85 \text{ mg.}$$

thus:

One tablet of nemural is equivalent to 9.85 mg. of

* Merck Index.

** National Formulary VII.

TABLE I

The Dosage of Arecoline and Nemural in Dogs
as Reported by Various Investigators

Drug: Arecoline Hydrobromide

Author	Therapeutic Dosage		Administration
	Metric	Apothecaries'	
N.F. VII (38)	1.5 mgm./kgm.	1/80 gr./lb.	per os
Parker (42)	6-12 mgm.	1/20-1/10 gr.	per os
Milks (35)	1.5 mgm./kgm.	1/12-1 gr.	per os
Hall (20)		1/8-1/4 gr.	per os
Lentz (29)		1/8-1/4 gr.	per os

Author	Fatal Dosage	Administration
Solis-Cohen (49)	8-10 mgm./kgm.	subcut.
Marne' (32)	100-120 mgm.	per os
Bocquillon-Limousin (5)	75 mgm. 1 1/6 gr.	subcut.

Drug: Nemural

Author	Therapeutic Dosage (Oral)	Equiv. to Arecoline HBr
Milks (38)	1 tablet per 8 lbs. body weight	2.7 mgm./kgm.
Davidson (10)	1 tablet per 15 lbs. body weight	1.4 mgm./kgm.

arecoline hydrobromide. When nemural in tablets was used, solutions were made containing 1 mg. per cc. of arecoline hydrobromide equivalent.

C. General Plan of the Experiment. The experimental work was divided into two main parts as follows:

1. Clinical Observations

a. Arecoline hydrobromide

- (1) Rate of 3.2 mg. per kgm. body weight
- (2) Rate of 4.8 mg. per kgm. body weight

b. Nemural

- (1) Equivalent to arecoline hydrobromide at the rate of 3.2 mg. per kgm. body weight
- (2) Equivalent to arecoline hydrobromide at the rate of 4.8 mg. per kgm. body weight

2. Experiments on Gut Activity

a. Ordinary fistulae

(1) Arecoline hydrobromide

- (a) Rate of 3.2 mg. per kgm. body weight
- (b) Rate of 4.8 mg. per kgm. body weight

(2) Nemural

- (a) Equivalent to arecoline hydrobromide at the rate of 3.2 mg. per kgm. body weight

- (b) Equivalent to arecoline hydrobromide at the rate of 4.8 mg. per kgm. body weight

b. Thiry loop

(1) Arecoline hydrobromide

- (a) Rate of 3.2 mg. per kgm. body weight
- (b) Rate of 4.8 mg. per kgm. body weight

(2) Nemural

- (a) Equivalent to arecoline hydrobromide at the rate of 3.2 mg. per kgm. body weight
- (b) Equivalent to arecoline hydrobromide at the rate of 4.8 mg. per kgm. body weight

c. Thiry-Vella fistulae

(1) Arecoline hydrobromide

- (a) Rate of 3.2 mg. per kgm. body weight
- (b) Rate of 4.8 mg. per kgm. body weight

(2) Nemural

- (a) Equivalent to arecoline hydrobromide at the rate of 3.2 mg. per kgm. body weight
- (b) Equivalent to arecoline hydrobromide at the rate of 4.8 mg. per kgm. body weight

D. Procedure for Clinical Observations. Before the drug was administered, each animal was weighed and the body temperature checked. When the subject was quiet, the pulse rate was taken by means of palpation of the femoral artery or by counting the heart beats by placing the hand on the left thorax in the region of the heart. The total dose was accurately weighed in milligrams and dissolved in from 30 to 50 cc. of tap water. Administration in all cases was made by passing the stomach tube and using a 50 cc. glass syringe to introduce the solution directly into the stomach. After the administration of the drug, the animal was maintained under constant observation. The pulse rate was taken at intervals of about ten minutes and special attention was paid to such symptoms as nausea, emesis, defecation, mucus from anus, micturition, etc. All observations were accurately timed as is shown in the data of the appendix. A total of 66 dogs were used in the experiments. In some dogs, one of the two drugs was given at the lower level only; in others, both drugs were given at the two levels and the alternation was as follows: arecoline hydrobromide at the lower level; nemural at the lower level; arecoline at the higher level and, finally, nemural at the higher level. The time elapsing between clinical experiments on the same animal with one or both drugs at different levels was from four to six days.

E. Procedure for Studies on Gut Motility. Selected female dogs were used for the observation on gut activity. These dogs were previously subjected to the clinical studies with

both arecoline hydrobromide and nemural at the two dosage levels previously described.

Experimental surgery was performed under general anesthesia using pentobarbital sodium at the rate of 30 to 40 mg. per kgm. of body weight injected intravenously. Anti-canine distemper anti-bronchiosepticus-streptococcus-typhimurium serum (Homologous) was given to the animal at the rate of one cubic centimeter per pound body weight after completion of the surgery. Animals were given sulfathalidine at the rate of 1 gr. per pound of body weight daily divided in two doses for at least six days after surgery.

Three different types of technical procedures were used in preparing the animals for experimental study:

An ordinary fistulae was made by bringing out a loop of lower ileum through the median line of the abdominal wall. After eight days, the loop of intestine was cut, using cocaine in crystals applied to the loop as the local anesthetic. These animals were ready for use one week after sectioning of the loop.

Thiry fistulae were performed in two adult female dogs. The lower ileum was chosen for this purpose and the length of the loops in each instance was about 10 inches. These animals were not used until ten days after the operation.

Thiry-Vella fistulae of the lower ileum were also prepared in three subjects. The ends of the loops were brought out through the median line. The length of the loops was about 12 inches. These animals were not used until two

weeks after the operation.

Records of the intestinal movements were obtained by means of the apparatus diagramed in Figure I. The balloon made of special thin rubber was passed into the isolated loop of the intestine. Then it was distended with air under a pressure of about 8 cm. of chloroform at the manometer arranged to record the rise and fall of the chloroform column representing the movements of the intestine at the level of the balloon. The advantages of the method used are: a direct graphic record of muscular contractions and tone of the viscus, the absence of anesthesia as a complicating factor during the experiment. In the Thiry and Thiry-Vella fistulae the effects of the drug on muscular activity are not modified by the presence of food, products of digestion or digestive juices, for although the loop has its normal blood and nerve supply, its lumen is not connected with the alimentary canal. The method also makes possible repeated observations on the same animal over a long period of time making possible comparative studies on the two drugs.

The records of intestinal movements, as reported by Plant (44) and others, show that there is a gradual relaxation of the intestinal musculature for a period of 30 to 120 minutes or more after insertion of the balloon. For this reason, 30 minutes were allowed to elapse following insertion of the balloon before bringing the manometer pressure to the 10 cm. level. A normal tracing of from 30 to 60 minutes was taken before administration of the drug. The

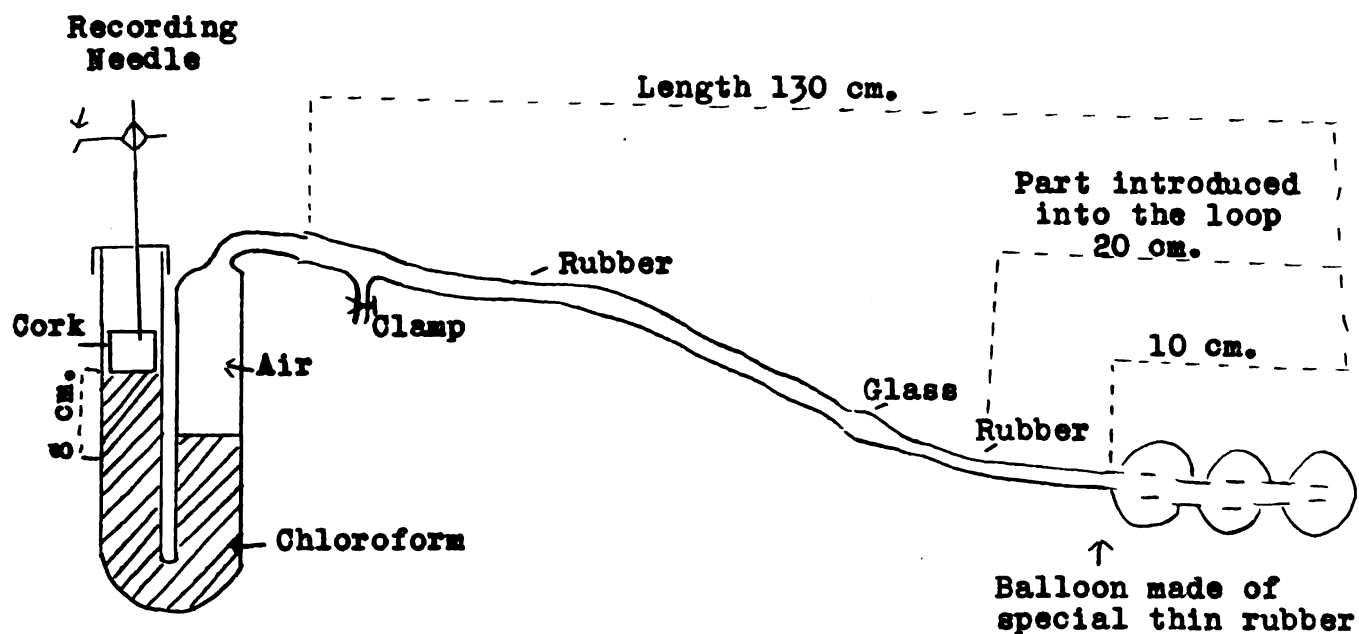


Figure I. Diagram of apparatus and hook-up used to record intestinal movements in the segments of isolated intestine.

effect of the drug was recorded continuously for periods ranging from 60 to 90 minutes.

Respiratory rate was recorded by means of an elastic stethograph placed on the thorax of the animal and arranged to record by means of a rubber tambour. Pulse rate was detected by slight pressure on the femoral artery about every five minutes, and these values were written on the base line of the record. An electric timer was used arranged to record at five seconds intervals. Any particular observations as to defecation, emesis, administration of the drug, etc., were written upon the base line of the record.

In the interpretation of the kymographic records, there will be considered the following kinds of intestinal movements: rhythmic contractions, peristaltic waves and tonus.

Rhythmic contractions (Segmenting and pendular). These are myogenic in nature (1) that is, they are dependent solely upon the rhythmical property of the intestinal muscle itself. This type of movement has been carefully studied by Cannon (7). It has also been reported (25) that there is a definite gradient of rhythmicity in the intact intestine of the dog, "The frequency of the rhythmic contraction varies inversely as the distance from the pylorus" (1).

The peristaltic contractions. These are probably dependent upon the intrinsic nerve plexuses (7). But though carried out through local reflexes in the bowel wall, they are readily influenced through the extrinsic nerves--the vagus and the sympathetic. The vagus, whose terminals connect with

ganglion cells in Auerbach's plexus, augments the movements. The sympathetic is inhibitory (4).

Tonus. Dukes (11) describes two types of tonus, "Tonus waves, which are slow changes in the length of the muscle fibers of the intestinal wall. They may exist alone or may show superimposed rhythmic contractions. Both muscular coats of the bowel may be involved". "Tonus rings, these are strong local contractions of the circular musculature of the intestine". The tone may be influenced by the extrinsic nerves, the vagus increasing, the sympathetic diminishing this property. In the present work the tone level would be the distance from the base line on the kymographic record to the lowest point reached by the ileum-balloon tracing.

III EXPERIMENTAL RESULTS

A. Clinical Observations

1. Arecoline Hydrobromide

a. Dosage Rate of 3.2 mgm. per kgm. Body Weight. Arecoline hydrobromide at the rate of 3.2 mgm. per kgm. of body weight was administered to 47 dogs ranging from 5 to 24 kgm. body weight. Protocols of each experiment with data and other observations are inserted in the appendix (see appendix pages 134 to 191).

The results of the more significant observations on 45 dogs according to the time of occurrence are summarized in Table II. Analysis of these data and of the corresponding protocols in the appendix shows that, with the exception of one dog, arecoline hydrobromide at the level of 3.2 mgm. per kgm. body weight caused slowing of the pulse rate. In some cases the number of beats decreased gradually and recovery to normal occurred by the end of the period of observation (see appendix, dogs No. 11-13-14-17-18-41-57-59-61). In some animals the slowing of the pulse was pronounced and lasted longer than the period of observation (see appendix, dogs No. 6-7-12-15-16-28-30-32-39-48-51-54). Other animals showed a decrease in pulse rate followed by an increase (see appendix, dogs No. 29-38-43-45-49-50-63). All of these dogs had one late emesis which may have some influence on the pulse rate.

Defecation occurred once or twice in more than fifty percent of the cases; a third defecation occurred in more

TABLE II

Summary of Certain Clinical Observations in Dogs
Following the Oral Administration
of Arecoline Hydrobromide, 3.2 mgm. per kgm.

Dog No.	Body Weight in kgm.	Total Dose in kgm.	Normal	Lowest Reached after Ad- ministration	Time	Defecations					Emesis			
						1st	2nd	3rd	4th	1st	2nd	3rd		
07	12.0	35.2	102	84	60'	2'	8'	22'	--	--	--	--	5'	13'
08	11.0	35.2	126	72	60'	70'	--	--	--	--	--	--	--	--
09	11.0	35.2	90	54	70'	70'	73'	73'	--	78'	--	--	--	--
10	12.0	35.2	102	88	60'	31'	63'	--	--	--	--	--	--	--
11	11.0	35.2	132	78	80'	16'	--	--	--	--	--	--	--	--
12	12.0	35.2	102	88	20'	31'	--	--	--	--	--	--	--	--
13	11.0	35.2	144	78	80'	16'	--	--	--	--	--	--	--	--
14	11.0	35.2	114	84	40'	16'	--	--	--	--	--	--	--	--
15	11.0	35.2	108	96	60'	127'	--	--	--	--	--	--	--	--
16	11.0	35.2	108	96	88'	23'	53'	--	--	38'	--	--	--	--
17	11.0	35.2	168	108	90'	30'	--	--	--	16'	--	--	--	--
18	11.0	35.2	108	54	95'	10'	17'	76'	--	--	--	--	--	--
21	11.0	35.2	108	72	47'	--	--	--	--	--	--	--	--	--
22	11.0	35.2	132	66	70'	6'	15'	45'	32'	--	--	--	--	--
23	11.0	35.2	108	90	70'	9'	19'	27'	--	--	--	--	--	--
24	11.0	35.2	108	90	75'	14'	41'	--	--	15'	--	--	--	--
25	11.0	35.2	72	66	70'	20'	--	--	--	86'	--	--	--	--
26	11.0	35.2	132	66	10'	11'	15'	19'	--	15'	18'	--	--	--
29	13.0	43.2	84	66	65'	37'	56'	--	--	20'	23'	54'	--	--
30	11.0	35.2	114	78	80'	16'	--	--	--	54'	92'	--	--	--
33	11.0	35.2	144	78	20'	31'	63'	--	--	7'	11'	--	--	--
35	12.0	35.2	102	54	60'	55'	73'	--	--	--	--	--	--	--
36	12.0	35.2	90	72	70'	70'	--	--	--	--	--	--	--	--
37	12.0	35.2	126	84	60'	2'	8'	22'	--	--	--	--	--	--
40	11.0	35.2	102	72	60'	70'	--	--	--	--	--	--	--	--
41	11.0	35.2	102	84	60'	70'	--	--	--	--	--	--	--	--
42	11.0	35.2	102	84	90'	70'	--	--	--	--	--	--	--	--
43	11.0	35.2	114	54	95'	70'	--	--	--	--	--	--	--	--
45	11.0	35.2	108	72	47'	70'	--	--	--	--	--	--	--	--

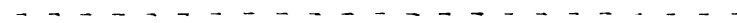
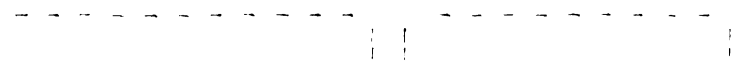
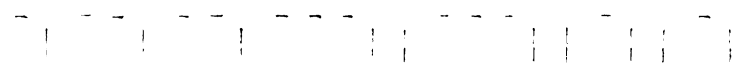
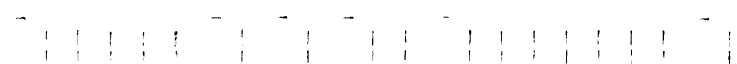
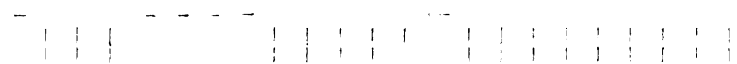
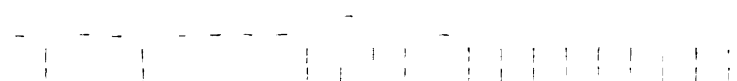


TABLE II (cont'd.)

Dog No.	Body Weight in kgm.	Total Dose in kgm.	Normal	Lowest Reached after Ad- ministration	Time	Defecations				Emesis				Motivation	Period of Observation
						1st	2nd	3rd	4th	1st	2nd	3rd	4th		
41	14.0	44.8	144	120	17'	4'	--	--	--	5'	--	--	--	--	2h.17'
43	16.5	20.8	88	76	22'	7'	23'	--	--	27'	--	--	--	--	1h.52'
44	6.0	19.2	108	90	40'	52'	--	--	--	92'	--	--	--	17'	1h.40'
47	13.0	41.6	132	--	--	19'	22'	24'	58'	20'	--	--	58'	11'	1h.28'
47	18.0	57.6	120	96	30'	15'	39'	--	--	59'	--	--	--	43'	1h.00'
47	14.5	46.4	102	60	30'	--	--	--	--	15'	--	--	--	--	2h.20'
49	8.8	25.6	96	78	38'	18'	41'	--	--	12'	29'	33'	--	43'	1h.58'
50	10.0	32.0	132	126	28'	17'	--	--	--	14'	--	--	--	--	1h.48'
51	11.0	35.0	102	60	71'	23'	--	--	--	54'	--	--	--	--	1h.31'
51	8.0	25.0	102	66	20'	--	--	--	--	13'	--	--	--	--	1h.20'
52	10.0	32.0	156	132	25'	20'	--	--	--	--	--	--	--	20'	1h.25'
53	11.5	36.0	120	60	60'	12'	25'	--	--	--	--	--	--	--	1h.20'
54	11.0	36.0	114	78	70'	11'	37'	63'	--	--	--	--	--	--	1h.30'
54	5.0	16.0	120	96	70'	17'	--	--	--	--	--	--	--	--	1h.20'
55	7.2	20.0	120	108	32'	3'	5'	21'	--	--	--	--	--	3'	1h.02'
55	5.5	24.0	96	60	11'	7'	25'	--	--	9'	19'	--	--	--	1h.21'
55	5.0	27.0	96	48	32'	14'	25'	--	--	15'	--	--	--	--	1h.17'
55	10.0	32.0	132	102	12'	7'	15'	20'	26'	--	--	--	26'	--	Oh.52'
59	8.0	25.0	96	72	60'	9'	13'	23'	--	44'	--	--	--	9-13'	1h.30'
59	6.0	20.0	120	96	41'	13'	17'	50'	--	49'	--	--	--	16'	1h.46'
59	10.0	32.0	144	60	10'	8'	24'	--	--	7'	9'	--	--	--	1h.22'
59	15.0	49.0	96	60	21'	16'	45'	--	--	10'	33'	--	--	18-32'	1h.36'

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

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701 702 703 704 705 706 707 708 709 710 711 712 713 714 715 716 717 718 719 720 721 722 723 724 725 726 727 728 729 730 731 732 733 734 735 736 737 738 739 740 741 742 743 744 745 746 747 748 749 750 751 752 753 754 755 756 757 758 759 760 761 762 763 764 765 766 767 768 769 770 771 772 773 774 775 776 777 778 779 780 781 782 783 784 785 786 787 788 789 790 791 792 793 794 795 796 797 798 799 800

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901 902 903 904 905 906 907 908 909 910 911 912 913 914 915 916 917 918 919 920 921 922 923 924 925 926 927 928 929 930 931 932 933 934 935 936 937 938 939 940 941 942 943 944 945 946 947 948 949 950 951 952 953 954 955 956 957 958 959 960 961 962 963 964 965 966 967 968 969 970 971 972 973 974 975 976 977 978 979 980 981 982 983 984 985 986 987 988 989 990 991 992 993 994 995 996 997 998 999 1000

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than one-third of the cases and four defecations occurred in a few cases (3 of 47 animals). As a rule, the first defecation appeared of soft consistency and those following were scanty, semi-fluid or liquid and repeated at frequent intervals. The first defecation occurred in from 3 to 20 minutes in 73 percent of the animals. A breakdown of these data shows that 29 percent defecated in from 3 to 10 minutes; 20 percent in from 11 to 15 minutes and 24 percent in from 16 to 20 minutes. The rest of the animals (27 percent) defecated in from 21 to 127 minutes. In general, mucus was expelled after the second defecation and in some cases, this was copious.

Emesis occurred in 64 percent of the dogs, but was repeated in only a few cases. In the majority of them (63 percent), it occurred in from 5 to 20 minutes. In all the animals in which emesis occurred later than 20 minutes, there was observed a prolonged period of nausea, the animal was somewhat depressed and the pulse rate was very irregular. Of the cases in which early emesis occurred, some expelled relatively large quantity of food material while only a few cases expelled a liquid, often foamy, material. In all cases where emesis occurred after 20 minutes the vomited material was liquid and often foamy. Vomition was also quite prone to occur following the ingestion of water.

Micturition occurred in less than 50 percent of the animals and with a few exceptions, it was more prone to occur in overweight dogs.

Small dogs weighing from 5 to 7.5 Kilos (see appendix dogs No. 5-11-13-38-43-45-55-56-57-61-66) showed almost no general depression; the decreased pulse rate was not marked and recovery was rapid. Bowels moved soon after administration of the drug (with the exception of dogs No. 38-45-55) and emesis occurred in less than 50 percent of them.

Dogs weighing from 8.5 to 9.5 Kilos (see appendix dogs No. 6-7-9-10-12-16-30-36-58) showed a marked increase in all symptoms of drug effect. Cardiac slowing was definite and persistent. Defecation occurred twice and three times in some of them. Emesis was present in the majority (early emesis).

In heavy dogs (from 11 Kilos up) symptoms were even more marked (see appendix dogs No. 14-15-17-18-28-29-32-37-39-40-41-46-47-63). Defecation occurred two and three times (dogs No. 14-17-28-32-46). Emesis was present and in some animals repeated twice (see dogs No. 14-29-32-40-63). Micturition occurred in most of them.

1. Arecoline Hydrobromide (cont'd.)

b. Dosage Rate of 4.8 mgm. per kgm. Body Weight. Arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight was administered to 21 dogs which had been previously subjected to the dosage rate of 3.2 mgm. per kgm. body weight.

The most significant symptoms are summarized in Table III. Protocols of each experiment with data and other observations are inserted in the appendix (see appendix pages 192 to 212).

TABLE III

Summary of Certain Clinical Observations in Dogs
Following the Oral Administration
of Arecoline Hydrobromide, 4.8 mgm. per kgm.

Dog No.	Body Weight in kgm.	Total Dose in kgm.	Normal	Lowest Reached After Ad- ministration	Time	Defecations				Emesis				Observation Period of
						1st	2nd	3rd	4th	1st	2nd	3rd	4th	
28	11.0	52.8	120	60	62	7	14	30	--	--	--	--	--	1h.25'
30	8.5	40.8	108	66	42	13	15	23	26	53	--	--	--	1h.00'
32	11.5	55.2	108	90	50	39	49	--	--	31	65	--	--	1h.15'
36	7.5	36.0	132	108	24	9	--	--	--	--	--	--	--	1h.39'
37	11.5	55.2	120	78	70	14	27	38	--	--	--	--	--	1h.20'
38	5.0	24.0	186	138	20	9	19	27	47	--	--	--	--	1h.10'
40	11.0	52.8	96	78	13	5	9	16	--	2	10	--	--	1h.23'
43	6.5	31.2	96	84	10	9	25	45	--	15	--	--	--	1h.30'
45	7.0	33.6	108	102	9	13	--	--	--	58	--	--	--	1h.33'
48	12.5	60.0	90	60	10	18	32	--	--	--	--	--	--	1h.13'
55	5.0	24.0	102	60	110	5	8	18	--	--	--	--	--	2h.18'
57	7.0	33.6	138	96	30	9	16	39	--	31	--	--	--	1h.00'
58	8.5	40.8	102	66	30	11	17	--	--	13	29	--	--	1h.12'
59	10.5	50.4	108	66	40	22	53	--	--	31	--	--	--	1h.51'
60	9.0	43.2	162	144	20	6	--	--	--	--	--	--	--	1h.44'
61	7.0	33.6	108	84	76	5	17	--	--	--	--	--	--	2h.06'
62	11.0	52.8	132	66	10	13	18	--	--	4	11	--	--	1h.35'
63	16.5	81.2	96	60	30	11	--	--	--	16	--	--	--	1h.10'
64	6.0	28.8	90	72	40	9	21	--	--	--	--	--	--	1h.40'
65	10.5	52.4	84	48	40	17	26	--	--	--	--	--	--	1h.52'
66	6.5	31.2	102	54	70	12	45	--	--	59	--	--	--	1h.41'

Analysis of the data in Table III and of the corresponding protocols in the appendix show that in most of the subjects arecoline hydrobromide at the level of 4.8 mgm. per kgm. body weight caused a marked and persisting slowing of the pulse rate. In a few cases (see dogs No. 32-40-43-45) the slowing of the pulse rate was of short duration and an increased pulse rate occurred instead. These cases showed a nauseant stage followed by emesis.

In all cases, defecation occurred once in from 5 to 39 minutes. Of these, 84 percent defecated in from 5 to 15 minutes and the rest of them (16 percent) in from 16 to 39 minutes. It was repeated twice in 80 percent and three times in 39 percent of the cases. Only two cases had a fourth defecation. Fecal material was of soft consistency the first time and semi-liquid, scanty when more than one occurred. Mucus was expelled in most of the cases, being copious and continuous.

Emesis occurred in 11 of the 21 dogs used and it was repeated in four cases. In some cases (see dogs No. 30-32-45-57-59-66) emesis was late, occurring in from 31 to 59 minutes and when early emesis occurred (see dogs No. 40-58-62) in from 2 to 29 minutes it was repeated twice.

Micturition occurred in less than 50 percent of the experimental animals.

c. Comparison of Results with Arecoline on the Same Animals at the Two Levels of Dosage: 3.2 and 4.8 mgm. per kgm. Body Weight. The data of Table IV illustrate the results of arecoline hydrobromide at the two

TABLE IV

Summary of the Comparative Effects in Dogs
with Arecoline Hydrobromide at the Levels of
3.2 and 4.8 mgm. per kgm. Body Weight
on the Same Animal (21 subjects)

Dose: 3.2 mgm. per kgm. body weight

Dog No.	Body Weight in kgm.	Total Dose in mgm.	Normal	Pulse Rate		Defecations					Emesis				Micturition	Period of Observation
				Lowest Reached	after Admini- stration	Time	1st	2nd	3rd	4th	1st	2nd	3rd			
28	11.0	35.2	132	66	70'	6'	15'	45'	--	86'	--	--	--	35'	1h.45'	
30	11.5	27.2	114	66	65'	11'	15'	19'	37'	20'	23'	37'	13'	1h.20'		
32	11.5	36.8	144	78	80'	37'	56'	--	--	54'	92'	--	59'	1h.32'		
36	12.5	27.2	132	88	20'	16'	--	--	--	7'	11'	--	--	2h.20'		
37	12.0	38.4	102	54	60'	31'	63'	--	--	--	--	--	63'	2h.10'		
38	12.0	19.2	90	72	70'	55'	73'	--	--	78'	--	--	105'	1h.50'		
40	12.0	38.4	102	84	60'	2'	8'	22'	--	5'	13'	--	3'	2h.30'		
43	12.5	20.8	88	76	22'	7'	23'	--	--	27'	--	--	--	1h.52'		
45	14.5	46.4	102	90	40'	52'	--	--	--	92'	--	--	17'	1h.40'		
48	14.5	16.0	114	60	80'	--	--	--	--	15'	--	--	43'	2h.20'		
55	5.0	16.0	114	78	70'	11'	37'	63'	21'	--	--	--	--	1h.30'		
57	7.5	24.0	120	108	32'	3'	5'	21'	--	--	--	--	3'	1h.02'		
58	8.5	27.2	96	60	11'	7'	25'	--	--	9'	19'	--	--	1h.21'		
59	10.0	32.0	96	84	32'	14'	25'	--	--	15'	--	--	--	1h.17'		
60	8.0	25.6	132	102	12'	7'	15'	20'	26'	26'	--	--	--	0h.52'		
61	6.5	20.8	96	72	60'	9'	13'	23'	50'	44'	--	--	9-13'	1h.30'		
62	10.0	32.0	120	96	41'	13'	17'	50'	--	49'	--	--	16'	1h.46'		
63	15.5	49.6	144	60	10'	8'	24'	--	--	7'	9'	--	--	1h.22'		
64	10.0	32.0	96	60	21'	16'	45'	--	--	10'	33'	--	18-32'	1h.36'		
65	12.0	38.4	96	72	30'	--	--	--	--	--	--	--	--	2h.17'		
66	6.5	20.8	84	60	20'	21'	--	--	--	15'	--	--	--	1h.50'		

TABLE IV (cont'd.)

Summary of the Comparative Effects in Dogs
with Arecoline Hydrobromide at the Levels of
3.2 and 4.8 mgm. per kgm. Body Weight
on the Same Animal (21 subjects)

Rate of 4.8 mgm. per kgm. body weight

Dog. No.	Body Weight in kgm.	Total Dosage in mgm.	Normal	Pulse Rate			Defecations				Emesis			Micturition	Period of Observation
				Lowest Reached	After Ad- ministration	Time	1st	2nd	3rd	4th	1st	2nd	3rd		
28	11.0	52.8	120	60	62	7	14	30	30	26	53	—	—	14	1h.25
30	8.5	40.8	108	66	42	13	15	23	23	—	53	—	—	23	1h.00
32	11.5	55.2	108	90	50	39	49	—	—	—	31	65	—	48	1h.15
37	7.5	36.0	132	108	24	9	—	—	—	—	—	—	—	—	1h.39
37	11.5	55.2	120	78	70	14	27	38	38	47	—	—	—	14	1h.20
38	5.0	24.0	186	138	20	9	19	27	27	—	—	—	—	17	1h.10
40	11.0	52.8	96	78	13	5	9	16	16	—	2	10	—	—	1h.23
43	6.5	31.2	96	84	10	9	25	45	45	—	15	—	—	—	1h.30
45	7.0	33.0	108	102	9	13	—	—	—	—	58	—	—	—	1h.33
48	12.5	60.0	90	60	10	18	32	—	—	—	—	—	—	—	1h.13
55	5.0	24.0	102	60	110	5	8	18	18	—	—	—	—	8	2h.18
57	7.0	33.0	138	96	30	9	16	39	39	—	31	—	—	—	1h.00
58	8.5	40.8	102	66	30	11	17	—	—	—	13	29	—	—	1h.12
59	10.5	50.4	108	66	40	22	53	—	—	—	31	—	—	—	1h.51
60	9.0	43.2	162	144	20	6	—	—	—	—	—	—	—	—	1h.44
61	7.0	33.0	108	84	76	5	17	—	—	—	—	—	—	—	2h.06
62	11.0	52.8	132	66	10	13	18	—	—	—	4	11	—	—	1h.35
63	16.5	81.2	96	60	30	11	—	—	—	—	16	—	—	13	1h.10
64	6.0	28.8	90	72	40	9	21	—	—	—	—	—	—	11	1h.40
65	10.5	52.8	84	48	40	17	26	—	—	—	—	—	—	22	1h.52
66	9.0	43.2	102	54	70	12	45	—	—	—	59	—	—	51	1h.41

levels used expressed by percentage of occurrence of the various drug effects in the experimental subjects.

Forty-eight percent of the animals showed a lower pulse rate on the 3.2 mgm. level than on the 4.8 mgm. level of dosage. In only 38 percent of the cases the reverse occurred. The remainder (14 percent) showed no difference in heart rate with the two different levels of the drug. It was also observed that when the lower level of the drug was administered the decrease in pulse rate persisted for a longer period than when the higher dose was used. However, these data give no comparison of value since the pulse rate is susceptible to variation (rise and fall) due to other manifestations (defecation, emesis, restlessness).

Attempts to defecate seem to be more numerous at the higher level. It was also more prompt as is shown in Table V. Repeated defecations were more frequent at the higher level and caused restlessness and each attempt was followed by scanty and continuous expulsion of feces of liquid consistency. Mucus was more copious at the higher level.

The summary of the data shows that emesis was more common at the lower level (76 percent) and it was also repeated twice and three times in a majority of the cases. When the lower level of the drug was administered, the subjects were more inclined to early emesis (from 7 to 30 minutes after administration of the drug). It also shows that in most of the cases when emesis occurred in less than 20 minutes it was repeated twice soon afterwards.

TABLE V
Comparison of the Effects of Arecoline Hydrobromide
at the Levels of 3.2 and 4.8 mgm. per kgm. Body Weight
Given to the Same Animal and Expressed by Percentage (21 subjects)

Level per kgm. Body Weight	Pulse Lowest Reached from Normal	Defecations				Emesis			Micturition
		1st	2nd	3rd	4th	1st	2nd	3rd	
3.2 mgm.	48%	90%	76%	38%	4%	76%	66%	4%	57%
4.8 mgm.	38%	100%	80%	38%	9%	52%	19%	0%	49%
Time of occurrence expressed in minutes									
3.2 mgm.	5-55'	5-73'	20-50'	26'	7-92'	9-92'	37'	3-105'	
4.8 mgm.	5-39'	8-53'	16-45'	26-47'	2-59'	11-65'	--	8-51'	

Micturition occurred in more cases at the lower (57 percent) than at the higher level (49 percent). When micturition occurred at the lower level it was more common in overweight animals (more than 10 kgm. body weight) appearing in 7 of 12 cases. One-half of the 10 cases showing micturition at the higher level of dosage were overweight animals.

2. Nemural

a. Dosage Equivalent to Arecoline Hydrobromide at the Rate of 3.2 mgm. per kgm. Body Weight. Nemural was given to 38 dogs* ranging from 5 to 17 kgm. body weight. The dosage used was equivalent to arecoline hydrobromide at the rate of 3.2 mgm. per kgm. of body weight and the total dose was obtained according to the procedure already discussed.

Table VI summarizes the results of the more important observations arranged in the chronological order of their occurrence from the time of administration of the drug.

Nemural caused slowing of the pulse rate in 35 of the 38 experimental subjects. The slowing of the pulse rate was very definite and it lasted longer than the period of observation. Most of the animals receiving this drug appeared quite depressed. In a few subjects, this was the most evident symptom (see dogs No. 20-24-28-29-30-32-35-55-56-66).

Defecation occurred in 92 percent of the cases and the majority of them (83 percent) defecated in from 3 to 25 minutes. A breakdown of these data shows that 36 percent

* Twenty-eight of these dogs were previously subjected to arecoline hydrobromide at the rate of 3.2 mgm. per kgm. of body weight.

TABLE VI

Summary of Certain Clinical Observations in Dogs
Following the Oral Administration of Nemural at a Dosage
Rate Equivalent to 3.2 mgm. per kgm. Body Weight of Arecoline HBr

Dog No.	Body Weight in kgm.	Equivalent in mgm. to Are- coline HBr	Total Dose		Pulse Rate		Defecations				Emesis				Micturition	Period of Observation
			Nemural in Powder mgm.	Nemural in Tablets	Normal	Lowest Reached After Ad- ministration	Time	1st	2nd	3rd	4th	1st	2nd	3rd		
19	6.0	19.2	--	1.94	96	60	60	19	32	42	--	15	31	--	30	1h.00
20	12.0	38.4	--	3.89	120	84	50	--	--	--	--	15	15	--	--	1h.40
21	9.5	30.4	--	3.08	84	66	--	15	--	--	--	5	17	--	28	1h.30
22	5.5	17.6	--	1.78	90	60	40	5	12	17	24	13	22	--	--	1h.10
23	10.5	32.0	--	3.24	72	60	80	19	76	56	--	21	--	--	--	1h.50
24	8.5	27.0	--	2.47	96	78	19	32	--	--	--	37	--	--	--	1h.44
28	5.5	30.4	--	3.08	108	66	30	25	--	--	--	11	--	--	--	1h.50
29	5.5	40.0	--	4.16	78	60	68	25	--	--	--	7	--	--	--	1h.30
30	12.0	25.6	46.8	--	120	66	50	4	15	16	25	14	20	22	25	1h.30
31	12.0	38.4	64.3	--	108	78	43	5	9	--	--	102	--	--	145	2h.03
32	11.0	35.2	70.2	--	120	66	135	145	16	34	--	21	23	29	--	1h.25
33	7.0	22.4	40.9	--	102	90	70	5	13	22	30	14	--	--	--	1h.00
34	9.0	28.8	52.8	--	72	48	25	8	13	--	--	14	--	--	--	1h.47
35	11.0	35.2	64.3	--	126	60	92	43	12	23	--	8	13	--	15	1h.25
36	8.5	27.2	--	2.47	114	84	20	5	31	38	79	--	--	--	--	1h.30
37	13.0	41.6	76.0	--	144	60	40	11	26	44	65	11	31	--	16	1h.30
38	6.0	19.2	--	1.94	84	--	--	22	20	28	--	11	--	--	30	1h.40
40	12.0	38.4	--	3.89	132	54	20	15	20	--	--	2	7	--	33	1h.35
41	13.0	41.6	--	4.22	120	72	20	33	--	--	--	--	--	--	--	1h.24
43	7.0	22.4	--	2.27	108	90	74	4	15	--	--	6	20	31	--	1h.40
44	8.0	25.6	2.5	2.59	132	120	10	5	11	15	23	26	38	--	5	1h.28
45	13.0	41.6	--	4.22	120	--	8	5	93	15	--	22	--	--	--	1h.48
47	17.0	54.4	--	5.52	120	--	--	19	--	--	--	--	--	--	--	--

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TABLE VI (cont'd.)

Summary of Certain Clinical Observations in Dogs
Following the Oral Administration of Nemural at a Dosage
Rate Equivalent to 3.2 mgm. per kgm. Body Weight of Arecoline HBr

Dog No.	Body Weight in kgm.	Equivalent in mgm. to Are- coline HBr	Nemural in Powder mgm.	Nemural in Tablets	Normal	Lowest Reached	Time after Ad- ministration	Defecations						Emesis		Micturition	Period of Observation
								1st	2nd	3rd	4th	1st	2nd	3rd	4th		
99	7.0	22.4	—	2.27	120	78	80	11	—	—	—	—	—	—	—	—	1h. 40
95	10.6	33.5	—	3.41	96	60	80	35	—	—	—	5	—	—	—	—	1h. 45
66	15.0	48.0	—	4.87	138	72	30	9	21	44	71	19	—	—	—	—	1h. 24
29	10.0	32.0	—	3.24	120	96	10	3	19	26	—	6	18	—	—	—	1h. 23
19	6.0	20.0	—	2.11	108	90	20	9	19	26	—	8	—	—	—	—	1h. 34
61	8.0	25.5	—	2.59	126	120	39	12	19	25	—	—	—	—	—	—	1h. 23
55	10.0	32.0	—	3.24	120	72	40	—	—	—	—	—	—	—	—	—	1h. 29
55	8.0	27.2	—	2.47	96	60	20	21	41	—	—	9	—	—	—	—	1h. 31
55	7.0	24.0	—	2.43	126	114	40	11	17	32	—	12	—	—	—	—	1h. 52
55	5.0	20.0	—	2.11	120	78	20	12	14	29	—	—	—	—	—	—	1h. 50
55	5.0	16.0	—	1.62	120	90	30	3	10	29	—	21	—	—	—	—	1h. 30
50	5.0	16.0	—	2.59	180	84	49	13	25	—	—	10	—	—	—	—	1h. 19
44	5.0	16.0	—	2.43	132	90	37	18	43	—	—	—	—	—	—	—	1h. 17
84	12.1	40.0	—	4.26	96	72	44	16	28	—	—	—	—	—	—	28	1h. 13

defecated in from 3 to 10 minutes; 25 percent in from 11 to 15 minutes; 14 percent in from 16 to 20 minutes; 8 percent in from 21 to 25 minutes and the rest of the cases (17 percent) in more than 25 minutes. Two-thirds of the cases defecated twice; one-half, three times and one-sixth a fourth time. When defecation was repeated three and four times, it was sometimes tinged with blood (see dogs No. 23-37-38-57-63) and accompanied by scanty mucus.

Emesis occurred in 73 percent of the cases and the time of occurrence was 36 percent in from 2 to 10 minutes; 36 percent in from 11 to 20 minutes and the rest (28 percent) in more than 20 minutes. Emesis occurred twice in 39 percent of the number showing this symptom and only a few animals (3 cases) had a fourth emesis.

Micturition occurred in less than one-third of the cases (12 of 38 dogs).

Dog No. 60 (see appendix), an eight kgm. animal, did not show any of the common effects such as defecation, emesis or micturition following the administration of the equivalent of 2.59 tablets of nemural in solution. Pulse rate decreased for but a short period from 126 to 120 after 39 minutes from the time of administration of the drug and most of the time the pulse rate was increased above the normal counted before administration of the drug. The observation period lasted for one hour and twenty-nine minutes. Other dogs (see appendix, dogs No. 24-43-55-60) from 5 to 8.5 kgm. body weight showed but one attempt to defecate and other manifestations

were not observed during the time of observation. In some other cases, however, (see dogs No. 19-22-31-33-36-38-45-46-63) pronounced effects were observed as evidenced by repeated defecation and emesis and the state of restlessness manifested by these animals. Shivering was observed in some animals (see dogs No. 36-38-41-45-47) about one hour following administration of the drug and persisted for the remainder of the period of observation.

b. Dosage Equivalent to Arecoline Hydrobromide at the Rate of 4.8 mgm. per kgm. of Body Weight. Nemural was given to 18 dogs*. The dosage used was equivalent to arecoline hydrobromide at the rate of 4.8 mgm. per kgm. of body weight and the total dose was obtained according to the procedure previously discussed.

Table VII summarizes in a more concise form the most important observations according to the time of occurrence. Analysis of these data and of the corresponding protocols in the appendix shows that nemural at the dosage used caused slowing of the pulse rate in all of the experimental subjects. There were, however, some variations in the various responses. In some dogs, the slowing of the pulse rate was definite and it lasted longer than the period of observation (see dogs No. 32-48-55-57-58-63-66). In some others there

* These animals were previously subjected to arecoline hydrobromide at the two levels of 3.2 and 4.8 mgm. per kgm. body weight and also to nemural in a dosage of an equivalent to arecoline hydrobromide at the level of 3.2 mgm. per kgm. of body weight.

TABLE VII

Summary of Certain Clinical Observations in Dogs
Following the Oral Administration of Nemural at a Dosage Rate
Equivalent to Arecoline Hydrobromide at the Rate of 4.8 mgm. per kgm. Body Weight

Dog No.	Body Weight in kgm.	Equivalent in mgm. to Are- coline HBr	Total Dose		Pulse Rate			Defecations			Emesis			
			Nemural in Powder mgm.	Nemural in Tablets	Normal	Lowest Reached	Time after Ad- ministration	1st	2nd	3rd	4th	1st	2nd	
32	11.5	55.2	--	5.60	102	66	93'	14'	54'	--	--	--	12'	--
36	11.5	40.8	--	4.14	102	84	45'	--	--	--	--	--	25'	--
37	11.5	55.2	--	5.60	126	96	110'	12'	21'	32'	55'	--	--	--
38	12.5	60.0	109.6	2.69	108	96	5'	7'	10'	50'	74'	--	6'	11'
40	12.5	31.2	56.6	--	96	72	18'	7'	10'	--	--	--	--	--
43	12.5	40.8	--	--	84	72	20'	11'	--	--	--	--	46'	--
45	12.5	60.0	--	4.14	84	54	21'	9'	43'	--	--	--	--	--
47	12.5	24.0	--	6.09	114	60	70'	6'	26'	51'	--	--	--	--
55	15.5	40.8	--	2.44	90	66	40'	8'	--	--	--	--	27'	--
57	15.5	40.8	--	4.14	144	96	70'	12'	28'	--	--	--	38'	--
58	17.5	36.0	--	3.65	120	72	62'	7'	11'	13'	25'	--	9'	--
59	10.5	50.4	92.3	--	96	72	30'	13'	15'	--	--	--	23'	68'
60	10.5	38.4	--	3.89	138	120	20'	7'	9'	--	--	--	--	--
61	10.5	31.2	--	3.26	96	72	20'	16'	37'	50'	--	--	--	--
63	15.5	74.4	--	7.55	120	90	30'	18'	29'	--	--	--	26'	--
64	10.5	50.4	--	5.11	96	78	70'	12'	28'	--	--	--	12'	--
65	10.0	45.0	82.2	--	96	78	40'	16'	29'	11'	--	--	43'	48'
66	7.5	36.0	65.8	--	126	78	50'	4'	6'	--	--	--	--	--

was a decrease followed by an increase in pulse rate which attained a rate, in some instances, above the previous normal (see dogs No. 36-37-38-40-60-61-64-65).

Defecation failed to occur in one case (see dog No. 36) during the period of observation (1h.45'). Other experimental subjects defecated once in from 4 to 18 minutes. Analysis of the data shows that one-half of the animals (9 of 18 dogs) defecated in from 4 to 10 minutes and the other one-half defecated in from 11 to 18 minutes. A second defecation occurred in 15 cases of the 18 subjected to the drug and the time of occurrence ranged from 6 to 54 minutes. One-third of the experimental subjects defecated three times in from 11 to 51 minutes after the administration of the drug and one-sixth (3 cases) of the cases defecated four times. As a rule the first defecation was of soft consistency and others were of liquid consistency, scanty but repeated at short intervals. With a few exceptions these animals expelled considerable amount of mucus and some cases showed defecations tinged with blood (see dogs No. 40-58).

More than one-half of the experimental subjects (11 of 18 cases) showed emesis and the time of occurrence was as follows: early emesis from 6 to 20 minutes occurred in only 4 cases; the rest of the cases (7 animals) vomited in from 23 to 46 minutes. Emesis was repeated twice in three cases only. No more emesis was recorded during the period of observation.

Micturition occurred in 10 of 18 subjects in from 7 to 44 minutes. With the exception of two cases, micturition

occurred in less than 22 minutes after the drug was given to the animal.

Dog No. 36 failed to defecate and had one emesis in 25 minutes. Dog No. 43 defecated once. This occurred in 11 minutes and was the only response to the drug shown by this animal. Some other animals (see dogs No. 37-38) showed considerable purging effect of the drug (four times), micturition was also present but emesis did not occur.

B. Results of Kymographic Studies from Intestinal
Balloons in Dogs under Arecoline and Nemural at
Two Levels of Dosage

1. Preliminary Trials in Anesthetized Animals.

Because of the greater amount of data obtainable in critical experiments under anesthesia using a larger number of dogs the feasibility of this method was first investigated. Eight dogs under pentobarbital or ether anesthesia arranged to record blood pressure, per minute volume and rate of respiration, and intestinal motility from balloon placed at various levels of the gut were used in these experiments. The results of these trials are enumerated below.

Dog Nos. 1 and 2 were anesthetized with pentobarbital sodium at the rate of 50 and 40 mgm./kgm. respectively and arecoline hydrobromide at the rate of 1.6 mgm./kgm. was given by stomach tube. No appreciable results were obtained. The same dose of arecoline hydrobromide was injected subcutaneously toward the end of the experiment and there was a slight decrease in blood pressure and heart rate.

Dog Nos. 3 and 4 were anesthetized with pentobarbital sodium at the rate of 35 mgm./kgm. After a short normal tracing arecoline hydrobromide at the rate of 1.6 mgm./kgm. was given by stomach tube and no results were obtained after 60 minutes. The same rate was injected directly into the duodenum and accompanied with 1gm of sodium bicarbonate dissolved in 20 cc. water. No appreciable results were obtained.

Dog No. 7 was anesthetized with ether. Arecoline hydrobromide at the rate of 1.6 mgm./kgm. was given by stomach tube. No appreciable changes were obtained. One hour later, arecoline hydrobromide at the rate of 3.2 mgm./kgm. was injected directly into the duodenum. It caused a fall in blood pressure and slowing of the heart rate.

Dog No. 8 was anesthetized with ether and after a short normal tracing, arecoline hydrobromide at the rate of 3.2 mgm./kgm. was given by stomach tube. No appreciable changes were seen in after 75 minutes following administration of the drug. At this time arecoline hydrobromide at the rate of 3.2 mgm./kgm. was administered directly into the duodenum. A slight fall in blood pressure and decrease in heart rate occurred.

Dog No. 9 was anesthetized with ether. Arecoline hydrobromide at the rate of 3.2 mgm./kgm. was administered directly into the duodenum. No appreciable changes were observed. After 50 minutes, the dose was repeated with no appreciable results. After 32 more minutes, arecoline hydrobromide at the

rate of 1.6 mgm./kgm. was injected subcutaneously. A fall in blood pressure and a decrease in heart rate occurred.

Dog No. 11 was anesthetized with ether. Arecoline hydrobromide at the rate of 3.2 mgm./kgm. was injected twice directly into the duodenum at an interval of one hour did not show any appreciable results.

The forgoing results indicate that anesthesia produces too great a depression of the gut to warrant the use of this method in evaluating the action of arecoline and nemural. This finding is in agreement with that observed by other investigators (44-45).

2. Ordinary Fistulae of the Ileum and Colon. The data derived from an analysis of the various kymographic records and other observations in this series are set forth in tables as follows:

Dog No. 25

Table VIII. Arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Dog No. 26

Table IX. Arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table X. Arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

Table XI. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table XII. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 4.8 mgm. per

kgm. body weight.

Dog No. 28

Table XIII. Arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight.

Table XIV. Arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight.

Table XV. Nemural in a dose equivalent to areco-
line hydrobromide at the rate of
3.2 mgm. per kgm. body weight.

Table XVI. Nemural in a dose equivalent to areco-
line hydrobromide at the rate of
4.8 mgm. per kgm. body weight.

Dog No. 29

Table XVII. Arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight.

Dog No. 30

Table XVIII. Nemural in a dose equivalent to areco-
line hydrobromide at the rate of
3.2 mgm. per kgm. body weight.

Dog No. 48

Table XIX. Arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight.

TABLE VIII

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 25

April 21, 1945

10 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. given in a piece of canned meat

Analysis of the kymographic record:

Time	<u>Ileum Balloon</u>						<u>Colon Balloon</u>			Other Obs.	
	Pulse Rate	Resp. Rate	Tone Level	<u>Waves</u>			Tone Level	<u>Waves</u>			
				Frequency	Amplitude	Rhythmic Contract.		Frequency	Amplitude		
5.05	120	16	--	--	--	--	--	--	--		
5.10	liquid material expelled from ileum										
5.15	114	15	75	4	34-36	--	145	7	10-50		
5.25	108	17	70	4	30-40	--	140	8	16-30		
5.26	administration of arecoline hydrobromide										
5.36	42	22	65	--	--	--	145	--	--		
5.46	84	18	60	1	37	--	130	--	--		
5.56	84	16	75	3	32	--	--	--	--		
6.03	liquid material expelled from ileum										
6.06	84	14	68	3	32-37	--	--	--	--		
6.16	90	13	70	2	35-37	--	--	--	--		
6.26	90	14	67	3	33-35	--	--	--	--		
6.33	liquid material expelled from ileum										
6.36	90	14	65	2	32-37	--	--	--	--		
6.46	90	13	75	2	25-28	--	--	--	--		
6.56	96	16	73	2	25-27	--	--	--	--		
7.06	90	14	83	3	12-17	--	--	--	--		

Analysis of the record and of the corresponding data presented in Table VIII shows that pulse rate decreased from 108 to 40 per minute after 14 minutes following the administration of the drug, than increased to 84 in 6 minutes. It remained below normal for the duration of the experiment (80 more minutes). Respiratory rate did not show any visible change.

The ileum tracing showed increase in the tone level especially a few minutes before liquid material was expelled from the opening of the fistula. Peristaltic waves decreased in number and amplitude. Rhythmic contractions could not be recorded due to the presence of peristaltic waves. Data on the colon tracing could not be obtained due to an enormous increase in tonus immediately after the administration of the drug which necessitated the release of air from the balloon to avoid overflow of the chloroform from the manometer.

TABLE IX

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 26

April 20, 1945

9 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 28.8 mgm. given in a piece of canned meat

Analysis of the kymographic record:

Time	Pulse Rate	Resp. Rate	Tone Level	<u>Ileum Balloon</u>			<u>Colon Balloon</u>			Other Obs.
				<u>Waves</u>			<u>Waves</u>			
				Frequency	Amplitude	Rhythmic Contract.	Tone Level	Frequency	Amplitude	
2.00	146	15	46	1	11	15	70	9	20-45	
2.10	132	14	46	2	7- 9	16	65	10	23-30	
2.11	administration of arecoline hydrobromide									
2.15	142	--	60	--	--	--	70	--	--	
2.21	132	13	37	--	--	18	65	9	15-50	
2.31	138	11	28	1	27	16	62	6	20-40	
2.39	liquid material expelled from ileum									
2.41	144	12	33	2	15-22	14	60	7	20-50	
2.51	150	12	26	2	14-21	14	78	10	20-30	
3.01	150	12	28	2	7	15	76	9	23-65	
3.11	152	11	35	--	--	--	71	8	25-30	
3.19	158	12	35	2	15-33	--	70	8	23-50	
3.25	2nd. paper									
3.35	144	11	42	--	--	14	74	8	25-40	
3.45	142	13	35	2	7-17	16	69	9	25-40	

This subject showed an increase in pulse rate after arecoline. This increase was from a normal of 132 to 158 per minute. No visible change was noted in the respiratory rate except when liquid material was expelled from ileum which was accompanied by restlessness and an increase in the respiratory rate. When the animal was not excited respiration remained slightly below normal (a decrease of 2 or 3 per minute). Ileum tracing shows an increase in tone level somewhat above normal immediately after administration of the drug, lasting only a few minutes (6 minutes), then it fell below normal. Peristaltic waves were invariably present after expulsion of liquid material from ileum. After 30 minutes following administration of the drug the frequency of peristaltic waves was 2 per 10 minutes. While the height of the contraction was not marked, the duration was more prolonged. No appreciable change was recorded in rhythmic contractions. The departure from normal was not more than ± 2 . The colon tracing shows an increase in tone level immediately after administration of the drug (5 mm.) and also when liquid material was expelled from ileum (10 mm.). While there was a decrease in rhythmic waves of 1 to 2 waves per 10 minutes the duration was increased.

Dog No. 26

April 15, 1945

Another experiment was conducted on the same animal using arecoline hydrobromide at the same rate as previously. Analysis of the tracing shows an increase in pulse rate (120 to 156) instead of a decrease following the administration of the drug. The rate remained above normal for the entire period of the experiment. Tracing of the ileum balloon showed an increase in tone level terminating in a spastic contraction after expulsion of liquid material from the ileum. The spastic contraction lasted from 3 to 5 minutes, but 30 minutes following arecoline the record shows peristaltic waves accompanied by frequent expulsions of liquid material from the ileum. The colon tracing showed a relaxation 20 minutes following drug administration. This lasted for about 25 minutes, then rhythmic waves were recorded at the rate of 12 per minute as compared to a rate of 10 per minute in the normal tracing.

TABLE X

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 26

May 19, 1945

9 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. per body weight

Total dose: 43.2 mgm. given in a piece of canned meat

Results:

Time	Pulse Rate	Resp. Rate	Tone Level	<u>Ileum Balloon</u>			<u>Colon Balloon</u>			Other Obs.
				Frequency	Amplitude	Rhythmic Contract.	Tone Level	Frequency	Amplitude	
3.20	72	13	68	--	--	15	102	8	12-25	
3.30	84	14	56	2	16	--	98	9	12-24	
3.40	72	13	66	1	7	14	95	9	20-29	
3.41	administration of arecoline hydrobromide									
3.46	60	--	77	--	--	--	118	--	--	
3.50	60	11	72	--	--	--	115	5	10-17	
3.57	90	12	83	--	--	--	--	--	--	
4.00	90	11	83	1	11	--	93	8	8-12	
4.09	liquid material expelled from ileum									
4.10	72	11	85	--	--	--	94	--	--	
4.13	66	--	liquid material expelled from ileum							
4.20	72	13	78	3	50-95	--	92	--	--	

In general only a slight decrease in pulse rate occurred in this subject following the administration of arecoline hydrobromide. This decrease was not marked and the rate was above normal in two occasions. Respiration showed slight variation in rate. From the normal of 13 to 14 to 11 to 13 respirations per minute.

The ileum balloon record shows an increase in tone level following arecoline administration. This increase was especially evident immediately after the drug was given and also when liquid material was expelled from the opening of the ileum. At the 16th minute following arecoline administration the record shows a spastic contraction which lasted for about 13 minutes. During this period an increase in tone level occurred which was terminated with an expulsion of liquid material from the ileum. The colon balloon record shows slight activity during the first 19 minutes following arecoline. During this period the tone level was somewhat above normal. Rhythmic waves decreased in frequency as well as in amplitude. It was followed by a period of quiescence which persisted for the rest of the recording time.

Two more records were taken on this subject using arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

Results of the record obtained on May 5, 1945:

Pulse rate showed a gradual increase from the normal of 84 to 114. It remained above normal for the entire experiment. Liquid material was expelled from the ileum several

times, accompanied in each instance by a spastic contraction of very short duration (3 minutes) and an increase in tone level. The colon balloon record showed an increase in tone during the first 60 minutes following arecoline.

Results of the record obtained on May 25, 1945:

Pulse rate decreased from 120 to 54 in 4 minutes following the administration of the drug, then gradually increased reaching 120 beats per minute in 16 more minutes. An increase above the normal was recorded toward the end of the experiment.

The ileum record showed a spastic contraction lasting for about 22 minutes after arecoline. The colon record showed a spastic contraction which lasted for the entire period of the experiment. At the end of this period there occurred scanty and repeated expulsion of material from ileum. This was accompanied by an increase in tone level.

TABLE XI

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 26

April 24, 1945

9 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 52.6 mgm. of nemural given in a piece of
canned meat

Results:

Time	Pulse Rate	Resp. Rate	<u>Ileum</u>		Tone Level	<u>Colon Balloon</u>	
			<u>Balloon</u>	Rhythmic Contract.		<u>Waves</u>	Amplitude
1.55	124	13	48	--	70	10	12-17
1.55	administration of nemural						
1.59	--	--	53	--	68	--	--
2.05	116	14	35	--	60	4	9-13
2.07	liquid material expelled from ileum						
2.10	129	15	42	--	70	9	11-15
2.19	liquid material expelled from ileum						
2.20	129	12	35	--	60	10	5-15
2.26	liquid material expelled from ileum						
2.30	135	--	57	--	55	6	5-21

In this subject, the pulse rate decreased for about 15 minutes following nemural, then increased slightly above normal for the remainder of the experiment. Respiratory rate did not show any variation. The ileum balloon record showed in general an increase in tone. This was especially evident immediately after the administration of the drug and also toward the end of the experiment. Data on rhythmic contractions could not be obtained due to interference by respiration. The colon balloon showed a rather marked decrease in the tone level. It also showed a decrease in frequency of rhythmic waves.

TABLE XII

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 26

June 20, 1945

9 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight

Total dose: 78.9 mgm. of nemural given in a piece of
canned meat

Analysis of the kymographic record:

Time	Pulse Rate	Resp. Rate	Tone Level	<u>Ileum Balloon</u>			<u>Colon Balloon</u>			Other Obs.
				Rhythmic Contract.	Frequency	Amplitude	Tone Level	Frequency	Amplitude	
3.37	60	12	45	9	--	--	77	9	10-20	Emesis
3.47	60	11	47	8	--	--	75	8	8-20	
3.48	administration of nemural									
3.51	54	--	--	--	--	--	--	--	--	
3.53	42	--	90	--	--	--	125	--	--	
4.03	36	20	70	9	--	--	105	--	--	
4.06	liquid material expelled from ileum									
4.13	60	15	60	11	--	--	105	10	11-18	
4.16	liquid material expelled from ileum									
4.23	56	13	95	9	--	--	83	--	--	
4.27	liquid material expelled from ileum									
4.39	48	11	72	10	--	--	77	--	--	
4.59	72	10	57	--	--	--	67	--	--	

Slowing of the pulse rate was evident after nemural was given. From the normal of 60 beats per minute, it decreased to 36 in about 15 minutes following the administration of the drug, then the rate increased reaching 72 at the end of the experiment. Respirations increased somewhat above normal after one early emesis had occurred and then it remained close to the previous normal rate.

The ileum balloon shows an increase in tone level. This increase was evident immediately after nemural was given. From the normal of 47 mm. it increased to 90 mm. in 5 minutes. The increased tone was especially obvious when liquid material was expelled from the opening of the ileum. Rhythmic contractions were increased by 1 to 2 contractions per minute. The amplitude was also increased when liquid material was expelled from the ileum. However, the amplitude was decreased from the normal in the periods between expulsions of liquid material. The colon balloon shows an increase in tonus for the entire experiment. This was greater following the administration of nemural. No rhythmic waves appeared during the first 10 minutes following nemural. The record shows a long period of quiescence of the colon. It started on the 30th minute following nemural and lasted for the remainder of the experiment. During this period of quiescence, no rhythmic waves were recorded.

TABLE XIII

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 28

May 12, 1945

9 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 28.8 mgm. given in a piece of canned meat

Analysis of the kymographic record:

Time	<u>Ileum Balloon</u>						<u>Colon Balloon</u>			
	Pulse Rate	Resp. Rate	Tone Level	<u>Waves</u>			Tone Level	<u>Waves</u>		Other Obs.
				Frequency	Amplitude	Rhythmic Contrac.		Frequency	Amplitude	
3.55	96	19	93	--	--	14	147	--	--	
3.59	liquid material expelled from ileum									
4.05	102	25	83	3	17	--	147	--	--	
4.08	liquid material expelled from ileum									
4.15	102	25	85	2	17-18	--	151	--	--	
4.15	administration of arecoline hydrobromide									
4.21	--	--	100	--	--	--	157	--	--	
4.22	liquid material expelled from ileum									
4.25	78	20	93	--	--	--	150	--	--	
4.30	--	21	95	--	--	--	--	--	--	
4.35	78	23	93	--	--	13	145	--	--	
4.41	--	--	104	--	--	--	146	liquid material expelled		
4.45	102	26	103	--	--	12	148	--	--	
4.55	108	25	90	1	14	12	145	--	--	
5.05	114	19	102	--	--	12	145	--	--	

A decrease in pulse rate from the normal of 102 to 60 per minute occurred in 6 minutes following administration of the drug. This lasted for about 20 minutes, then started to increase and 40 minutes later the rate was above the previous normal. Respiratory rate did not show any significant change. The recording of the ileum balloon shows an increase in tone level. This remained above normal for about one hour after the drug was given. Peristaltic waves were not well marked in this case. Rhythmic contractions remained almost constant and in some instances they were so irregular in character due largely to interference by respiration that accurate determinations of rate could not be made. This was especially evident immediately following administration of the drug. The colon record shows a slight increase in tone level immediately after administration of the drug. Rhythmic waves were not present in the normal, although after the drug was administered some rhythmic waves appeared. When liquid material was expelled from the ileum the record showed an increase in tone level and also the presence of a peristaltic wave.

TABLE XIV

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 28

May 22, 1945

8.5 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 40.8 mgm. given in a piece of canned meat

Results:

Time	Pulse Rate	Resp. Rate	Tone Level	<u>Ileum Balloon</u>			Tone Level	<u>Colon Balloon</u>		Other Obs.	
				Frequency	Amplitude	Rhythmic Contract.		Frequency	Amplitude		
1.25	96	16	56	--	--	11	116	9	7-21		
1.35	82	13	58	2	12-32	10	120	11	15-42		
1.45	96	14	72	--	--	11	111	9	18-37		
1.45	administration of arecoline										
1.50	48	--	85	--	--	12	170	--	--		
1.55	36	27	73	--	--	12	155	10	28-56		
2.05	48	18	70	1	27	11	158	7	15-42		
2.10	2nd paper										
2.20	72	12	69	2	7-9	--	138	8	22-25		
2.30	84	14	63	--	--	11	135	9	24-28		
2.40	90	13	65	1	31	12	135	9	20-40		
2.50	84	12	65	--	--	11	133	9	30-60		
3.00	66	14	60	1	18	12	130	--	--		

In this subject there was a definite slowing of the pulse rate in 7 minutes following the administration of the drug. The rate decreased from 96 to 36 and remained at this level for about 5 minutes, then increased gradually reaching a rate of 90 in 65 minutes following the drug. At this time the pulse rate started decreasing again. Respiratory rate was somewhat increased shortly after the administration of the drug. This may have been due to excitement since the data show no appreciable change afterward. The record obtained from the ileum balloon showed an increase in tone level of 13 mm. following the administration of the drug. The level then remained above normal for the remainder of the record and was especially evident before and during the recording of a peristaltic wave. Peristaltic waves were somewhat indistinct, of low amplitude and resembling tone waves. The presence of these waves, however, is not accompanied by any increase in the tone level of the colon. Rhythmic contractions did not vary in frequency from the normal. A deviation of one contraction above normal was sometimes noted. The record obtained from the colon balloon shows an increase in tone immediately after the administration of arecoline hydrobromide, which persisted for the remainder of the experiment. In general, the amplitude of the rhythmic waves was increased. The highest value was recorded in 12 minutes following administration of the drug.

TABLE XV

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 28

May 17, 1945

9 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 52.6 mgm. of nemural given in a piece of
canned meat

Analysis of the kymographic record:

Time	Pulse Rate	Resp. Rate	Tone Level	<u>Ileum Balloon</u>			<u>Colon Balloon</u>			Other Obs.
				Rhythmic Contrac.	Frequency	Amplitude	Tone Level	Frequency	Amplitude	
2.04	96	12	42	10	1	28	107	10	12-31	
2.14	108	11	55	10	--	--	106	8	21-49	
2.24	114	12	51	10	--	--	94	--	--	
2.25	administration of nemural									
2.31	78	17	87	10	--	--	120	--	--	
2.41	90	11	46	10	--	--	95	8	12-23	
2.43	liquid material expelled from ileum									
2.53	102	11	64	9	--	--	117	9	10-32	
3.00	108	11	51	10	--	--	95	--	--	

This subject showed a decrease in pulse rate after drug administration. From the previous normal of 114 the rate fell to 78 beats per minute in about 6 minutes following nemural, then started to increase and finally reached a rate of 108 in 29 more minutes. Respiration did not show any variation in rate during the entire experimental period.

The ileum balloon tracing showed an increase in tone from a normal of 51 mm. to 87 mm. immediately after nemural was given. This increase lasted for about 6 minutes. The general tone level was increased above normal; this was especially evident when liquid material was expelled from the ileum. Rhythmic contractions did not vary in frequency from the previous normal. The colon balloon showed also an increase in tone level. This was particularly evident immediately after the administration of the drug and also when liquid material was expelled from the ileum. Two periods of partial quiescence occurred: the first one occurred 12 minutes after nemural and lasted for about 6 minutes, while the second occurring 29 minutes following nemural also lasted for about 6 minutes.

TABLE XVI

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 28

May 29, 1945

8 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight

Total dose: 70.2 mgm. of nemural given in a piece of
canned meat

Results:

Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	<u>Ileum Balloon</u>		<u>Colon Balloon</u>		
					<u>Waves</u>		<u>Waves</u>		
					Frequency	Amplitude	Tone Level	Frequency	Amplitude
9.50	96	20	50	9	--	--	86	--	--
10.00	96	16	56	9	--	--	90	--	--
10.01	administration of nemural								
10.08	liquid material expelled from ileum								
10.10	66	19	75	10	--	--	95	--	--
10.20	78	12	68	9	--	--	88	7	13-27
10.30	78	13	76	--	--	--	90	7	8-20
10.40	84	15	64	--	--	--	83	--	--
10.50	72	17	59	9	--	--	84	--	--
11.03	2nd paper								
11.13	96	17	78	10	--	--	92	--	--
11.23	78	12	67	9	--	--	88	--	--
11.33	90	13	70	--	--	--	89	--	--
11.43	90	11	75	--	--	--	90	--	--

In this subject a decrease in pulse rate occurred immediately after the nemural was given, from the normal of 96 to 66 in 9 minutes following the administration of the drug. Then the rate increased in a progressive manner returning to the normal of 96 beats per minute in 72 minutes from the time of the drug administration. Respiration did not show a marked variation from the normal contrary to observations in other experimental subjects.

The ileum balloon record shows an increase in tone level following nemural. There were alternate increases and decreases of a few millimeters but the tone level was always above the normal for the entire experiment. Rhythmic contractions increased by one contraction per minute on two occasions. The colon balloon record showed a transient increase in tone immediately after the drug was given. It remained slightly below normal coincident with the occurrence of several periods of quiescence during which no rhythmic waves appeared on the record.

TABLE XVII

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 29

May 15, 1945

10 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. given in a piece of canned meat

Analysis of the kymographic record:

Time	<u>Ileum Balloon</u>						<u>Colon Balloon</u>			Other Obs.
	Pulse Rate	Resp. Rate	Tone Level	Frequency	Amplitude	Rhythmic Contract.	Tone Level	Frequency	Amplitude	
2.34	78	9	85	--	--	--	120	--	--	
2.44	90	14	84	1	23	--	127	10	12-18	
2.54	90	11	85	1	21	--	125	5	20-28	
2.55	administration of arecoline hydrobromide									
3.05	78	17	105	--	--	--	155	8	12-18	
3.10	78	14	liquid material expelled from ileum							
3.15	96	14	86	--	--	--	144	7	20-24	
3.23	liquid material from ileum									
3.25	102	16	86	--	--	--	140	9	10-21	
3.35	2nd paper									
3.45	90	14	106	--	--	--	130	--	--	
3.55	78	13	100	--	--	--	130	--	--	
4.05	90	13	85	--	--	--	128	--	--	
4.15	78	12	91	--	--	--	133	9	15-18	
4.25	90	13	93	--	--	--	130	5	12-20	

An initial decrease in pulse rate of short duration was seen in this subject following which considerable variations in rate occurred. Occasionally the rate was above the previous normal. Respiratory rate was slightly increased above normal. Immediately after the drug was given the tone level of the ileum was increased from 85 to 105 mm. on the record and remained in spastic contraction for about 9 minutes, then liquid material was expelled from ileum and the recording showed a succession of increases and decreases in tone level. Rise of the tone level was especially evident following the expulsion of liquid material from the ileum and the record resembled that which might be produced by a long peristaltic wave. After 90 minutes the ileum record showed a spastic contraction which lasted for about 5 minutes. The entire record failed to show the presence of any peristaltic waves, although following the expulsion of liquid material from ileum the record showed long waves which could be classified as peristaltic waves. Rhythmic contractions were not sufficiently distinct to be considered in this experiment. If present, they were so small as to be obscured by respiratory interference on the record. The colon record showed an increase in tone level immediately after the administration of the drug. The tone level remained increased for the duration of the experiment. Twenty minutes after administration of the drug, the record showed a relaxation of the colon lasting for about 25 minutes; during this time, the rhythmic waves were not present.

TABLE XVIII

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 30

May 18, 1945

5.5 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 32.3 mgm. of nemural given in a piece of
canned meat

Results:

Time	<u>Ileum Balloon</u>						<u>Colon Balloon</u>		
	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	<u>Waves</u>		Tone Level	<u>Waves</u>	
					Frequency	Amplitude		Frequency	Amplitude
2.10	120	12	58	12	--	--	103	10	10-20
2.20	126	12	90	11	--	--	105	12	23-28
2.21	administration of nemural								
2.27	84	18	119	--	--	--	162	--	--
2.37	84	12	88	10	--	--	110	11	15-51
2.47	102	11	90	10	--	--	98	11	13-32
2.57	108	10	86	11	--	--	98	9	16-34
3.07	114	11	87	10	1	31	89	--	--
3.22	102	11	85	--	2	36	87	--	--
3.25	2nd paper								
3.35	102	12	87	11	1	25	91	11	15-29
3.45	102	10	93	11	2	29-31	83	--	--
3.55	102	10	90	10	1	36	97	11	9-38
4.05	114	11	95	--	2	32-35	84	--	--
4.15	108	12	100	11	--	--	98	9	11-41

A decrease in pulse rate occurred after nemural was given. It was especially evident immediately after drug administration. From the last normal of 126 beats per minute it fell to 84 in 5 minutes following the drug and remained at this rate for about 10 minutes, then pulse rate increased to 102 to 108 for the remainder of the experiment. Data on respiration show an increase in rate immediately after the nemural was given, but after this transient increase the rate fell somewhat below normal. This decrease was not more than 1 to 2 respirations per minute.

The ileum balloon record shows an increase in tone level from the normal of 90 mm. to 119 mm. during the first 6 minutes following nemural. Then the tone remained at a level varying from 85 to 100 for the rest of the record. Rhythmic contractions decreased occasionally by one contraction per minute. From the previous normal of 11 to 12 it fell to 10 to 11. Peristaltic waves were present in this subject. They appeared 45 minutes after administration of the drug. The frequency varied from 1 to 2 waves per 10 minutes intervals and the amplitude ranged from 25 to 36 mm. on the record. The colon balloon record also showed a definite increase in tone following nemural administration. From the last normal of 105 mm. it increased to 162 mm. and lasted until the 6th minute. In 10 more minutes the tone level decreased to 110 mm. and for the remainder of the experiment, it alternated between 84 to 98 mm. The frequency of the rhythmic waves showed some variations. From the normal of 10 to 12 waves in a period of

10 minutes there was a decrease to 9 to 11. However, amplitude was increased in some of the rhythmic waves. Periods of partial quiescence of the colon appeared on the record. During these periods rhythmic waves were small and few in number.

TABLE XIX

Tabulated Data from an Ordinary Fistula
of the Ileum in One Dog

Dog No. 48

July 18, 1945

10 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. given in a piece of canned meat

Results:

Time	<u>Ileum</u>						
	<u>Waves</u>						
	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	Frequency	Amplitude	Quiescence
3.00	126	26	36	9	--	--	--
3.01	administration of arecoline hydrobromide						
3.08	24	44	65	10	--	--	--
3.18	30	37	36	9	3	35-45	35'
3.28	96	28	26	--	--	--	--
3.38	104	31	27	--	--	--	--
3.48	108	36	24	--	--	--	--
3.53	96	36	27	--	--	--	--
4.05	120	35	28	10	--	--	--
4.15	2nd paper						
4.22	114	40	27	9	--	--	--
4.27	120	35	34	10	--	--	19'
4.37	132	32	25	--	--	--	--
4.47	144	38	25	--	--	--	--

From the previous normal of 126 the pulse rate fell to 24 beats per minute in 7 minutes following arecoline hydrobromide. Then the rate increased progressively to reach 108 in about 40 minutes. After this time, the pulse rate was irregular but increased above normal toward the end of the experiment. The respiratory rate was above normal during the whole experiment and especially increased immediately after arecoline hydrobromide was given.

The ileum balloon record showed a great activity during the first 15 minutes following the administration of the drug. During this time, the tone level increased from the normal of 36 mm. to 65 mm. Rhythmic contractions increased in frequency from 9 to 10 contractions per minute; they also increased in amplitude. Three peristaltic waves appeared on the record ranging in amplitude from 35 to 45 mm. This period of gut activity was followed by one of quiescence lasting for about 35 minutes. During this time no rhythmic contractions appeared on the record and tone decreased reaching a low of 24 mm. Another period of quiescence of the ileum lasting about 19 minutes occurred in 86 minutes following arecoline hydrobromide.

3. Thiry Loop. The data derived from an analysis of the various kymographic records and other observations in this series are set forth in tables as follows:

Dog No. 57

- | | |
|--------------|--|
| Table XX. | Arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight. |
| Table XXI. | Arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight. |
| Table XXII. | Nemural in a dose equivalent to are-
coline hydrobromide at the rate of
3.2 mgm. per kgm. body weight. |
| Table XXIII. | Nemural in a dose equivalent to are-
coline hydrobromide at the rate of
4.8 mgm. per kgm. body weight. |

Dog No. 61

- | | |
|--------------|--|
| Table XXIV. | Arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight. |
| Table XXV. | Arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight. |
| Table XXVI. | Nemural in a dose equivalent to are-
coline hydrobromide at the rate of
3.2 mgm. per kgm. body weight. |
| Table XXVII. | Nemural in a dose equivalent to are-
coline hydrobromide at the rate of
4.8 mgm. per kgm. body weight. |

TABLE XX

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 57

October 15, 1945

8 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. given in a piece of canned meat

Analysis of the record:

Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	<u>Ileum</u> <u>Waves</u>			Other Obs.
					Frequency	Amplitude	Quiescence	
5.00	108	19	11	69	--	--	--	
5.10	108	19	11	70	--	--	--	
5.20	102	17	11	64	--	--	--	
5.25	administration of arecoline hydrobromide							
5.35	84	30	11	60	--	--	--	
5.45	84	27	11	60	1	16	--	
5.50	90	33	--	48	--	--	13'	borborygmus defecation
5.59	102	27	--	50	--	--	--	
6.03	102	--	--	48	--	--	--	
6.13	114	24	9	51	--	--	--	

Analysis of the record and of the corresponding data contained in Table XX shows a decrease in pulse rate immediately following the administration of the drug. From a previous normal of 102 beats per minute it fell to 84 in 6 minutes following drug administration. This rate persisted for approximately 10 minutes then it began to increase and reached the previous normal in about 10 more minutes. This rate was maintained for the remainder of the experiment. The respiratory rate was increased after drug administration. From a previous normal of 17 respirations per minute increased to 33 in 20 minutes, then decreased toward the end of the experiment to 24 respirations per minute.

The recording of the gut activity shows a decrease in tone which was especially evident during a period when no rhythmic contractions appeared on the record. For a period lasting from the 25th to the 38th minute following arecoline no contractions of any type were recorded. This phenomenon was preceded by considerable borborygmus with defecation occurring toward the end of this period of evident quiescence.

TABLE XXI

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 57

October 27, 1945

9 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 43.2 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	<u>Ileum</u> <u>Waves</u>			Other Obs.
					Frequency	Amplitude	Quiescence	
10.50	108	13	73	12	--	--	--	
11.00	96	11	73	12	--	--	--	
11.10	96	14	70	12	--	--	--	
11.15	administration of arecoline hydrobromide							
11.20	96	16	70	12	--	--	19'	
11.25	138	--	61	--	--	--	--	defecation
11.28	102	--	65	--	--	--	--	defecation
11.32	--	--	64	--	--	--	--	defecation
11.35	96	26	64	--	--	--	--	defecation
11.39	90	--	63	--	--	--	--	
11.42	--	17	62	--	--	--	--	defecation and mucus
11.52	84	14	62	11	--	--	--	
12.00	84	15	60	11	--	--	--	
12.07	--	--	--	--	--	--	--	2nd paper
12.17	96	15	57	11	--	--	--	Rhythmic contractions increased in amplitude
12.27	84	11	60	11	--	--	--	
11.37	90	14	55	--	--	--	--	

In this subject the administration of arecoline was followed by a decrease in pulse rate from the normal of 96 to 84 to 90 per minute. There was, however, an increase in rate to 138 per minute shortly after drug administration. Respiratory rate was in general slightly increased. This was especially evident when scanty and repeated defecations occurred. The ileum balloon tracing shows a progressive but irregular decrease in tone level. In 5 minutes following administration of the drug, the record shows a period of complete quiescence lasting for about 19 minutes. However, four defecations occurred during this period. The frequency of the rhythmic contractions decreased from 12 to 11 per minute. In one hour following arecoline hydrobromide rhythmic contractions increased in amplitude. No other waves appeared on the record in this subject.

TABLE XXII

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 57

November 28, 1945

9.5 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 55.5 mgm. of nemural dissolved in water and
given by stomach tube

Results:

Time	<u>Ileum</u>							Other Obs.
	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	<u>Waves</u>		Quiescence	
					Frequency	Amplitude		
3.09	72	15	8	73	--	--	--	
3.19	84	14	7	75	--	--	--	
3.29	90	16	9	73	--	--	--	
3.30	administration of nemural							
3.40	90	18	9	75	--	--	--	
3.48	--	--	--	--	--	--	--	defecation preceded by borborygmus
3.49	--	--	--	--	--	--	--	
3.50	96	22	8	70	--	--	17'	
3.53	--	--	--	--	--	--	--	emesis
4.00	78	25	--	69	--	--	--	
4.09	--	--	--	--	--	--	--	defecation, borborygmus
4.10	84	31	--	73	--	--	--	
4.16	--	--	--	--	--	--	--	defecation
4.20	90	33	10	71	--	--	--	
4.30	90	20	12	72	--	--	--	
4.32	2nd paper							
4.42	90	15	11	73	--	--	--	
4.52	90	13	12	74	--	--	--	
5.02	96	12	10	74	--	--	--	

This subject did not show any appreciable changes in pulse rate after nemural was given at the level mentioned above. The respiratory rate showed an increase above normal during the first 16 minutes following the administration of the drug. From the previous normal of 16 respirations per minute, the rate increased to a maximum of 33. Toward the end of the experiment the respiratory rate was below the last normal counted.

The ileum balloon record shows a slight variation in tone from the normal. There were small decreases and increases ranging from 2 to 4 mm. Rhythmic contractions showed some increase in frequency, from the normal of 9 contractions per minute to 10 to 12 after 50 minutes following the drug. This rate persisted for the remainder of the experiment.

Other observations recorded were a period of quiescence at the 20th minute following nemural which lasted for about 17 minutes. During this period no rhythmic contractions occurred. Defecation occurred three times, one in one minute before and two during the period of quiescence of the isolated loop. Emesis occurred once during this period. Defecations were always preceded by borborygmus.

TABLE XXIII

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 57

August 30, 1945

6 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight

Total dose: 52.6 mgm. of nemural given in a piece of
canned meat

Results of the kymographic record:

<u>Ileum Balloon</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
3.04	78	27	11	50	--	--	--	
3.14	84	29	11	50	--	--	--	
3.15	administration of nemural							
3.18	36	--	12	60	--	--	10'	
3.28	66	65	--	46	--	--	--	
3.30	72	--	--	43	--	--	--	defecation
3.34	--	--	--	43	--	--	--	defecation
3.37	72	--	--	46	--	--	--	defecation
3.47	72	28	11	41	--	--	--	
3.50	54	15	10	39	--	--	--	defecation
4.00	72	14	11	38	1	8	--	
4.08	84	13	10	48	--	--	--	

In this subject the pulse rate fell, from the last normal of 84, to 36 beats per minute in 3 minutes following nemural administration. This was followed by an increase reaching a rate of 72 in 12 more minutes. This last rate was maintained for about 17 minutes, then dropped again to 54. In 8 more minutes, the pulse rate returned to 84. Data on respiratory rate show some variations. Immediately after nemural was given, respiration increased considerably reaching a rate of 65 per minute from the last normal of 29. For about 32 minutes, the respiratory rate remained above normal in which time defecation occurred three times. Toward the end of the experiment, respiratory rate fell below normal.

The ileum balloon tracing shows in general a decrease in tone; however, an increase of 10 mm. on the record is observed immediately after nemural was given. This increase in tone lasted for about 3 minutes in which time rhythmic contractions were seldom seen. It was followed by a period of quiescence of the isolated loop lasting for about 10 minutes. No rhythmic contraction appeared during this time. Following the period of quiescence, three defecations occurred at very short intervals. During this period rhythmic contractions were somewhat irregular. In the final 20 minutes of the experiment a fourth defecation occurred. One peristaltic wave 8 mm. in amplitude appeared in this subject. The rate of the rhythmic contractions varied between 10 and 11 per minute.

TABLE XXIV

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 61

October 22, 1945

8 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

<u>Ileum</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
3.50	96	47	11	81	--	--	--	
4.00	96	38	10	78	--	--	--	
4.10	96	31	11	73	--	--	--	
4.20	78	28	10	71	--	--	--	
4.20	administration of arecoline hydrobromide							
4.26	90	31	11	83	--	--	--	
4.30	--	--	--	--	--	--	--	defecation
4.31	90	34	--	70	--	--	6	
4.37	90	33	--	75	--	--	--	
4.40	90	34	10	79	--	--	--	defecation
4.50	84	28	11	75	--	--	--	
5.00	78	26	10	70	--	--	--	
5.10	90	30	10	67	--	--	--	
5.12	--	--	--	--	--	--	--	2nd paper
5.22	96	38	10	65	--	--	--	
5.32	84	39	10	64	--	--	--	
5.42	96	21	10	64	--	--	--	
5.52	96	29	10	65	--	--	--	

In this subject the pulse rate remained essentially the same as the previous normal. Respiration did not show any changes except when defecation occurred at which time an increase in the rate was observed.

The ileum balloon record shows a definite increase in tone level and also rhythmic contractions were sharply defined and of equal amplitude following administration of the drug. This latter effect lasted for about 5 minutes. In 7 minutes following arecoline a period of a quiescence of the gut lasting for about 6 minutes occurred. During this time, no rhythmic contractions were recorded and tone level decreased somewhat. Toward the end of the experiment, the tone decrease again and rhythmic contractions showed alternating period of increased and decreased amplitude. Frequency of rhythmic contractions, when present, did not show any difference from the previous normal.

TABLE XXV

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 61

October 29, 1945

8 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 38.4 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

<u>Ileum</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	Frequency	Amplitude	Quiescence	Other Obs.
2.45	96	32	80	11	--	--	--	
2.55	84	26	78	11	--	--	--	
3.05	84	34	77	11	--	--	--	
3.15	84	24	75	12	--	--	--	
3.15	administration of arecoline hydrobromide							
3.25	72	44	74	11	--	--	--	
3.34	--	--	--	--	--	--	--	defecation
3.35	96	35	72	11	--	--	17'	
3.37	78	--	68	--	--	--	--	defecation
3.39	66	--	68	--	--	--	--	defecation
3.47	72	--	66	--	--	--	--	defecation with mucus
3.52	72	--	65	--	--	--	--	Emesis
4.02	--	--	--	--	--	--	--	2nd paper
4.12	66	33	67	11	--	--	--	
4.22	60	17	66	11	--	--	--	
4.32	84	26	70	11	--	--	--	

Arecoline hydrobromide in this subject caused a definite and sustained decrease in the pulse rate. From a previous normal of 84 it decreased to 66 in 24 minutes following administration of the drug. In 43 more minutes the pulse rate decreased further to 60 per minute. Then it increased to normal at the end of the experiment. Respiratory rate showed an increase immediately after the drug was given. From a previous normal of 24 it reached 44 in 10 minutes. It remained above normal for about 47 minutes in which time defecation occurred four times and emesis once. Toward the end of the experiment, the respiratory rate returned to normal.

The record of the ileum balloon shows a rather slight decrease in tone level. This was not marked and the values in the table show some rhythmic variability. A period of quiescence occurred after 20 minutes following administration of the drug. This lasted for about 17 minutes and no contractions or waves were recorded during this time. Rhythmic contractions did not vary in frequency; however, the amplitude increased somewhat for short periods toward the end of the experiment.

TABLE XXVI

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 61

July 23, 1945

7 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 40.9 mgm. of nemural dissolved in water and
given by stomach tube

Analysis of the record:

Ileum Balloon

Waves

Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	Frequency	Amplitude	Quiescence	Other Obs.
1.59	90	--	50	10	--	--	--	
2.00	administration of nemural							
2.10	78	--	49	9	--	--	--	
2.16	--	--	--	--	--	--	--	defecation
2.20	66	--	41	--	--	--	--	
2.24	--	--	--	--	--	--	--	defecation
2.30	72	--	42	--	--	--	--	gut partially relaxed
2.40	72	--	39	10	--	--	--	
2.50	84	--	56	10	--	--	--	rhythmic contractions increased amplitude
3.00	78	--	54	10	--	--	--	
3.10	78	--	46	10	--	--	--	" " "
3.20	--	--	--	--	--	--	--	2nd paper
3.30	72	--	46	10	--	--	--	
3.40	78	--	46	10	--	--	--	rhythmic contractions increased amplitude

From a previous normal of 90 the pulse rate decreased to 66 per minute in 20 minutes following nemural. Data on the respiratory rate was not obtainable due to continuous panting of the animal. The ileum balloon record shows a decrease in tone level during the first 40 minutes. This was from a normal of 50 mm. to 39 mm. It was followed by an increase above normal reaching 56 mm. in 10 more minutes, then decreased progressively to a level of 46 mm. at the end of the observation period. Rhythmic contractions did not vary in frequency, although there were periodic increases in amplitude similar to those seen in previous records. Defecation occurred twice.

TABLE XXVII

Tabulated Data from a Thiry Loop
of the Ileum in One Dog

Dog No. 61

July 31, 1945

7.5 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate
of 4.8 mgm. per kgm. body weight

Total dose: 65.8 mgm. of nemural given in a piece of
canned meat

Results of the kymographic record:

<u>Ileum Balloon</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
2.20	84	--	9	61	--	--	--	
2.30	84	--	10	54	--	--	--	
2.40	84	--	9	43	--	--	--	
2.41	administration of nemural							
2.44	72	--	--	60	--	--	--	
2.45	90	--	--	--	--	--	--	emesis
2.55	66	--	10	49	--	--	--	
2.58	72	--	--	--	--	--	--	defecation
3.08	84	--	10	35	--	--	--	
3.11	--	--	--	35	--	--	--	defecation
3.14	66	--	--	33	--	--	--	defecation
3.24	66	--	10	37	--	--	--	
3.34	72	--	10	37	--	--	--	rhythmic contractions increased in amplitude
3.44	2nd paper							
3.54	84	--	10	41	--	--	--	" " "
4.04	78	--	10	37	--	--	--	" " "
4.14	84	--	10	37	--	--	--	
4.24	72	--	10	37	--	--	--	

In general a decrease in the pulse rate was observed in this subject, although alternated decreases and increases occurred. From the normal of 84 it increased to 90 beats per minute in about 5 minutes following nemural. Emesis occurred at this time, then pulse rate decreased to 66 in 10 more minutes. It increased again reaching 84 in 13 more minutes. Defecation occurred twice during this time. It was followed again by a decrease to 66 in 6 more minutes. From this time to the end of the experiment, pulse rate was 72 to 84 in alternative manner. Respiratory rate could not be recorded due to continuous panting of the animal.

The ileum balloon record shows a transient increase in tone immediately after the drug was given. This increase was from the normal of 43 mm. to 60 mm. and lasted for about 3 minutes. Rhythmic contractions during this period were of very low amplitude. Alternated periods of increases and decreases in the tone level occurred for the remainder of the experiment but in general there was a mean decrease in tone. Rhythmic contractions remained consistently at 10 per minute counted at 10 minute intervals during the whole time of the experiment. An increase in amplitude of the rhythmic contractions was observed after 53 minutes following nemural. Defecation occurred three times and the animal vomited once.

4. Thiry-Vella Loop. The data derived from an analysis of the various kymographic records and other observations in this series are set forth in tables as follows:

Dog No. 60

Table XXVIII. Arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table XXIX. Arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

Table XXX. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table XXXI. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

Dog No. 66

Table XXXII. Arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table XXXIII. Arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

Table XXXIV. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

Table XXXV. Nemural in a dose equivalent to arecoline hydrobromide at the rate of 4.8 mgm. per kgm. body weight.

The salient features of the data are summarized after each table.

TABLE XXVIII

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 60

October 23, 1945

8 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	<u>Ileum</u>			Other Obs.
					<u>Waves</u>			
					Frequency	Amplitude	Quiescence	
3.00	132	--	70	12	--	--	--	
3.10	120	--	66	11	1	16	--	
3.20	120	--	65	11	--	--	--	
3.30	126	--	58	12	3	7-19	--	
3.40	126	--	56	12	1	19	--	
3.43	administration of arecoline hydrobromide							
3.48	150	--	52	10	--	--	--	
3.53	132	--	61	10	--	--	--	
3.54	114	--	48	--	--	--	9'	
4.03	114	--	53	12	--	--	--	
4.05	108	--	47	--	--	--	6'	
4.11	108	--	47	--	--	--	--	
4.21	120	--	54	12	--	--	--	
4.32	--	--	--	--	--	--	--	2nd
4.42	120	--	49	12	--	--	--	
4.52	96	--	50	12	2	15	--	

2nd paper

The following summarizes the results from the analysis of the kymographic record obtained in this subject. A transient increase in pulse rate from the previous normal of 126 to a rate of 150 beats per minute was reached in 5 minutes following administration of the drug. This was followed by a progressive decrease reaching a low of 96 toward the end of the experiment. It was not possible to obtain data on respiratory rate due to a continuous panting of the subject.

The ileum balloon tracing shows an increase in tone from 56 mm. to 61 mm. in 10 minutes following arecoline. Rhythmic contractions during this period decreased in frequency from 12 to 10 contractions per minute following which there was a period of quiescence of the gut lasting for about 9 minutes. This quiescence of the ileum was accompanied by a decrease in tone from 61 mm. to 48 mm. on the record and no rhythmic contractions were evident. At the end of this period of inactivity tone level was restored to 53 mm. and frequency of rhythmic contractions appeared. These were similar to those seen in the previous normal. After 2 minutes of activity a second quiescent period is recorded lasting for about 6 minutes. Tone level decreased again from 53 mm. to 47 mm. and no waves of any type were recorded during this period of time. When gut activity was restored, tone increased from 47 mm. to 54 mm. and rhythmic contractions returned to normal. Toward the end of the experiment (in about 1h. and 10') the record shows a very slight decrease in tone level. Rhythmic contractions are to normal frequency but amplitude is increased for very short periods.

TABLE XXIX

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 60

November 12, 1945

8.5 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 40.8 mgm. given by stomach tube

Analysis of the kymographic record:

<u>Ileum Balloon</u>								
	<u>Waves</u>							
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
3.29	150	--	13	66	--	--	--	
3.39	180	--	12	63	--	--	--	
3.49	--	--	--	60	--	--	--	
3.50	administration of arecoline							
3.58	144	--	--	54	--	--	--	defecation
4.03	--	--	12	60	--	--	--	defecation
4.06	--	--	12	58	--	--	--	defecation
4.09	--	--	--	60	--	--	--	
4.19	--	--	12	60	--	--	--	
4.29	--	--	12	59	--	--	--	
4.32	--	--	--	--	--	--	10'	
4.42	--	--	12	53	--	--	--	
4.50	--	--	--	53	2	8	--	

It was impossible to obtain pulse and respiratory rates due to the extremely excited and the nervous condition of this animal. The ileum balloon record showed in general a decrease in tone. There were alternated decreases and increases but the main value was always below normal. Rhythmic contractions remained normal in frequency. A period of 10 minute quiescence of the ileum was recorded after 42 minutes following arecoline. During this period of quiescence no rhythmic contractions were recorded. Toward the end of the experiment 2 peristaltic waves of 8 mm. amplitude were recorded. Other manifestations in this subject were defecation three times.

TABLE XXX

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 60

November 1, 1945

9 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 52.6 mgm. of nemural dissolved in water and
given by stomach tube

Analysis of the record:

Ileum Balloon

Waves

Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
4.02	156	--	10	70	--	--	--	
4.12	144	--	12	70	--	--	--	
4.22	150	--	10	66	--	--	--	
4.23	administration of nemural							
4.33	180	--	--	61	--	--	--	
4.35	--	--	--	--	--	--	--	defecation
4.43	168	--	12	66	--	--	--	
4.44	--	--	--	--	--	--	--	defecation
4.47	--	--	--	--	--	--	--	defecation
4.53	132	--	12	59	--	--	--	

In this case there was observed a transient increase in pulse rate immediately after nemural. From a previous normal of 150 per minute, the rate increased to 180 in 11 minutes. It was followed by a decrease reaching 132 in 20 more minutes. Data on respiratory rate were unobtainable due to continuous panting of the animal. The ileum balloon record shows alternate increases and decreases in tone level. Rhythmic contractions increased in frequency from a normal of 10 to 12 contractions per minute. Defecation occurred three times.

[illegible]

Due to nervousness of this subject representative data on pulse and respiratory rates could not be obtained. The ileum balloon tracing showed an increase in tone level immediately after nemural was given. From the normal of 63 mm. it increased to 66 mm. lasting for about 45 minutes. During this time rhythmic contractions decreased in frequency by one contraction per minute. At the 53rd minute following the drug, tone level and rhythmic contractions returned to the previous normal. During the experiment, three defecations occurred, preceded by borborygmus. Micturition occurred at the end of the experiment.

TABLE XXXII

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 66

6 kgm. body weight

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 19.2 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

<u>Ileum</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Tone Level	Rhythmic Contract.	Frequency	Amplitude	Quiescence	Other Obs.
3.45	120	20	81	9	--	--	--	
3.55	120	17	75	9	--	--	--	
4.05	114	16	65	9	1	20	--	
4.15	114	14	57	9	--	--	--	
4.16	administration of arecoline hydrobromide							
4.26	102	15	65	9	2	25-28	--	
4.36	90	16	58	9	1	32	--	
4.46	90	15	60	10	2	20-23	--	
4.56	96	15	62	10	2	20-25	--	
4.56	--	--	--	--	--	--	--	emesis
4.59	--	--	--	--	--	--	--	emesis
5.05	84	14	66	10	5	12-26	--	
5.07	--	--	--	--	--	--	--	2nd paper
5.13	--	--	--	--	--	--	--	emesis
5.17	96	18	59	--	4	14-34	--	
5.27	90	13	60	--	2	30-32	--	
5.37	102	13	55	9	1	38	--	
5.47	102	12	52	--	2	20-23	--	
5.57	84	12	52	--	2	13-28	--	

Analysis of the kymographic record and of the corresponding data inserted in Table XXXII show that arecoline hydrobromide at the level used in this case caused a decrease in pulse rate from the previous normal of 114 to a frequency of 84 beats per minute in about 49 minutes following administration of the drug. A progressive increase is shown toward the end of the experiment. Data on respiratory rate shows no appreciable changes from the previous normal during 60 minutes following the drug, then a slight decrease occurred.

The ileum balloon record shows an increase in tone following administration of arecoline. This increase was from 57 mm. to 65 mm. in about 10 minutes. Following the initial increase there was a progressive but irregular decrease in tone for the remainder of the experiment. Rhythmic contractions increased in frequency from 9 to 10 per 10 minute interval. Waves other than rhythmic contractions were recorded in this subject. These varied in frequency from 1 to 5 per 10 minute period. They also varied in amplitude from 12 to 38 mm. Other manifestations recorded in this case were emesis which occurred three times.

TABLE XXXIII

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 66

October 30, 1945

6 kgm. body weight

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 28.8 mgm. dissolved in water and given by
stomach tube

Analysis of the record:

Time	<u>Ileum</u>							
	<u>Waves</u>							Other Obs.
	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	
2.35	90	19	9	63	--	--	--	
2.45	96	19	10	60	--	--	--	
2.55	90	18	10	62	--	--	--	
3.05	90	17	10	60	--	--	--	
3.05	administration of arecoline hydrobromide							
3.15	78	18	10	61	--	--	--	rhythmic contractions increased amplitude
3.25	72	15	11	60	--	--	--	
3.35	72	16	10	58	--	--	--	
3.39	--	--	--	--	--	--	--	emesis
3.40	--	--	--	--	--	--	--	2nd paper
3.50	84	15	12	54	--	--	--	rhythmic contractions increased amplitude
4.00	66	14	10	58	--	--	--	
4.10	78	11	11	50	--	--	6'	
4.20	78	12	12	52	--	--	4'	

This subject showed a marked decrease in pulse rate following arecoline. From a previous normal of 90 it fell to 66 in 55 minutes following administration of the drug. Respiratory rate decreased in progressive manner from a normal of 17 to 12 respirations per minute at the end of the experiment.

The ileum balloon record showed alternating periods of increased and decreased tone but the level was in general decreased somewhat from the previous normal. The record also shows two short periods of partial relaxation of the gut occurring toward the end of the experiment. Rhythmic contractions increased in frequency from 10 to 12 per 10 minute intervals and they also increased in amplitude. This animal vomited once, 34 minutes following the drug.

TABLE XXXIV

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 66

November 8, 1945

7.5 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
3.2 mgm. per kgm. body weight

Total dose: 28.8 mgm. of nemural dissolved in water and
given by stomach tube

Analysis of the record:

<u>Ileum Balloon</u>								
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	<u>Waves</u>		Quiescence	Other Obs.
					Frequency in 10'	Amplitude		
3.14	78	25	10	70	--	--	--	
3.24	78	23	11	69	--	--	--	
3.34	66	23	11	67	--	--	--	
3.35	administration of nemural							
3.45	60	20	11	64	--	--	--	
3.55	60	16	12	62	--	--	3'	
3.59	--	--	--	--	--	--	--	emesis
4.05	54	31	--	60	--	--	26'	
4.15	60	22	--	60	--	--	--	
4.25	72	20	11	58	--	--	6'	
4.33	--	--	--	--	--	--	--	2nd paper
4.43	84	30	12	58	--	--	--	
4.53	84	17	11	55	--	--	--	
4.55	84	17	11	56	1	19	--	
5.05	78	14	11	55	1	15	3'	
5.15	66	13	--	55	1	18	7'	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	1225	1226	1227	1228	1229	1230	1231	1232	1233	1234	1235	1236	1237	1238	1239	1240	1241	1242	1243	1244	1245	1246	1247	1248	1249	1250	1251	1252	1253	1254	1255	1256	1257	1258	1259	1260	1261	1262	1263	1264	1265	1266	1267	1268	1269	1270	1271	1272	1273	1274	1275	1276	1277	1278	1279	1280	1281	1282	1283	1284	1285	1286	1287	1288	1289	1290	1291	1292	1293	1294	1295	1296	1297	1298	1299	1300	1301	1302	1303	1304	1305	1306	1307	1308	1309	1310	1311	1312	1313	1314	1315	1316	1317	1318	1319	1320	1321	1322	1323	1324	1325	1326	1327	1328	1329	1330	1331	1332	1333	1334	1335	1336	1337	1338	1339	1340	1341	1342	1343	1344	1345	1346	1347	1348	1349	1350	1351	1352	1353	1354	1355	1356	1357	1358	1359	1360	1361	1362	1363	1364	1365	1366	1367	1368	1369	1370	1371	1372	1373	1374	1375	1376	1377	1378	1379	1380	1381	1382	1383	1384	1385	1386	1387	1388	1389	1390	1391	1392	1393	1394	1395	1396	1397	1398	1399	1400	1401	1402	1403	1404	1405	1406	1407	1408	1409	1410	1411	1412	1413	1414	1415	1416	1417	1418	1419	1420	1421	1422	1423	1424	1425	1426	1427	1428	1429	1430	1431	1432	1433	1434	1435	1436	1437	1438	1439	1440	1441	1442	1443	1444	1445	1446	1447	1448	1449	1450	1451	1452	1453	1454	1455	1456	1457	1458	1459	1460	1461	1462	1463	1464	1465	1466	1467	1468	1469	1470	1471	1472	1473	1474	1475	1476	1477	1478	1479	1480	1481	1482	1483	1484	1485	1486	1487	1488	1489	1490	1491	1492	1493	1494	1495	1
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While the pulse rate in this subject showed some variation, it was decreased for the first 40 minutes following nemural. This decrease varied from 6 to 12 beats per minute below the lowest normal reading. Then an increase in rate occurred which lasted for 50 minutes. The rates observed during this period were from 6 to 18 beats per minute faster than the lowest normal. The rate was normal at the end of the period of observation. Respiratory rate showed no significant changes other than a decrease in rate toward the end of the experiment. The ileum balloon record shows a progressive but slight decrease in tone. Periods of partial relaxation of the gut were observed and during these periods rhythmic contractions were seldom seen. The frequency of rhythmic contractions was in general the same as the previous normal; however, an increase from 11 to 12 was observed on two occasions. Peristaltic waves at the frequency of one every 10 minutes followed by partial quiescence of the gut were seen after 80 minutes following the administration of the drug. Emesis occurred once.

TABLE XXXV

Tabulated Data from a Thiry-Vella Loop
of the Ileum in One Dog

Dog No. 66

November 15, 1945

6.5 kgm. body weight

Drug: nemural

Dose: equivalent to arecoline hydrobromide at the rate of
4.8 mgm. per kgm. body weight

Total dose: 57 mgm. of nemural dissolved in water and
given by stomach tube

Results of the kymographic record:

<u>Ileum Balloon</u>								
<u>Waves</u>								
Time	Pulse Rate	Resp. Rate	Rhythmic Contract.	Tone Level	Frequency	Amplitude	Quiescence	Other Obs.
4.33	84	20	10	63	--	--	--	
4.43	72	15	11	63	--	--	--	
4.53	72	16	10	60	--	--	--	
4.54	administration of nemural							
5.04	90	15	12	61	--	--	--	
5.14	60	20	11	57	--	--	--	
5.24	72	17	12	57	--	--	--	
5.34	72	17	14	58	--	--	--	
5.36	78	--	--	--	--	--	--	emesis
5.44	72	14	18	56	--	--	--	
5.52	2nd paper							
6.02	66	14	10	52	--	--	--	
6.12	78	14	12	53	--	--	--	
6.22	66	13	11	55	--	--	--	
6.32	78	12	10	55	--	--	--	

Data on pulse rate showed a transient increase in the rate during the first 10 minutes following nemural. From a previous normal of 72 it increased to 90 beats per minute. A slight decrease from normal was recorded for the remainder time of the experiment. Respiratory rate was in general below the last normal counted. A very transient increase of 4 respirations per minute above normal occurred in about 20 minutes following the drug.

The ileum balloon record shows a slight decrease in tone level. Alternated periods of decreases and increases in tone were recorded but these were always below normal. Rhythmic contractions varied in frequency. From the previous normal of 10 contractions per minute it increased to 11 to 12. However, a frequency of 14 and 18 contractions per minute was recorded before and after emesis occurred.

IV DISCUSSION

A. Effects with Arecoline. In general, arecoline hydrobromide caused the same kind of physiological responses in the 47 dogs used. However, differences in degree were shown by groups of these experimental subjects.

1. Pulse Rate. Arecoline hydrobromide at the two levels used in dogs caused a decrease in pulse rate. One case, however, Dog No. 46, showed an increase from the previous normal. Variations in degree of responses were observed. Some of the experimental subjects* showed a gradual decrease in heart rate with recovery to normal by the end of the experiment. Other subjects** showed a pronounced slowing of the pulse lasting for the complete observation time (This period varied from 60 to 145 minutes). A third group of subjects*** showed a transient decrease in pulse rate followed by an increase above previous normal. This latter occurred toward the end of the experiment.

It was also observed that when arecoline hydrobromide powder was given in meat to the experimental subjects, a

* Dogs No. 11-13-14-17-18-41-57-59-61 given arecoline hydrobromide at the rate of 3.2 mgm. per kgm. body weight.

** Dogs No. 6-7-12-15-16-28-30-32-39-48-51-54 given arecoline hydrobromide at the rate of 3.2 mgm. per kgm. Also the majority of the subjects at the rate of 4.8 mgm. per kgm.

*** Dogs No. 29-38-43-45-49-50-63 at the rate of 3.2 mgm. per kgm. and Dogs No. 32-40-43-45 at the rate of 4.8 mgm. per kgm.

sudden but transient decrease in pulse rate occurred. This decrease was in some cases very marked and always occurred in from 6 to 10 minutes following the administration of the drug.

TABLE XXXVI

Effects on Heart Rate When Arecoline Powder
Was Given in a Piece of Meat

Dose: 3.2 mgm./kgm.

Dog No.	Pulse Rate		Time in Minutes
	Last Normal	Lowest Reached from Normal	
25	108	42	10'
26	123	increased	
28	102	60	6'
29	90	78	10'
48	126	24	7'

Dose: 4.8 mgm./kgm.

26	72	60	5'
28	96	36	10'

Table XXXVI contains a group of subjects in which arecoline hydrobromide powder was given in meat. It shows the differences in response immediately after drug administration. Dog No. 26 at the lower level of arecoline showed an increase in pulse rate instead of a decrease. Dog No. 29 showed a very slight decrease in pulse rate. Dogs No. 25, 48 and 28, on the other hand, showed a great fall in pulse rate.

The literature shows that arecoline in its systemic action causes cardiac slowing mainly by stimulation of the parasympathetic nerve endings. In the very early study of its actions Marmé (32) reported a temporary slowing of the heart when concentrated solutions (1%) were dropped into the eyes of rabbits. The temporary cardiac slowing previously described was seen to occur in some dogs when the powdered drug was given orally in meat or when small quantities of the pure drug was placed in the mouth. When meat alone was given or when the drug was administered by stomach tube this phenomenon was absent. Placing in the mouth of these same animals bitter or irritant agent such as gentian, quinine and alcohol likewise produced no cardiac slowing. These results indicate a possible similarity of reflex effect from the local action of arecoline on the buccal mucosa to those observed by Marmé with concentrated solution in the eyes of rabbits. This paradox is difficult to explain in the light of the usual results from irritation of sensory nerve endings by such agents as for example dilute ammonia vapor.

It is evident that the slowing of the pulse rate is caused by the systemic action of arecoline hydrobromide and also by a reflex stimulation upon the cardio inhibitor mechanism when in direct contact with mucous membrane, at least in certain areas. However, some animals may respond differently and an increase in pulse rate instead of a decrease may occur. Dog No. 26 was given arecoline hydrobromide three times at the level of 4.8 mgm. per kgm. body weight. Pulse rate showed varying results. An increase occurred the first

time. The second time only a slight decrease in pulse rate occurred and the third time there resulted a very marked decrease.

A possible explanation for the increased rate seen in some subjects may be that it is part of the reflex effects accompanying nausea, as described by Traube (52), Brooks and Luckhardt (6) and others (Miller (37)).

2. Purgative Action. The literature contains several reports which show that arecoline causes a rather quick evacuation of the bowels (21, 32, 36, 47). Feces are described to be of soft consistency at first, followed by foamy and liquid stools. Presence of mucus after several defecations has also been reported (32). The results in this study are in confirmation with those reported in the references cited.

TABLE XXXVII

Summary of the Incidence of Defecation
with Arecoline at Two Levels of Dosage

No. of Cases	Level of Arecoline HBr	Total Number of Defecations					Time of Observ.
		None	1	2	3	4	
47	3.2 mgm./kgm.	6	14	15	9	3	52-155
21	4.8 mgm./kgm.	-	4	9	6	2	60-138

Table XXXVII shows the variation in total number of defecations after arecoline hydrobromide was given orally by stomach tube. Of 47 dogs treated with arecoline hydrobromide at the level of 3.2 mgm. per kgm. body weight, 6 cases failed to defecate; 14 cases showed but one defecation; 15 defecated

twice; 9 defecated three times and only 3 cases defecated four times during periods of observation ranging from 52 to 155 minutes. In 21 of these dogs arecoline hydrobromide at a rate of 4.8 mgm. per kgm. body weight was given by stomach tube and the results as to number of defecations is inserted in the same table. In this group of animals, the majority of them defecated twice and almost one-third defecated three times during periods of observation ranging from 60 to 138 minutes.

As a rule the first defecation was of soft consistency, then scanty and repeated liquid or semi-liquid feces followed. It has been already reported (28) that arecoline causes dehydration of the tissues. It was observed that these animals were thirsty when returned to their cages at the termination of the experiment.

TABLE XXXVIII

The Time at Which First Defecation Occurred and Number of the Experimental Subjects Expressed by Percentage, with Arecoline at Two Levels of Dosage

Time	47 Dogs 3.2 mgm./kgm.	21 Dogs 4.8 mgm./kgm.
-- 10'	29.0%	47.6%
11-15'	20.0%	33.3%
16-20'	24.0%	9.5%
21-25'	6.4%	4.7%
26-30'	2.1%	0.0%
31-up'	18.5%	4.9%

Table XXXVIII shows the time and percentage of occurrence of the first defecation. According to these data

defecation occurred in the majority of the cases during the first 20 minutes following administration of arecoline hydrobromide at the level of 3.2 mgm. per kgm. body weight and during the first 15 minutes when 4.8 mgm. per kgm. body weight was given. However, in some cases no defecation had occurred 60 minutes following the drug and one case (Dog No. 10) defecated after 127 minutes.

3. Nauseant and Emetic Effects. Another relatively frequent symptom observed after arecoline hydrobromide was the presence of nausea accompanied by one or more emeses. Table XXXIX contains the occurrence of emeses expressed in percentage. Emesis occurred once in more than one-half of the cases.

TABLE XXXIX

Number of Emeses Occurring in Experimental Animals
after Arecoline Hydrobromide at Two Levels of Dosage

No. of Cases	Dose	Number of Emeses			
		None	1	2	3
47	3.2 mgm./kgm.	36.2%	63.8%	21.2%	4.2%
21	4.8 mgm./kgm.	23.8%	76.2%	33.3%	4.7%

Table XXXX gives the time in which the first emesis occurred. It may be observed that emesis occurred early (within 20 minutes) in the majority of the cases treated with arecoline at the level of 3.2 mgm. per kgm. body weight.

TABLE XXXX

Time of Occurrence of the First Emesis with Arecoline
at Two Levels of Dosage

Time	47 Dogs	21 Dogs
	3.2 mgm./kgm.	4.8 mgm./kgm.
-- 10'	16.6%	18.1%
11-20'	43.3%	27.2%
21-30'	6.6%	0.0%
31-up'	33.5%	54.7%

It is well known that emesis may occur by drugs that stimulate the vomiting center located in the medulla oblongata (Weiss and Hatcher). Mechanical and chemical irritants of various kinds acting upon vagal or sympathetic afferent terminations in the gastric mucosa may initiate vomiting reflexly (4). Marme (32) states that solutions of arecoline as weak as .04 percent causes a burning sensation with hyperemia when applied to the tongue. The presence of emesis after arecoline hydrobromide administration may be due to its irritant effects upon the gastric mucosa.

It was also observed that when early emesis occurred (within 20 minutes) the animal recovered soon from the drug effects. This is possibly by reason of loss of unabsorbed drug from the stomach. When emesis occurred later than 30 minutes following drug administration the animal exhibited a prolonged nauseant stage. A characteristic standing position was observed. The animal remained standing with his head down, his eyes fixed on one point and paying no attention to his surroundings. This state of depression was observed

especially in some overweight dogs to which, for this reason, relatively large total doses of arecoline hydrobromide was given. It also occurred in a few animals of normal weight when the higher level of the drug was administered.

4. Urinary Effects. Micturition did not occur as a constant effect of arecoline hydrobromide. However, it occurred in 19 of 47 cases when arecoline hydrobromide was used at the level of 3.2 mgm. per kgm. body weight. It was particularly observed in overweight dogs and the time of occurrence ranged from 1 to 105 minutes. It was repeated once in three cases. Micturition occurred in 10 of 21 dogs under the same drug at the level of 4.8 mgm. per kgm. body weight in from 8 to 48 minutes.

5. Effects on Gut Motility. Table XXXXI contains in a more concise form the comparative results from the analysis of the kymographic records taken on four dogs in two of which Thiry fistulae (Dogs No. 57 and 61) and the other two (Dogs No. 61 and 66) Thiry-Vella fistulae were prepared. These experimental subjects received arecoline hydrobromide at the levels of 3.2 mgm. and 4.8 mgm. per kgm. body weight.

TABLE XXXXI

Comparative Results from the Analysis of the Kymographic Records
Taken on 4 Dogs Prepared with Thiry Fistulae (Nos. 57 and 61) and
Thiry-Vella Fistulae (Nos. 60 and 66) after Arecoline Hydrobromide

Dosage: 3.2 mgm./kgm.

Animal No.	Pulse Rate		Rhythmic Contractions		Tone Level in mm.		Quiescence of the Gut	Other Obs.			
	Last Normal	Lowest Reached	Time in Minutes	Frequency	Normal	After Arecoline			Amplitude	Normal	Maximum Reached
57	102	84	10'	11-11	9-11	--	64	60	48	13'	1 defecation
60	126	96	69'	11-12	10-12	--	56	61	47	9-6'	--
61	78	78	40'	10-11	10-11	incr.	71	83	64	6'	2 defecations
66	114	84	49'	9-9	9-9	--	57	66	52	--	3 emeses

Dosage: 4.8 mgm./kgm.

57	96	84	37'	12-12	11-11	--	70	70	55	19'	5 defecations
60	180	144	8'	12-13	12-12	--	60	60	53	10'	"
61	84	60	67'	11-12	11-11	incr.	75	74	65	17'	"
66	90	66	55'	9-10	10-12	incr.	60	61	50	6-4'	1 emesis

The effects of arecoline on the motility of the gut can be studied somewhat satisfactorily with respect to the frequency of rhythmic contractions and to the number of peristaltic waves because both of these can be evaluated quantitatively. However, the method used was not suitable for recording peristaltic waves which are supposed to be increased in number after arecoline (8, 31, 40, 50, 51). Rhythmic contractions seem to decrease in frequency by 1-2 contractions per minute from the previous normal. However, in two cases (Dogs No. 61 and 66), the amplitude definitely increased. This was especially evident after 60 minutes following drug administration. Alvarez (2) has studied the influence of drugs on intestinal rhythmicity and concludes that drugs which increase or decrease the tone and amplitude of the contractions do not necessarily affect the rate.

The tone level varied somewhat after drug administration. An increase above previous normal was observed in the majority of the cases, but this increase lasted for short periods and alternated with decreases below the normal.

Periods of quiescence of the gut appeared on the record in all the cases, with the exception of Dog No. 66 at the 3.2 mgm./kgm. level of arecoline. During these periods of quiescence, no rhythmic contractions were recorded, the tone level decreased somewhat and several defecations of semi liquid feces occurred.

B. Discussion of Results with Nemural as Compared to Arecoline Hydrobromide on the Same Animals. While these two related drugs cause the same type of physiological

responses, they differ somewhat in degree and in the time of onset of action in the 18 experimental subjects used.

1. Pulse Rate. Both drugs cause slowing of the heart rate. This decrease rate was very definite and it lasted longer than the period of observation when nemural was used. Most of the animals receiving this drug appeared quite depressed. Under arecoline, these experimental subjects showed less depression or it was absent and heart rate recovered to normal toward the end of the observation period. An increase in heart rate instead of the expected decrease may occur with either one of these drugs. Also, a decrease followed by an increase above the normal was observed with both drugs.

2. Purgative Action. Table No. XXXXII illustrates the results in 18 experimental subjects in which both drugs were given at two different levels. At least one defecation occurred in each of the cases. Two defecations occurred in about three-fourth of the animals under both drugs. A third and fourth defecation were more prone to occur when nemural was given. Two cases under arecoline and two under nemural failed to defecate during the observation time.

There were some differences in the time of occurrence of the first defecation. With arecoline hydrobromide, 43.7% of the cases at the lower level and 50.0% of the cases at the higher level of dosage defecated once during the first 10 minutes following administration of the drug. The values for nemural were 28.2% and 47.0% at the lower and higher levels respectively. However, at the 20th minute, the incidence of occurrence of the first defecation was somewhat greater with nemural than with

TABLE XXXXII

Comparative Study of Arecoline Hydrobromide and Nemural
in 18 Dogs. Occurrence of Defecation
and Emesis Expressed in Percentage

Drug and Dosage	Defecations			Emeses		
	None	1st	2nd	3rd	4th	None
Arecoline 3.2 mgm./kgm.	11.1%	88.8%	72.2%	27.7%	5.5%	27.7%
Arecoline 4.8 mgm./kgm.	0.0%	100%	83.3%	38.8%	11.1%	50.0%
Nemural *	5.5%	94.4%	66.6%	50.0%	16.6%	44.4%
Nemural **	5.5%	94.4%	83.3%	33.3%	16.6%	38.8%

* Equivalent to arecoline hydrobromide at the rate of 3.2 mgm./kgm.

** Equivalent to arecoline hydrobromide at the rate of 4.8 mgm./kgm.

TABLE XXXXIII

The Time of Occurrence of First Defecation
with Arecoline and Nemural

Time	Arecoline Hydrobromide		Nemural	
	3.2 mgm./kgm.	4.8 mgm./kgm.	*	**
-- 10'	43.7%	50.0%	28.2%	47.0%
11-15'	12.5%	27.7%	35.2%	35.2%
16-20'	12.5%	11.1%	5.8%	17.8%
21-25'	6.2%	5.5%	11.7%	0.0%
26-30'	0.0%	0.0%	0.0%	0.0%
31-up'	25.1%	5.7%	19.1%	0.0%

TABLE XXXXIV

The Time of Occurrence of First Emesis
with Arecoline and Nemural

Time	Arecoline Hydrobromide		Nemural	
	3.2 mgm./kgm.	4.8 mgm./kgm.	*	**
-- 10'	38.4%	11.1%	50.0%	18.1%
11-15'	23.0%	22.2%	30.0%	18.1%
16-20'	0.0%	11.2%	10.0%	0.0%
21-25'	0.0%	0.0%	0.0%	18.1%
26-30'	7.6%	0.0%	0.0%	18.1%
31-up'	31.0%	55.5%	10.0%	26.6%

* Equivalent to arecoline hydrobromide at the rate of 3.2 mgm./kgm.

** Equivalent to arecoline hydrobromide at the rate of 4.8 mgm./kgm.

arecoline. With nemural at this time 69.2% at the lower and 100% at the higher level had shown a first defecation. The values for arecoline at a comparable period were 68.7% and 88.8% at the lower and higher levels respectively. The remainder of the first defecation with arecoline at both levels and nemural at the lower level were irregularly scattered throughout the balance of the period of observation. These periods ranged from 84 to 140 minutes.

3. Nauseant and Emetic Effect. Table XXXXII shows that the occurrence of emesis was of about equal frequency with both drugs. The incidence of occurrence of emesis, however, was not as great as that of defecation. The time of occurrence of the first emesis seems to vary with the dose used. With both drugs emesis was more delayed at the higher level of dosage. During the first 10 minutes following administration of the drug, emesis occurred in 38.4% at the lower and 11.1% at the higher level of dosage of arecoline. The values for nemural were 50.0% and 18.1% at the lower and higher levels respectively. At the 15th minute following administration of the drug, the incidence of occurrence of the first emesis was 61.4% and 33.3% with arecoline at the lower and higher level of dosage respectively and the values for nemural were 80.0% and 36.2%. Late emesis (in more than 31 minutes) was more prone to occur with arecoline than with nemural. The influence which the organic arsenic present in the nemural may have had on the differences in emetic effects would be difficult to evaluate. The somewhat earlier occurrence of emesis with nemural as compared to arecoline may

indicate some differences in these two compounds.

4. Effects on Gut Motility. Tables No. XXXXI and XXXXV give the results from the analysis of the kymographic records taken on four dogs prepared with Thiry fistulae (Nos. 57 and 61) and Thiry-Vella loops (Nos. 60 and 66) after arecoline hydrobromide and nemural respectively. Rhythmic contractions seem to decrease in frequency in 1-2 contractions per minute when arecoline was given. An increase in 1-3 contractions per minute occurred under nemural. Tone level increases somewhat with both drugs and it was especially evident when the drug was given in a piece of canned meat. Periods of quiescence of the gut appeared on the record almost always when arecoline was used and it appeared less frequent under nemural.

Five dogs (Nos. 25, 26, 28, 29 and 48) were prepared with ordinary fistulae on which kymographic records were taken after arecoline and nemural in powder were given in a piece of canned meat. Analysis of these records show an immediate and marked decrease in pulse rate after arecoline as it is shown in Table No. XXXVI. This decrease in heart rate was not observed when nemural was given. The ileum balloon record showed also an increase in tone level immediately after either one of the drugs was given. This increase seems to be more marked under nemural than with arecoline. There was a tendency for rhythmic contractions to be decreased in frequency under arecoline and to be increased under nemural.

Besides the 18 dogs treated with arecoline and nemural at the two levels already discussed, 20 more dogs were given nemural at a dosage equivalent to arecoline hydrobromide at the rate of 3.2 mgm./kgm. In these subjects one defecation occurred in 95% of the cases; a second defecation occurred in 60%; a third in 40% and a fourth defecation in 20% of the cases. The time of occurrence of the first defecation was as follows: During the first 10 minutes following nemural, 42.1% of the cases had shown the first defecation. At the 25th minute, 84.1% had defecated once and the rest (15.9%) defecated in more than 26 minutes following nemural. These results indicate some differences in time of onset and number of defecations as compared with the results obtained with 47 dogs under arecoline hydrobromide at the level of 3.2 mgm./kgm. It would appear that nemural has a more marked purgative effect causing more defecations in short time than arecoline.

One emesis occurred in 80% of the cases and it was repeated once in 53.8%. The first emesis occurred in 15 minutes in about 62.5% of the cases. At the 25th minute following nemural, the first emesis had occurred in 87.5% of the cases. The remainder (12.5%) vomited once after the 25th minute. These data show that early emesis is more frequent with nemural. All emetic effects occurred during the first 31 minutes following the administration of nemural.

TABLE XXXV

Comparative Results from the Analysis of the Kymographic Records
Taken on 4 Dogs Prepared with Thiry-Fistulae (Nos. 57 and 61) and
Thiry-Vella Fistulae (Nos. 60 and 66) after Nemural

Dose: equivalent to arecoline HBr at the rate of 3.2 mgm./kgm.

Animal No.	Pulse Rate		Rhythmic Contraction		Tone Level in mm.		Frequency					Quiescence of the Gut	Other Obs.
	Last Normal	Lowest Reached	Time in Minutes	Normal	After Nemural	Amplitude	Normal	Maximum Reached	Minimum Reached				
57	90	78	20'	7-9	8-12	--	73	75	69	17'	3 def.; 1 eme.		
60	150	132	30'	10-12	12-12	--	66	66	59	--	3 def.		
61	90	66	20'	10-10	9-10	incr.	50	56	41	--	2 def.		
66	66	54	30'	10-11	11-12	--	67	64	55	3'-26'	1 eme.		
Dose: equivalent to arecoline HBr at the rate of 4.8 mgm./kgm.													
57	84	36	3'	11-11	10-12	--	50	60	38	10'	4 def.		
60	144	144	10'	12-13	11-12	--	63	66	63	--	3 def.; 1 mict.		
61	84	66	14'	9-10	10-10	incr.	43	60	33	--	3 def.; 1 eme.		
66	72	60	20'	10-11	10-14	--	60	61	52	--	1 eme.		

V SUMMARY

1. Both drugs caused slowing of the heart rate. However, this slowing was more persistent with nemural than with arecoline hydrobromide when given by stomach tube. When the powdered drug was given in a piece of meat, arecoline caused an immediate and definite slowing of the heart rate which did not occur with nemural.

2. Purgative effect was more rapid in onset, and repeated defecations resulted in many subjects when either one of the drugs was given at the higher level of dosage. In general, the purgative action of arecoline hydrobromide appeared to be more rapid in onset than nemural, although the latter drug produced a more complete emptying of the bowels.

3. Early emesis occurred more often under nemural than with arecoline. Emesis was delayed with both drugs when the higher level was used. A prolonged state of nausea was observed under nemural similar to that observed with an increased dosage of arecoline. The animals exhibited greater and more prolonged depression with nemural than with arecoline.

4. The kymographic records showed that arecoline causes a decrease in rhythmic contractions by 1 to 2 contractions per minute and an increase in the tone level followed by a decrease. They also showed periods of quiescence of the isolated loop of intestine. Nemural caused an increase in the rate of the rhythmic contractions by 1 to 3 contractions per minute. The tone level is also increased followed by a decrease. Complete quiescence of the gut was less frequently

seen with nemural.

5. Micturition may be present following arecoline hydrobromide and less frequent following nemural.

6. There exists considerable variation in individual responses. The expected results may fail to occur with either one of these two drugs.

7. Both drugs caused the animal to be thirsty after medication. The ingestion of large amounts of water may aggravate the emetic effects.

REFERENCES

1. Alvarez, W. C. "The Metabolic Gradient Underlying Intestinal Peristalsis", Amer. Jour. of Physiol., 46:186, 1918.
2. Alvarez, W. C. "The Influence of Drugs on Intestinal Rhythmicity", Amer. Jour. of Physiol., 46:554, 1918.
3. Amadon, R. S. "Arecoline Hydrobromide", Jour. Amer. Vet. Med. Assoc., 29(1):65-74, 1930.
4. Best, C. H. and N. B. Taylor "The Physiological Basis of Medical Practice", p. 838, Williams and Wilkins Co., 1943, Baltimore.
5. Best, C. H. and N. B. Taylor Ibid., p. 823.
6. Bocquillon-Limousin, Cited by Fish, P. A. "Arecoline Hydrobromide", Abstr. of Work Done in the Lab. of Vet. Physiol. and Pharm., Cornell Univ., No. 4, 1907.
7. Brooks, C. and A. B. Luckhardt, Cited by Torald Sollman "A Manual of Pharmacology", p. 575, W. B. Saunders Co., 1942, Philadelphia.
8. Cannon, W. B. "Peristalsis, Segmentation, and the Myenteric Reflex", Amer. Jour. of Physiol., 30:114, 1912.
9. Coenders, "Vergleich zwischen Arekolin und Physostigminwirkung beim tier", Inaug-Diss-Giessen, 1904. Cited by Patz (43).
10. Dale, A. S. "The Relation between Amplitude of Contraction and Rate of Rhythm in the Mammalian

- Ventricle", Jour. Physiol., 70(4):455-473, 1930.
11. Davidson, W. G. "A Tenuicide for Dogs", The North Amer. Vet., 21:161-164, 1940.
 12. Dukes, H. H. "The Physiology of Domestic Animals", p. 332, Comstock Publishing Co., Inc., 1943, New York.
 13. Epstein, D. "The Responses of the Batrachian Alimentary Canal to Autonomic Drugs. *Xenopus laevis* (the South African Clawed toad)-Arecoline", Quart. Jour. Exptl. Physiol., 22:1-5, 1932.
 14. Fanslau, C. E. "Laboratory Data-Nemural", Obtained from the Biologic and Research Laboratories of Winthrop Chemical Company, New York, 9 pages, August 18, 1939.
 15. Fish, P. A. "Arecoline Hydrobromide", Abstr. of Work Done in the Laboratory of Vet. Physiol. and Pharm., Cornell Univ., No. 4:37-41, 1907.
 16. Fluckinger, Cited by Patz (43).
 17. Frohner, E. "Untersuchungen uber das Arekolin ein Ersatzmittel fur Pilocarpin und Eserin", Monats. f. prakt. Thierh., 5:336, 1894.
 18. Goodman, L. and A. Gilman "The Pharmacological Basis of Therapeutics", p. 393, The MacMillan Company, New York, 1940.
 19. Graefe, Cited by Patz (43).
 20. Hall, M. C. Cited by Greig, J. and G. Boddie "Hoare's Veterinary Materia Medica and Therapeutics", Alexander Eger Co., 1942, Chicago.

21. Hall, M. C. and Shillinger, J. "Critical Tests of Miscellaneous Anthelmintics", Jour. Agri. Res., 29:313, 1925.
22. Jackson, D. E. "The Action of Certain Drugs on the Bronchioles", Jour. of Pharm. and Exp. Therap., 5:479-510, 1913.
23. Jahns, E. "Ueber die Alkaloide der Arecanuss", Berichte d. d. Chem., 21:3404, 1888.
24. Kadonaga, C. "Beitrage uber die Pharmakologischen Wirkungen der Areca-Alkaloid I. Uber das Arecolinhydrochloride. Fol. Pharmacol. Japon. 26(2):73-84, 1938 (German Summary). Abstr. from Biol. Abstr., 12(12):16218, 1938.
25. Kenneth, B. C. "An Experimental Study of the Movements of the Small Intestine", Amer. Jour. of Physiol., 107:641-646, 1934.
26. Kobert, Arch. f. exp. Path. u. Pharm., Cited by Marmé (32).
27. Lavagna, G. "Experimentelle Notizen uber die physiologische Wirkung eines neuen myotischen Alkaloides (Arecolin)", Therap. Monats., 9:364-366, 1895.
28. Leepin, "Quantitative Hamoglobinbestimmung nach Fleischl an Thieren unter der Einwirkung pharmakologischer Agentien", Inaug-Diss. Dorpat S. 103, 1891. Cited by Patz (43).
29. Lentz, W. J. "Treatment of Tapeworms in Dogs", Jour. Amer. Vet. Med. Assoc., 13:396, 1921-22.

30. Lieb, C. C. and M. G. Mulinos "Some Further Observations on Sodium Iso-Amyl Ethyl-Barbiturate as a Laboratory Anesthetic", Proc. of the Soc. for Exp. Biol. and Med., 26(8), 1929.
31. Magnus, R. "Versuch am überlebenden Dünndarm von Säugethieren", Archiv für die gesammte Physiologie cii:123, 1904.
32. Marmé, "Arecanusse", Therap. Monats, 4:291-294, 1890.
33. Meier, H. "Exper. Untersuch. über die Wirkung des Arekolins auf d. Organismus", Bioch. Zeitschr., 2:415-420, 1907.
34. Mentova, V. N. "Coronary Vessels and Cardiac Reactions to Vascular Poisons in Experimental Myocarditis. II. Effect of Parasympathetic Poisons on Coronary Vessels", Farmakol i. Toksikol., 3(4):10-15, 1940. Abstr. in Chem. Abstr., 35:7, 7032, 1941.
35. Milks, H. J. "Practical Veterinary Pharmacology, Materia Medica and Therapeutics", p. 236, Alexander Eger Co., 1940, Chicago.
36. Milks, H. J. "Arecoline Hydrobromate", Abstr. of Work Done in the Lab. of Vet. Phys. and Pharm., Cornell Univ., No. 3:9-13, 1906.
37. Miller, F. R., Cited by Torald Sollman "A Manual of Pharmacology", p. 575, W. B. Saunders Co., 1942, Philadelphia.
38. N. F. VII. "The National Formulary", p. 56, American Pharmaceutical Association, Washington, D. C., 1942.

39. Olmsted, J. and Giragossintz, G. "Barbitals", Proc. Soc. Expt. Biol. Med., 27:103, 1929.
40. Oppenheimer, M. J. and F. C. Mann "Influence of Cathartics on the Activity of Small Intestine", Amer. Jour. of Digest. Dis., 8:90-93, 1941.
41. Pacheco, D. Veterinary School of Colombia, S. A., Personal Information.
42. Parker, F. F. "Some Common Conditions Encountered in Cat Practice", Jour. Amer. Vet. Med. Assoc., 45:33-41, 1938.
43. Patz, W. "Beitrage zur kenntniss der Wirkung des Arekolins auf den Darm", Zeitsch. f. Exp. Path. u. Therap., 7:577-614, 1910.
44. Plant, O. H. and G. H. Miller "Effects of Morphine and Some Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal I. Action on the Small Intestine in Unanesthetized Dogs and Man", Jour. Pharm. and Exp. Therap., 27:361, 1926.
45. Plesch, "Beitrage zur kenntnis der Wirkung des Arekolins", Inaug-Diss. Kiel., 1895. Cited by Patz (43).
46. Richter, R. "Untersuchung uber die Wirkungsweise des Nikotins am isolierten uberlebenden Meerschweinchendarm", Arch. exp. Path. u. Pharm., 139(3):381-292, 1939.
47. Ross, C. I. "The Possible Use of Arecoline Hydrobromide as an Anthelmintic", Jour. of Comp. Path. and Therap., 37:246-259, 1924.
48. Schwarte, L. H. and H. H. Dukes "The Action of Drugs on

- the Cardiovascular Mechanism of the Pig", Jour. Amer. Vet. Med. Assoc., 32(2):180-194, 1931.
49. Solis-Cohen, S. and T. S. Githens "Pharmacotherapeutics, Materia Medica and Drug Action", p. 475, D. Appleton and Co., 1928, New York.
50. Stefanson, K. "The Action of Arecoline on the Intestine", Arch. exp. Path. Pharm., 185:429-434, 1937.
Abstr. in Chem. Abstr., 27:5916, 1938.
51. Tierarztliche Hochschule, 16 pages, Anonymous Dissertation. Berlin, 1933. Abstr. in Biol. Abstr., 10(2):13376, 1936.
52. Traube, J., Cited by T. Sollman "A Manual of Pharmacology", p. 575, W. B. Saunders Co., 1942, Philadelphia.

A P P E N D I X

PROTOCOLS OF CLINICAL EXPERIMENTS
WITH ARECOLINE HYDROBROMIDE AT A
DOSAGE RATE OF 3.2 MGM. PER KGM.

Dog No. 5

February 17, 1945

Male

7 kgm. body weight

Temperature: 101.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 22.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
1.57 P.M.	90	
2.05		Administration of arecoline hydrobromide.
2.10	84	
2.17	84	
2.28	84	
2.38	78	Animal is very quiet. He rests on the floor and seems to be depressed.
2.52	72	
2.58	72	
3.08	78	Animal is restless. Attempt to defecation.
3.26	84	
3.47	84	
4.27	78	

Dog No. 6

February 17, 1945

Female

8.5 kgm. body weight

Temperature: 101.8 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.25 P.M.	114	
3.30		Administration of arecoline hydrobromide.
3.38	114	
3.40		Defecation of soft consistency.
3.45	96	
3.47		Defecation; feces of semi-liquid consistency in fairly large amount.
3.50	84	
4.00	78	Animal shows restlessness. Respiration seems to be increased.
4.15	60	Animal seems somewhat depressed. Salivation is present.
4.30	60	
4.45	60	
4.46		Defecation; feces of liquid consistency.

Dog No. 6 (cont'd.)

TIME	PULSE	OBSERVATIONS
5.00	54	
5.25	66	
5.50	72	
6.00	66	

Dog No. 7

February 19, 1945

Male

8.5 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.00 P.M.	168	
3.10		Administration of arecoline hydrobromide.
3.25	132	
3.26		Emesis.
3.37	132	
3.40		Defecation; feces of soft consistency.
3.50	132	
4.05	120	
4.15	120	Animal is quiet.
4.30	108	
4.45	114	
5.00	120	
5.15	120	
5.45	132	

Dog No. 8

February 21, 1945

Male

9.5 kgm. body weight

Temperature: 101.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 30.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.20 P.M.	108	
2.35		Administration of arecoline hydrobromide.
2.49		Defecation; feces of soft consistency.
2.55	120	
3.02	96	
3.10	78	
3.15	78	
3.25	78	
3.35	72	
3.45	66	
3.55	72	
5.10	120	

Dog No. 9

February 23, 1945

Male

8.5 kgm. body weight

Temperature: 101.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.05 P.M.	120	
2.17		Administration of arecoline hydrobromide.
2.30	114	
2.40		Defecation; feces of soft consistency.
2.45	114	
2.55		Nausea followed by emesis.
3.00	108	
3.10		Defecation; feces of liquid consistency.
3.20	108	Respiration seems to be increased.
3.30	102	Mucus material is expelled from anus.
3.45	96	

Dog No. 10

Female

8.5 kgm. body weight

Temperature: 100.8 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
1.35 P.M.	108	
1.45		Administration of arecoline hydrobromide.
1.55	108	
2.05	96	
2.15	96	Animal is very quiet.
2.25	90	
2.35	90	
2.45	84	
2.55	84	
3.05	84	
3.15	90	
3.25	90	
3.35	84	
3.50	84	
3.52		Defecation; feces of solid consistency followed by liquid material.
4.00	90	

Dog No. 11

Male

7 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 22.4 mgm. dissolved in water and given by
stomach tube

TIME	PULSE	OBSERVATIONS
4.10 P.M.	126	
4.15		Administration of arecoline hydrobromide.
4.30	126	
4.31		Defecation; feces of soft consistency and in small quantity.
4.45	126	
4.55	114	
5.05	114	
5.15	120	

Dog No. 12

March 1, 1945

Female

8.5 kgm. body weight

Temperature: 101.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.35 P.M.	150	
3.44		Administration of arecoline hydrobromide.
3.52	150	
3.54		Defecation. Animal shows increase respiration.
4.00		Emesis.
4.02	144	
4.12	132	
4.15		Defecation; feces of soft consistency.
4.21	126	
4.31	114	
4.41	126	
4.51	114	
5.01	120	
5.11	120	

Dog No. 13

March 7, 1945

Female

7 kgm. body weight

Temperature: 101.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 22.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
1.35 P.M.	132	
1.45		Administration of arecoline hydrobromide.
1.55	128	
1.57		Defecation; feces of soft consistency.
2.00	132	
2.15	120	
2.20	132	
2.25		Defecation; feces of liquid consistency and accompanied by mucus.
2.26	120	
2.35	108	
2.45	120	

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Dog No. 14

March 14, 1945

Male

11 kgm. body weight

Temperature: 101.3 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 35.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.10 P.M.	120	
3.20		Administration of arecoline hydrobromide.
3.30	108	
3.37		Emesis; fairly large amount of foodstuff.
3.39		Defecation; feces of soft consistency.
3.40	102	
3.43		Emesis; liquid material and foamy.
3.44		Micturition.
3.46		Defecation; scanty and repeated.
3.55	102	
3.56		Defecation; feces somewhat liquid.
4.05	114	Mucus is expelled from anus.
4.20	108	
4.30	114	Mucus is expelled from anus.

Dog No. 15

March 19, 1945

Male

13 kgm. body weight

Temperature: 101.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 41.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
4.10 P.M.	102	
4.15		Administration of arecoline hydrobromide.
4.25	84	
4.35	72	
4.38		Emesis; fairly large amount of foodstuff.
4.45	66	
4.55	66	Animal seems to be depressed.
5.05	66	
5.25	60	Animal still depressed.
5.35	54	" " "
5.40		Salivation.
5.45	60	
5.55	60	
6.05	66	

Dog No. 16

March 20, 1945

Female

9 kgm. body weight

Temperature: 103.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 28.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.35 P.M.	108	
3.37		Administration of arecoline hydrobromide.
3.45	108	
3.55	108	Animal is quiet.
4.05	108	
4.15	102	
4.25	84	Animal shows trembling movements on his rear legs.
4.35	78	
4.45	72	
4.55	72	
5.05	78	
5.15	78	
5.25	66	
5.35	78	

Dog No. 17

March 22, 1945

Female

24 kgm. body weight

Temperature: 103.5 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 76.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.25 P.M.	108	
3.30		Administration of arecoline hydrobromide.
3.39		Defecation; feces of soft consistency.
3.40	108	
3.49		Defecation.
3.55	108	
3.57		Defecation; feces somewhat liquid.
3.58		Micturition.
4.02		Defecation; liquid feces and scanty.
4.05	102	
4.10		Defecation followed by small quantity of mucus.
4.13		Micturition.
4.20	102	
4.30	102	

Dog No. 17 (cont'd.)

TIME	PULSE	OBSERVATIONS
4.40 P.M.	90	
5.00	108	
5.08		Micturition.
5.15	114	

Dog No. 17

March 28, 1945

Male

11 kgm. body weight

Temperature: 100.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 35.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
8.45 A.M.	72	
9.10		Administration of arecoline hydrobromide.
9.20	84	
9.24		Defecation; feces somewhat liquid.
9.25		Nausea followed by emesis; foamy material.
9.30	78	
9.40	72	
9.50	72	
9.51		Defecation; feces of liquid consistency and accompanied by mucus.
10.00	66	
10.15	66	
10.30	72	

Dog No. 28

April 16, 1945

Male

11 kgm. body weight

Temperature: 102.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 35.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	132	
9.45		Administration of arecoline hydrobromide.
9.51		Defecation; feces of soft consistency.
9.55	120	
10.00		Defecation; feces of liquid consistency scanty and repeated.
10.05	96	
10.15	78	
10.20		Micturition.
10.25	78	
10.33		Defecation
10.35	78	
10.45	66	
11.10	72	Nausea
11.11		Nausea followed by emesis.
11.20	72	
11.30	84	

Dog No. 29

April 18, 1945

Male

13.5 kgm. body weight

Temperature: 100.3 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 43.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.25 A.M.	84	
10.30		Administration of arecoline hydrobromide.
10.40	66	
10.45		Emesis.
10.48		Emesis; foamy material.
10.50		Defecation; feces blood tinged.
10.51	84	
11.00	108	
11.08		Micturition.
11.10	90	
11.20	96	
11.30	96	
11.40	90	

Dog No. 30

April 20, 1945

Male

8.5 kgm. body weight

Temperature: 102.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.30 A.M.	114	
10.35		Administration of arecoline hydrobromide.
10.45	114	
10.46		Defecation; feces of soft consistency.
10.48		Micturition.
10.50		Defecation; feces of liquid consistency.
10.54		Defecation; feces of liquid consistency and scanty.
10.55		Emesis; fairly large amount of foodstuff.
10.58		Emesis; scanty and foamy liquid material.
11.00	96	
11.10	84	

Dog No. 30 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.12 A.M.		Emesis; liquid and foamy material.
11.17		Emesis; liquid and foamy material.
11.20	96	
11.30	90	
11.40	66	
11.55	84	

Dog No. 32

April 19, 1945

Male

11.5 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight.

Total dose: 36.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.10 A.M.	144	
9.20		Administration of arecoline hydrobromide.
9.30	126	
9.40	114	
9.50	102	
9.57		Defecation; feces of soft consistency.
10.00	102	Nausea.
10.10	96	
10.14		Emesis.
10.16		Defecation.
10.19		Micturition.
10.20	84	
10.30	84	
10.40	78	
10.50	84	
10.52		Emesis; small quantity of liquid material and foamy.

Dog No. 36

April 28, 1945

Male

8.5 kgm. body weight

Temperature: 101.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.15 A.M.	132	
9.25		Administration of arecoline hydrobromide.
9.32		Emesis; fairly large amount of foodstuff.
9.35	90	
9.36		Emesis; liquid material and foamy.
9.41		Defecation and nausea.
9.45	88	
9.55	96	
10.05	102	
10.15	108	
10.25	126	
10.35	120	
10.45	114	
10.55	114	

Dog No. 36 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.05 A.M.	114	
11.15	96	
11.25	114	
11.35	120	
11.45	168	

Dog No. 37

April 28, 1945

Male

12 kgm. body weight

Temperature: 101.5 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 38.4 mgm. dissolved in water and administered by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	102	
9.40		Administration of arecoline hydrobromide.
9.50	104	
10.00	96	
10.10	96	
10.11		Defecation; feces of soft consistency.
10.20	72	
10.30	78	
10.40	54	
10.43		Defecation and micturition.
10.50	60	
11.00	84	
11.10	72	
11.20	84	
11.30	96	
11.40	96	
11.50	96	

Dog No. 38

April 28, 1945

Male

6 kgm. body weight

Temperature: 101.5 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 19.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.50 A.M.	90	
10.00		Administration of arecoline hydrobromide.
10.10	90	
10.20	96	
10.30	102	
10.40	90	
10.50	108	Nausea and salivation.
10.55		Defecation; feces of soft consistency.
11.00	84	
11.10	72	
11.13		Defecation; feces of liquid consistency.
11.18		Emesis; accompanied with foamy material.

Dog No. 38 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.20	72	
11.30	72	
11.40	120	
11.45		Micturition.
11.50	120	

Dog No. 39

April 28, 1945

Male

11 kgm. body weight

Temperature: 101.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 35.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	126	
10.30		Administration of arecoline hydrobromide.
10.40	126	
10.50	144	
11.00	102	
11.10	96	
11.20	84	
11.30	72	
11.40		Defecation.
11.41	96	

Dog No. 40

April 28, 1945

Male

12 kgm. body weight

Temperature: 102.7 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 38.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
1.40 P.M.	102	
1.50		Administration of arecoline hydrobromide.
1.52		Defecation; feces of soft consistency.
1.53		Micturition.
1.55		Emesis.
1.58		Defecation; feces of liquid consistency.
2.00	168	
2.03		Emesis.
2.10	96	
2.12		Defecation.
2.20	96	
2.30	96	
2.40	96	
2.50	84	
3.00	84	

Dog No. 40 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.10 P.M.	84	
3.20	96	
3.30	120	
3.40	96	
3.50	90	
4.00	84	
4.10	102	
4.20	102	

Dog No. 41

April 28, 1945

Male

14 kgm. body weight

Temperature: 103.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 44.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
1.50 P.M.	144	
1.58		Administration of arecoline hydrobromide.
2.02		Defecation; feces of soft consistency.
2.03		Emesis.
2.05	132	
2.15	120	
2.25	120	
2.35	120	
2.45	132	
2.55	120	
3.05	120	
3.15	132	
3.25	132	
3.35	120	

Dog No. 41 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.45 P.M.	120	
3.55	120	
4.05	138	
4.15	144	

Dog No. 43

April 28, 1945

Male

6.5 kgm. body weight

Temperature: 100.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 20.8 mgm. dissolved in water and given by
stomach tube.

Results:

TIME	PULSE	OBSERVATIONS
2.20 P.M.	88	
2.28		Administration of arecoline hydrobromide.
2.35		Defecation; feces of soft consistency.
2.40	102	
2.50	76	
2.51		Defecation; feces of liquid consistency.
2.55		Emesis.
3.00	80	
3.10	80	
3.20	96	
3.30	120	
3.40	80	
3.50	80	
4.00	92	
4.10	120	
4.20	80	

Dog No. 45

April 28, 1945

Male

6 kgm. body weight

Temperature: 101.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 19.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.00 P.M.	108	
3.10		Administration of arecoline hydrobromide.
3.20	126	
3.27		Micturition.
3.30	114	
3.40	108	
3.50	90	
4.00	102	
4.02		Defecation.
4.10	102	
4.20	98	
4.30	98	
4.40	120	
4.42		Emesis
4.50	120	

Dog No. 46

April 28, 1945

Male

13 kgm. body weight

Temperature: 100.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 41.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.15 P.M.	132	
3.22		Administration of arecoline hydrobromide.
3.30	140	
3.33		Micturition.
3.40	136	
3.41		Defecation; feces of soft consistency.
3.42		Emesis.
3.44		Defecation; feces of liquid consistency and scanty and repeated.
3.46		Defecation.
3.50	152	
4.00	152	
4.10	160	

Dog No. 46 (cont'd.)

TIME	PULSE	OBSERVATIONS
4.20 P.M.		Defecation.
4.20	152	
4.30	152	
4.40	152	
4.50	152	

Dog No. 47

April 28, 1945

Male

18 kgm. body weight

Temperature: 101.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 57.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.45 P.M.	120	
3.50		Administration of arecoline hydrobromide.
4.00	102	
4.05		Defecation; feces of soft consistency.
4.10	102	
4.20	96	
4.29		Defecation; liquid feces, scanty and repeated.
4.30	102	
4.40	96	
4.49		Emesis.
4.50	96	

Dog No. 48

April 28, 1945

Male

14.5 kgm. body weight

Temperature: 101.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 46.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.00 P.M.	102	
2.05		Administration of arecoline hydrobromide.
2.15	102	
2.20		Emesis; fairly large amount of foodstuff.
2.25	88	
2.35	88	
2.45	84	
2.48		Micturition.
2.55	68	
3.05	68	
3.15	68	
3.25	60	
3.35	72	
3.45	64	

Dog No. 48 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.55 P.M.	64	
4.05	64	
4.15	64	
4.25	64	

Dog No. 49

May 3, 1945

Male

8 kgm. body weight

Temperature: 101.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
8.55 A.M.	96	
9.02		Administration of arecoline hydrobromide.
9.12	120	
9.14		Emesis.
9.20		Defecation; semi-liquid feces.
9.22	90	
9.30	84	
9.31		Emesis; liquid and foamy material.
9.35		Emesis; foamy material.
9.40	78	
9.43		Defecation; feces of liquid consistency.
9.49		Emesis; scanty and foamy material.
9.50	108	
10.00	90	
10.10	108	

Dog No. 49 (cont'd.)

TIME	PULSE	OBSERVATIONS
10.20 A.M.	114	
10.30	108	
10.40	108	
10.50	108	
11.00	102	

Dog No. 50

May 3, 1945

Male

10 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.05 A.M.	132	
9.07		Administration of arecoline hydrobromide.
9.14	156	
9.21		Emesis.
9.24		Defecation; feces of soft consistency.
9.25	126	
9.35	138	
9.45	150	
9.50		Micturition.
9.55	150	
10.05	132	
10.15	174	
10.25	162	
10.35	132	
10.45	132	
10.55	156	

Dog No. 51

May 3, 1945

Male

11 kgm. body weight

Temperature: 101.8 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 35.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.15 A.M.	102	
9.24		Administration of arecoline hydrobromide.
9.32	90	
9.42	78	
9.47		Defecation.
9.52	78	
10.02	72	
10.15	78	
10.18		Emesis.
10.25	66	
10.35	60	
10.45	60	
10.55	72	

Dog No. 52

May 5, 1945

Female

8 kgm. body weight

Temperature: 102.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.50 A.M.	84	
9.55		Administration of arecoline hydrobromide.
10.05	84	
10.08		Emesis.
10.15	66	
10.25	72	
10.35	84	
10.45	84	
10.55	84	
11.05	84	
11.15	72	

Dog No. 53

May 5, 1945

Female

10 kgm. body weight

Temperature: 103.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.55 A.M.	156	
10.00		Administration of arecoline hydrobromide.
10.15	150	
10.20		Defecation; feces blood tinged and micturition.
10.25	132	
10.35	180	
10.45	144	
10.55	150	
11.05	144	
11.15	132	
11.25	132	

Dog No. 54

June 4, 1945

Male

11.5 kgm. body weight

Temperature: 101.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 36.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.00 A.M.	120	
10.05		Administration of arecoline hydrobromide.
10.15	108	
10.17		Defecation; feces of soft consistency.
10.25	84	
10.30		Defecation; feces of semi-solid consistency.
10.35	90	
10.45	72	
10.55	72	
11.05	60	
11.15	84	
11.25	60	

Dog No. 55

June 4, 1945

5 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 16 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	114	
10.15		Administration of arecoline hydrobromide.
10.25	144	Animal is excited.
10.26		Defecation; feces of soft consistency.
10.35	96	
10.45	120	
10.52		Defecation; feces of liquid consistency.
10.55	108	
11.05	108	
11.15	120	
11.23		Defecation; feces of liquid consistency.
11.25	78	
11.35	144	
11.45	96	

Dog No. 56

June 4, 1945

Female

6.5 kgm. body weight

Temperature: 101.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 20.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.20 A.M.	120	
10.25		Administration of arecoline hydrobromide.
10.26		Micturition.
10.35	144	
10.42		Defecation.
10.45	120	
10.55	126	
11.05	108	
11.15	108	
11.25	102	
11.35	96	
11.45	102	

Dog No. 57

June 4, 1945

Female

7.5 kgm. body weight

Temperature: 103.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 24 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.50 A.M.	120	
9.53		Administration of arecoline hydrobromide.
9.56		Defecation; fairly large amount of feces and micturition.
9.58		Defecation; feces of semi-liquid consistency.
10.05	126	
10.14		Defecation; scanty and repeated mucus.
10.15	108	
10.25	120	Mucus, scanty but repeated.
10.35	114	
10.45	120	
10.55	120	

Dog No. 58

June 4, 1945

Female

8.5 kgm. body weight

Temperature: 102.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 27.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.45 A.M.	96	
9.49		Administration of arecoline hydrobromide.
9.56		Defecation; feces of soft consistency.
9.58		Emesis; fairly large amount of foodstuff.
10.00	60	
10.08		Emesis, somewhat liquid and foamy.
10.10	60	
10.14		Defecation; scanty and repeated feces of liquid consistency.
10.20	60	Mucus, scanty but repeated.
10.30	78	
10.40	90	
10.50	90	
11.00	90	
11.10	96	

Dog No. 59

June 9, 1945

Female

10 kgm. body weight

Temperature: 102.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.55 A.M.	96	
9.58		Administration of arecoline hydrobromide.
10.10	90	
10.12		Defecation; feces of soft consistency.
10.13		Emesis.
10.20	90	
10.23		Defecation; feces of liquid consistency.
10.30	84	
10.40	84	
10.50	90	
11.00	90	
11.15	96	

Dog No. 60

June 9, 1945

Female

8 kgm. body weight

Temperature: 102.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 25.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.20 A.M.	132	
10.23		Administration of arecoline hydrobromide.
10.30		Defecation; feces of soft consistency.
10.35	102	
10.38		Defecation; liquid feces and scanty.
10.43		Defecation; feces of liquid consistency.
10.45	108	
10.49		Defecation; scanty, repeated, liquid feces accompanied by mucus.
10.55	126	
11.05	132	
11.15	132	

Dog No. 61

June 14, 1945

Female

6.5 kgm. body weight

Temperature: 101.8 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 20.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.15 P.M.	96	
3.20		Administration of arecoline hydrobromide.
3.29		Defecation and micturition.
3.30	84	
3.33		Defecation and micturition.
3.40	84	
3.43		Defecation; feces of liquid consistency, scanty and repeated.
3.50	96	
4.00	84	
4.04		Emesis.
4.10	78	
4.20	72	
4.30	90	
4.40	72	
4.50	96	

Dog No. 62

June 4, 1945

Female

10 kgm. body weight

Temperature: 101.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
3.25 P.M.	120	
3.29		Administration of arecoline hydrobromide.
3.40	126	
3.42		Defecation; feces of soft consistency.
3.45		Micturition.
3.50	126	
4.00	102	
4.10	96	
4.18		Emesis.
4.19		Defecation; feces accompanied with mucus.
4.20	126	
4.30	132	
4.40	108	
5.15	102	

Dog No. 63

June 9, 1945

Female

15.5 kgm. body weight

Temperature: 103.6 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 49.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.15 A.M.	144	
10.18		Administration of arecoline hydrobromide.
10.25		Emesis; foodstuff.
10.26		Defecation; feces of semi-liquid consistency.
10.27		Emesis, liquid and foamy material.
10.28	60	
10.38	66	
10.42		Defecation; feces of liquid consistency, scanty and repeated and accompanied with mucus.
10.48	96	
10.58	120	
11.08	126	
11.18	138	
11.30	150	
11.40	150	

Dog No. 64

June 9, 1945

Female

10 kgm. body weight

Temperature: 101.4 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 32 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	96	
10.14		Administration of arecoline hydrobromide.
10.24		Emesis.
10.25	72	
10.30		Defecation.
10.32		Micturition; animal seems to be depressed.
10.35	60	
10.45	60	
10.46		Micturition.
10.47		Emesis.
10.55	60	
10.59		Defecation; liquid feces and followed by mucus.
11.05	60	
11.15	66	

Dog No. 64 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.30 A.M.	72	
11.40	78	
11.50	84	

Dog No. 65

June 11, 1945

Female

12 kgm. body weight

Temperature: 101.8 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 38.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.10 P.M.	96	
2.18		Administration of arecoline hydrobromide.
2.28	96	
2.38	84	
2.48	78	
2.58	90	
3.08	108	
3.18	78	
3.28	90	
3.38	78	
3.48	72	
3.58	72	
4.08	72	
4.20	72	
4.35	78	

Dog No. 66

June 11, 1945

Female

6.5 kgm. body weight

Temperature: 101.2 F

Drug: arecoline hydrobromide

Dose: 3.2 mgm. per kgm. body weight

Total dose: 20.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.05 P.M.	84	
2.15		Administration of arecoline hydrobromide.
2.25	78	
2.30		Emesis.
2.35	60	
2.36		Defecation.
2.45	60	
2.55	60	
3.05	60	
3.15	60	Mucus expelled from anus, scanty and repeated.
3.25	66	
3.35	78	
3.45	90	
3.55	96	
4.05	90	

PROTOCOLS OF CLINICAL EXPERIMENTS
WITH ARECOLINE HYDROBROMIDE AT A
DOSAGE RATE OF 4.8 MG. PER KG.

Dog No. 32

April 27, 1945

Male

11.5 kgm. body weight

Temperature: 101.5 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 55.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.35 A.M.	108	
10.40		Administration of arecoline hydrobromide.
10.50	96	
11.00	102	
11.10	114	
11.11		Emesis.
11.19		Defecation; feces of soft consistency.
11.20	96	
11.28		Micturition.
11.29		Defecation; feces of liquid consistency.
11.30	90	
11.40	96	
11.45		Emesis.
11.55	108	

Dog No. 55 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.42	78	
3.52	72	
4.02	60	
4.20	84	
4.30	90	

Dog No. 57

June 19, 1945

Female

7 kgm. body weight

Temperature: 104.0 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 33.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.30 A.M.	138	
10.35		Administration of arecoline hydrobromide.
10.44		Defecation; feces of soft consistency.
10.45	132	
10.51		Defecation.
10.55	120	
11.05	96	
11.06		Emesis.
11.14		Defecation; liquid material followed by expulsion of mucus.
11.15	114	
11.25	120	
11.35	138	

Dog No. 58

June 19, 1945

Female

8.5 kgm. body weight

Temperature: 102.4 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 40.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.35 A.M.	102	
10.38		Administration of arecoline hydrobromide.
10.40	78	
10.49		Defecation; feces of soft consistency.
10.51		Emesis.
10.55		Defecation accompanied with mucus.
10.58	72	
11.07		Emesis.
11.08	66	
11.18	72	Copious mucus expelled from anus.
11.28	78	
11.45	102	
11.50	102	

Dog No. 59

June 20, 1945

Female

10.5 kgm. body weight

Temperature: 102.2 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 50.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.40 A.M.	108	
9.44		Administration of arecoline hydrobromide.
9.54	96	
10.04	78	
10.06		Defecation; feces of soft consistency.
10.14	78	
10.15		Emesis.
10.24	66	
10.34	78	
10.37		Defecation; liquid material.
10.44	72	
10.54	84	
11.04	96	
11.20	102	
11.35	84	

Dog No. 60

June 20, 1945

Female

9 kgm. body weight

Temperature: 101.8 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 43.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.50 A.M.	162	
9.54		Administration of arecoline hydrobromide.
10.00		Defecation; semi-solid feces.
10.04	150	
10.14	144	
10.24	150	
10.34	132	
10.44	144	
10.54	144	
11.04	144	
11.21	156	
11.38	144	

Dog No. 61

June 12, 1945

Female

7 kgm. body weight

Temperature: 102.1 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 33.6 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.28 A.M.	108	
9.30		Administration of arecoline hydrobromide.
9.35		Defecation; feces somewhat liquid.
9.46	108	
9.52		Defecation, scanty and repeated.
9.56	90	
10.06	96	Mucus expelled from anus.
10.16	96	
10.26	90	
10.36	132	
10.46	84	
10.56	90	
11.06	90	
11.16	90	
11.26	84	
11.36	96	

Dog No. 62

September 15, 1945

Female

11 kgm. body weight

Temperature: 100.0 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 52.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.05 A.M.	132	
10.25		Administration of arecoline hydrobromide.
10.29		Nausea followed by emesis.
10.35	66	Animal seems to be depressed.
10.36		Nausea followed by emesis.
10.38		Defecation; liquid and scanty feces.
10.41		Nausea and foamy material is vomited.
10.43		Defecation; scanty and liquid feces. Animal seems to increase respiration.
10.45	72	
10.47		Nausea. Respiration is increased.
10.55	72	Mucus material expelled from anus.
11.05	78	
11.15	78	Mucus material.
11.25	90	
11.35	96	
11.50	120	
12.00	116	

Dog No. 53

August 23, 1945

Female

16.5 kgm. body weight

Temperature: 102.6 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 81.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
2.30 P.M.	96	
2.34		Administration of arecoline hydrobromide.
2.44	144	
2.45		Defecation; feces of soft consistency.
2.47		Micturition.
2.50		Emesis; material somewhat liquid and scanty foamy.
2.54	78	Animal seems to be depressed.
3.04	60	
3.08		Mucus material expelled from anus.
3.14	90	Copious mucus material.
3.24	96	
3.34	108	Animal is more active.
3.44	96	

Dog No. 64

September 15, 1945

Female

6 kgm. body weight

Temperature: 102.0 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 28.8 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	90	
10.20		Administration of arecoline hydrobromide.
10.29		Defecation; feces of soft consistency.
10.30	90	
10.31		Micturition.
10.40	72	
10.41		Defecation; feces of liquid consistency.
10.50	90	
11.00	72	
11.10	84	Mucus material expelled from anus.
11.20	90	
11.30	90	
11.50	72	
12.00	84	

Dog No. 65

June 20, 1945

Female

10.5 kgm. body weight

Temperature: 101.1 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 52.4 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.45 A.M.	84	
9.48		Administration of arecoline hydrobromide.
9.58	78	
10.05		Defecation; feces of soft consistency.
10.08	66	
10.10		Micturition.
10.14		Defecation; scanty and semi-liquid material.
10.18	66	
10.28	48	
10.38	48	
10.48	60	
10.50	60	
11.08	54	
11.24	72	
11.40	96	

Dog No. 66

June 20, 1945

Female

6.5 kgm. body weight

Temperature: 101.1 F

Drug: arecoline hydrobromide

Dose: 4.8 mgm. per kgm. body weight

Total dose: 31.2 mgm. dissolved in water and given by
stomach tube

Results:

TIME	PULSE	OBSERVATIONS
9.55 A.M.	102	
9.59		Administration of arecoline hydrobromide.
10.09	78	
10.11		Defecation; feces of soft consistency.
10.19	72	
10.29	66	
10.39	72	
10.44		Defecation.
10.49	60	
10.50		Micturition.
10.58		Emesis.
10.59	72	
11.09	54	
11.25	54	
11.40	72	

PROTOCOLS OF CLINICAL EXPERIMENTS WITH NEMURAL
AT A DOSAGE RATE EQUIVALENT TO
ARECOLINE HYDROBROMIDE 3.2 MGM. PER KGM.

Dog No. 19

March 28, 1945

Female

6 kgm. body weight

Temperature: 101.2 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 1.9⁴ tablets of nemural (equivalent to 19.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.50 A.M.	96	
10.55		Administration of nemural in solution and given by stomach tube.
11.05	120	
11.10		Emesis.
11.14		Defecation; feces of soft consistency.
11.15	102	
11.20		Micturition.
11.25	102	
11.26		Emesis; liquid and foamy material.
11.27		Defecation; feces somewhat liquid.
11.35	96	
11.37		Defecation; liquid feces, scanty and repeated. Animal is depressed; shows nausea.
11.45	84	
11.55	60	

Dog No. 20

March 28, 1945

Male

12 kgm. body weight

Temperature: 101.0 F.

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.89 tablets of nemural (equivalent to 38.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.40 P.M.	120	
2.10		Administration of nemural in so- lution and given by stomach tube
2.20	96	
2.25		Emesis
2.30	90	
2.40	90	
2.50	90	
3.00	84	
3.10	84	
3.20	90	
3.30	84	
3.40	84	
3.50	84	

Dog No. 21

March 29, 1945

Male

9.5 kgm. body weight

Temperature: 101.4 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.08 tablets of nemural (equivalent to 30.4 mgm.
of arecoline hydrobromide

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	84	
9.50		Administration of nemural in so-
		lution given by stomach tube.
9.55		Emesis; liquid material and foodstuff.
10.00	84	
10.05		Defecation; feces of soft consistency.
10.07		Emesis; liquid and foamy material.
10.10	84	
10.18		Micturition.
10.20	84	Animal seems to be depressed. Mucus expelled from anus.
10.30	102	
10.40	90	
10.50	84	
11.00	84	
11.10	84	
11.20	84	Animal is very quiet, somewhat depressed.

Dog No. 22

March 30, 1945

Male

5.5 kgm. body weight

Temperature: 102.5 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 1.78 tablets of nemural (equivalent to 17.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.20 A.M.	90	
10.30		Administration of nemural in solution given by stomach tube.
10.35		Defecation; feces of soft consistency.
10.40	84	
10.42		Defecation; feces of liquid consistency.
10.43		Emesis; fairly large amount of foodstuff.
10.47		Defecation; liquid scanty and repeated.
10.50	72	
10.52		Emesis.
10.54		Defecation; liquid feces and accompanied with mucus.
11.00	72	

Dog No. 22 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.05 A.M.		Defecation; scanty and repeated; mucus.
11.10	66	
11.20	72	
11.30	84	
11.40	84	

Dog No. 23

March 31, 1945

Male

10 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.24 tablets of nemural (equivalent to 32 mgm. of
arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.55 A.M.	72	
10.05		Administration of nemural in so- lution given by stomach tube.
10.15	66	
10.24		Defecation; feces of soft consistency.
10.26		Emesis.
10.27	100	
10.30	102	
10.31		Defecation; liquid feces.
10.35	120	
10.43	132	
10.55	96	
11.00		Defecation; feces of liquid con- sistency and blood tinged.
11.05	96	
11.25	60	Animal is depressed.
11.55	84	

Dog No. 24

March 31, 1945

Female

8.5 kgm. body weight

Temperature: 100.6 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.47 tablets of nemural (equivalent to 27.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.00 A.M.	96	
10.11		Administration of nemural in solution given by stomach tube.
10.20	90	
10.30	78	
10.40	78	
10.43		Defecation; feces of soft consistency.
10.55	84	
11.05	84	
11.25	78	
11.55	84	

Dog No. 28

April 10, 1945

Male

9.5 kgm. body weight

Temperature: 101.2 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.08 tablets of nemural (equivalent to 30.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.45 A.M.	108	
9.55		Administration of nemural in solution. given by stomach tube.
10.05	96	
10.15	78	
10.20		Defecation; feces of soft consistency.
10.25	66	
10.32		Emesis.
10.35	72	
10.45	72	
10.55	78	
11.05	78	
11.15	84	
11.30	84	
11.45	84	

Dog No. 29

April 11, 1945

Male

12.5 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.16 tablets of nemural (equivalent to 40 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.15 A.M.	78	
10.27		Administration of nemural in solution given by stomach tube.
10.35	66	
10.38		Nausea followed by emesis.
10.45	66	
10.52		Defecation; feces of soft consistency.
10.54		Salivation.
10.55	90	Nausea.
11.05	78	
11.15	66	
11.25	66	
11.35	60	
11.45	66	

Dog No. 30

April 12, 1945

Male

8 kgm. body weight

Temperature: 101.4 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 46.8 mgm. of nemural (equivalent to 25.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.00 A.M.	120	
9.15		Administration of nemural in solution given by stomach tube.
9.19		Defecation; feces of soft consistency.
9.22		Emesis; foodstuff.
9.25	90	Animal seems to be depressed.
9.30		Defecation; liquid feces, scanty and repeated.
9.35	84	
9.45	90	
9.55	78	
10.05	66	
10.15	72	
10.25	90	
10.35	78	
10.45	78	

Dog No. 31

April 13, 1945

Male

12 kgm. body weight

Temperature: 101.5 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 64.3 mgm. of nemural (equivalent to 38.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.30 A.M.	120	
10.47		Administration of nemural in solution given by stomach tube.
10.52		Defecation; feces of soft consistency.
10.56		Defecation; fairly large amount of feces.
11.00	120	Nausea.
11.01		Emesis; food material and foamy.
11.03		Defecation; feces somewhat liquid.
11.07		Emesis; liquid and foamy material.
11.09		Emesis and defecation.
11.10	126	
11.12		Defecation and micturition.
11.16		Emesis; liquid and foamy material.
11.20	102	
11.30	78	
11.40	84	
11.50	84	

Dog No. 32

April 13, 1945

Male

11 kgm. body weight

Temperature: 101.2 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 70.2 mgm. of nemural (equivalent to 35.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.20 P.M.	108	
2.30		Administration of nemural in so-
		lution given by stomach tube.
2.35		Nausea.
2.40	102	
2.50	78	
3.00	84	
3.10	84	
3.20	72	
3.30	72	
3.40	84	
3.50	72	
4.00	78	
4.10	78	
4.12		Nausea followed by emesis.
4.20	78	
4.30	84	

Dog No. 32 (cont'd.)

TIME	PULSE	OBSERVATIONS
4.45 P.M.	66	
4.55		Defecation and micturition.

Dog No. 33

April 15, 1945

Kale

7 kgm. body weight

Temperature: 101.8 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 40.9 mgm. of nemural (equivalent to 22.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.20 A.M.	120	
10.25		Administration of nemural in solution given by stomach tube.
10.30		Defecation; semi-solid feces.
10.31	114	
10.41		Defecation; feces of soft consistency.
10.45	96	
10.46		Emesis.
10.48		Emesis.
10.54		Emesis, liquid and foamy.
10.55	90	
10.59		Defecation; liquid feces, scanty and repeated.
11.03		Nauseant state.
11.05	102	

Dog No. 33 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.15 A.M.	96	
11.25	96	.
11.35	84	
11.45	84	

Dog No. 34

April 23, 1945

Female

9 kgm. body weight

Temperature: 102.0 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 52.8 mgm. of nemural (equivalent to 28.8 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.35 A.M.	102	
10.45		Administration of nemural in solution given by stomach tube.
10.53		Defecation; feces of soft consistency.
10.58		Defecation.
11.00	108	
11.07		Defecation; feces somewhat liquid, scanty and repeated.
11.10	90	
11.12		Nausea.
11.15		Defecation; liquid feces.
11.20	114	
11.24		Defecation; liquid feces accompanied with mucus.
11.30	120	
11.40	120	

Dog No. 35

April 24, 1945

Male

11 kgm. body weight

Temperature: 100.0 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 64.3 mgm. of nemural (equivalent to 35.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	72	
9.43		Administration of nemural in so- lution given by stomach tube.
9.55	60	
9.57		Nausea followed by emesis.
10.05	54	
10.15	54	
10.26		Defecation; feces of soft consistency.
10.30	60	
10.40	56	
10.50	56	
11.00	52	
11.15	48	
11.30	52	

Dog No. 36

May 1, 1945

Male

8.5 kgm. body weight

Temperature: 99.6 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.47 tablets of nemural (equivalent to 27.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.30 A.M.	126	
10.37		Administration of nemural in solution given by stomach tube.
10.42		Defecation; feces of soft consistency, repeated several times.
10.45		Emesis; foodstuff.
10.48	96	
10.49		Defecation; feces somewhat liquid, scanty and repeated.
10.50		Emesis; liquid and foamy material.
10.52		Micturition.
10.57	60	
11.00		Defecation; liquid feces accompanied with mucus.
11.02	90	
11.15	120	

Dog No. 36 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.23 A.M.	132	
11.35	120	
11.45	132	Animal is trembling.
11.54	132	
12.02	136	

Dog No. 37

May 1, 1945

Male

13 kgm. body weight

Temperature: 101.0 F

Drug: nemural in powder

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 76 mgm. of nemural (equivalent to 41.6 mgm. of
arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
5.23 P.M.	114	
5.29		Administration of nemural in so- lution given by stomach tube.
5.39	114	
5.40		Defecation; feces of soft consistency.
5.49	96	
5.59	96	
6.00		Defecation; feces of soft consistency.
6.07		Defecation; liquid feces, scanty and repeated.
6.09	84	
6.19	84	
6.29	90	
6.39	84	
6.48		Defecation; blood tinged feces.
6.49	96	
6.59	108	

Dog No. 38

May 1, 1945

Male

6 kgm. body weight

Temperature: 101.5 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 1.94 tablet of nemural (equivalent to 19.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
5.20 P.M.	144	
5.25		Administration of nemural in solution given by stomach tube.
5.35	168	
5.36		Emesis.
5.41		Micturition.
5.45	156	
5.47		Defecation; feces of soft consistency.
5.51		Defecation; feces somewhat liquid.
5.55	156	
5.56		Emesis; liquid and foamy material.
6.05	146	
6.09		Defecation; liquid feces and scanty.
6.15	156	
6.25	156	
6.30		Defecation; blood tinged feces.

Dog No. 38 (cont'd.)

TIME	PULSE	OBSERVATIONS
6.35 P.M.	168	
6.44		Nauseant stage.
6.45	168	Animal is trembling.
6.55	162	

Dog No. 40

May 2, 1945

Male

12 kgm. body weight

Temperature: 101.5 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.89 tablets of nemural (equivalent to 38.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	84	
10.20		Administration of nemural in solution given by stomach tube.
10.30	108	
10.31		Emesis.
10.35		Defecation; feces of soft consistency.
10.40		Defecation; semi-liquid feces.
10.40	60	
10.48		Defecation; liquid feces, scanty and repeated.
10.50		Micturition.
10.52	62	
10.55		Animal seems to be depressed.
11.00	60	
11.13	78	

Dog No. 40 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.20 A.M.	84	
11.34	138	
11.42	96	
11.51	90	
12.00	78	

Dog No. 41

May 2, 1945

Male

13 kgm. body weight

Temperature: 104.4 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.22 tablets of nemural (equivalent to 41.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.10 A.M.	132	
10.28		Administration of nemural in solution given by stomach tube.
10.30		Emesis; somewhat liquid.
10.35		Emesis; food material.
10.38	108	
10.48	54	Animal is quite depressed.
11.00	126	
11.01		Defecation and micturition.
11.14	120	
11.15		Nauseant stage.
11.19		Animal starts trembling.
11.26	126	
11.38	126	Animal is trembling.
11.44	132	
11.55	138	
12.03	132	Animal is trembling.

Dog No. 43

May 1, 1945

Male

7 kgm. body weight

Temperature: 101.5 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.27 tablets of nemural (equivalent to 22.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
5.30 P.M.	120	
5.36		Administration of nemural in so-
		lution given by stomach tube.
5.40		Defecation
5.50	90	
6.00	108	
6.10	108	
6.20	80	
6.30	102	
6.40	78	
6.50	72	
7.00	84	

Dog No. 45

May 1, 1945

Male

8 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.59 tablets of nemural (equivalent to 25.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
12.45 P.M.	108	
12.50		Administration of nemural in so- lution given by stomach tube.
12.55		Defecation; feces of soft consistency.
12.56		Emesis.
1.00	90	
1.05		Defecation; feces of soft consistency.
1.10	120	Emesis; liquid material is expelled.
1.20	126	
1.21		Emesis; liquid and foamy material.
1.30	120	
1.40	96	
1.50	90	
2.00	96	Animal starts trembling.
2.10	96	Animal is trembling.
2.20	108	
2.30	108	

Dog No. 46

May 2, 1945

Male

13 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.22 tablets of nemural (equivalent to 41.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.05 P.M.	132	
1.07		Administration of nemural in solution given by stomach tube.
1.12		Defecation and micturition.
1.15	120	
1.18		Defecation; feces of soft consistency.
1.22		Defecation; somewhat liquid and scanty.
1.25	114	
1.30		Defecation; liquid feces, scanty and repeated.
1.33		Emesis; liquid and foamy material.
1.35	150	
1.40		Defecation and copious mucus.
1.45	156	Emesis.
1.55	132	
2.05	162	Defecation; liquid feces and mucus.
2.15	168	
2.29	174	

Dog No. 47

May 2, 1945

Male

17 kgm. body weight

Temperature: 101.4 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 5.52 tablets of nemural (equivalent to 54.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
12.50 P.M.	120	
12.55		Administration of nemural in solution given by stomach tube.
1.05	120	
1.14		Defecation; feces of soft consistency.
1.15	168	
1.17		Emesis; fairly large amount of foodstuff.
1.25	168	
1.35	132	
1.45	120	
1.55	120	Animal starts trembling.
2.05	126	
2.15	126	
2.25	120	
2.28		Defecation; feces somewhat liquid, mucus.
2.43	156	

Dog No. 48

May 1, 1945

Male

12.5 kgm. body weight

Temperature: 101.6 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.26 tablets of nemural (equivalent to 40 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
5.44 P.M.	96	
5.47		Administration of nemural in so- lution given by stomach tube.
5.54	102	
6.03		Defecation; feces of soft consistency.
6.04	102	
6.14	90	
6.15		Defecation and micturition.
6.24	96	
6.34	72	
6.44	72	
6.54	78	
7.00	96	

Dog No. 49

May 11, 1945

Male

7.5 kgm. body weight

Temperature: 102.2 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.43 tablets of nemural (equivalent to 24 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.25 A.M.	132	
10.28		Administration of nemural in solution given by stomach tube.
10.35	126	
10.45	102	
10.46		Defecation; feces of soft consistency.
10.55	103	
11.05	90	
11.10		Micturition.
11.11		Defecation.
11.15	96	
11.25	90	
11.35	90	
11.45	102	

Dog No. 50

May 11, 1945

Male

8 kgm. body weight

Temperature: 105.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.59 tablets of nemural (equivalent to 25.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.20 A.M.	180	
10.26		Administration of nemural in solution given by stomach tube.
10.35	156	
10.36		Emesis.
10.39		Defecation; feces of soft consistency.
10.45	102	
10.51		Defecation; somewhat liquid, scanty and repeated.
10.55	90	
11.05	90	
11.15	84	
11.25	108	
11.35	132	
11.45	120	

Dog No. 55

June 7, 1945

Female

5 kgm. body weight

Temperature: 101.2 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 1.62 tablets of nemural (equivalent to 16 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.45 P.M.	120	
1.50		Administration of nemural in so- lution given by stomach tube.
2.00	108	
2.10	102	
2.20	90	
2.30	108	
2.40	90	
2.50	90	
2.58		Defecation and micturition.
3.00	120	
3.10	96	

Dog No. 56

June 7, 1945

Female

6.5 kgm. body weight

Temperature: 102.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.11 tablets of nemural (equivalent to 20.8 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.35 P.M.	120	
1.40		Administration of nemural in so- lution given by stomach tube.
1.43		Defecation; feces of soft consistency.
1.50		Defecation.
1.50	102	
2.00	78	
2.01		Emesis.
2.09		Defecation; liquid feces, scanty and repeated.
2.10	78	
2.20	78	
2.30	90	
2.40	114	
2.50	96	
3.00	108	
3.10	108	

Dog No. 57

June 12, 1945

Female

7.5 kgm. body weight

Temperature: 103.4 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.43 tablets of nemural (equivalent to 24 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.30 A.M.	126	
9.40		Administration of nemural in so- lution given by stomach tube.
9.50	126	
9.52		Defecation; feces of soft consistency.
9.54		Defecation; feces of semi-liquid consistency.
10.00	120	
10.09		Defecation; blood tinged feces and mucus.
10.10	120	
10.20		Copious mucus expelled from anus.
10.30	120	
10.40	120	
10.50	132	
11.00	120	
11.20	126	
11.30	132	

Dog No. 58

June 12, 1945

Female

8.5 kgm. body weight

Temperature: 102.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.47 tablets of nemural (equivalent to 27.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	96	
9.43		Administration of nemural in solution given by stomach tube.
9.53	66	
9.54		Defecation; feces of soft consistency.
9.55		Nausea followed by emesis.
10.00		Defecation; liquid feces, scanty and repeated.
10.03	60	
10.13	60	
10.15		Defecation; liquid, scanty and repeated.
10.23	66	
10.33	60	Copious mucus expelled from anus.
10.43	72	
10.53	72	

Dog No. 58 (cont'd.)

TIME	PULSE	OBSERVATIONS
11.03	72	
11.13	72	
11.23	72	
11.35	90	

Dog No. 59

June 12, 1945

Female

10 kgr. body weight

Temperature: 100.8 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgr. body weight

Total dose: 3.24 tablets of nemural (equivalent to 32 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.00 P.M.	120	
2.09		Administration of nemural in so- lution given by stomach tube.
2.18		Emesis.
2.19	108	
2.29	78	
2.30		Defecation; feces of soft consistency.
2.39	78	
2.49	72	
2.50		Defecation; semi-liquid feces.
2.59	84	
3.09	78	
3.19	84	
3.29	96	
3.40	102	

Dog No. 60

June 12, 1945

Female

8 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.59 tablets of nemural (equivalent to 25.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.05 P.M.	126	
2.11		Administration of nemural in so- lution given by stomach tube.
2.20	126	
2.30	144	
2.40	126	
2.50	120	
3.00	132	
3.10	156	
3.25	150	
3.40	150	

Dog No. 61

June 7, 1945

Female

6.5 kgm. body weight

Temperature: 102.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.11 tablets of nemural (equivalent to 20.8 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.45 P.M.	108	
1.47		Administration of nemural in so- lution given by stomach tube.
1.57	90	
1.59		Defecation; feces somewhat liquid.
2.06		Defecation; liquid consistency.
2.07	108	
2.12		Defecation; liquid feces and scanty.
2.17	102	
2.27	108	
2.37	90	
2.47	132	
3.00	108	
3.10	120	

Dog No. 62

June 12, 1945

Female

10 kgm. body weight

Temperature: 100.3 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.24 tablets of nemural (equivalent to 32 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.00 P.M.	120	
2.06		Administration of nemural in so- lution given by stomach tube.
2.14		Emesis.
2.15		Defecation; feces of soft consistency.
2.16	103	
2.25		Defecation; liquid feces.
2.26	96	
2.32		Defecation; liquid feces and repeated.
2.36	103	
2.46	96	
2.53		Copious mucus expelled from anus.
2.56	103	
3.06	144	
3.16	138	
3.26	132	
3.40	126	

Dog No. 63

June 13, 1945

Female

15 kgm. body weight

Temperature: 102.8 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.87 tablets of nemural (equivalent to 48 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.15 A.M.	138	
9.27		Administration of nemural in solution given by stomach tube.
9.30		Defecation; feces of soft consistency.
9.33		Emesis; fairly large amount of foodstuff.
9.37	66	Animal is depressed.
9.45		Emesis.
9.46		Defecation; feces blood tinged.
9.47	84	
9.53		Defecation; liquid feces, blood tinged and accompanied by mucus.
9.57	108	
10.07	150	Animal is depressed.
10.17	138	
10.27	132	
10.37	150	
10.50	150	

Dog No. 64

June 13, 1945

Female

9.5 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.08 tablets of nemural (equivalent to 30.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.15 A.M.	96	
9.24		Administration of nemural in so- lution given by stomach tube.
9.33		Defecation; feces of soft consistency.
9.34	78	
9.43		Emesis.
9.44	78	
9.45		Defecation; liquid feces accompanied by mucus.
9.54	72	
10.04	72	
10.08		Defecation; liquid feces, scanty and repeated followed by expulsion of mucus.
10.14	72	
10.24	84	

Dog No. 64 (cont'd.)

TIME	PULSE	OBSERVATIONS
10.34	102	
10.35		Defecation; liquid feces accompanied by mucus.
10.48	84	

Dog No. 65

June 15, 1945

Female

10.5 kgm. body weight

Temperature: 102.5 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.41 tablets of nemural (equivalent to 33.6 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.40 P.M.	78	
2.50		Administration of nemural in so- lution given by stomach tube.
2.55		Emesis; foodstuff and liquid material.
3.00	78	
3.10	78	
3.20	90	
3.25		Defecation; feces of soft consistency.
3.30	72	
3.40	66	
3.50	72	
4.00	66	
4.10	60	
4.20	66	
4.35	72	

Dog No. 66

June 15, 1945

Female

7 kgm. body weight

Temperature: 101.1 F

Drug: nemural in tablets

Dose: equivalent to 3.2 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.27 tablets of nemural (equivalent to 22.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.45 P.M.	120	
2.47		Administration of nemural in so- lution given by stomach tube.
2.57	120	
2.58		Defecation; feces of soft consistency.
3.07	84	
3.17	96	
3.27	90	
3.37	90	
3.47	90	
3.57	84	
4.07	78	
4.17	78	
4.27	78	

PROTOCOLS OF CLINICAL EXPERIMENTS WITH NEMURAL
AT A DOSAGE RATE EQUIVALENT TO
ARECOLINE HYDROBROMIDE 4.8 MGM. PER KGM.

Dog No. 32

May 8, 1945

Male

11.5 kgm. body weight

Temperature: 100.0 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 5.60 tablets of nemural (equivalent to 55.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.20 A.M.	102	
9.37		Administration of nemural in so- lution given by stomach tube.
9.47	132	
9.49		Emesis.
9.51		Defecation; feces of soft consistency.
9.54		Micturition.
10.00	84	
10.10	78	
10.20	96	
10.30	84	
10.31		Defecation; feces somewhat liquid.
10.40	78	
10.50	72	Copious mucus expelled from anus.
11.00	90	" " " " "
11.10	66	" " " " "
11.20	72	

Dog No. 36

May 8, 1945

Male

8.5 kgm. body weight

Temperature: 101.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.14 tablets of nemural (equivalent to 38.8 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.35 A.M.	102	
9.45		Administration of nemural in so- lution given by stomach tube.
9.50	96	
10.00	108	
10.10		Emesis.
10.11	114	
10.20	96	
10.30	84	
10.40	90	
10.50	102	
11.00	108	
11.10	96	
11.20	96	
11.30	108	

Dog No. 37

May 7, 1945

Male

11.5 kgm. body weight

Temperature: 101.0 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 5.60 tablets of nemural (equivalent to 55.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.35 P.M.	126	
1.40		Administration of nemural in solution given by stomach tube.
1.50	126	
1.52		Defecation; feces of soft consistency.
2.00	120	
2.01		Defecation and micturition.
2.10	108	
2.12		Defecation; liquid feces, scanty and repeated.
2.20	108	
2.30	108	
2.35		Defecation; liquid feces, scanty and repeated.
2.40	132	
2.45		Micturition.
2.50	120	Copious mucus from anus.

Dog No. 37 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.00 P.M.	108	Mucus from anus.
3.10	108	
3.20	102	Mucus, scanty and repeated.
3.30	96	
3.40	102	

Dog No. 38

May 7, 1945

Male

5.5 kgm. body weight

Temperature: 102.3 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.69 tablets of nemural (equivalent to 26.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.40 P.M.	108	
1.45		Administration of nemural in so- lution given by stomach tube.
1.50	96	
1.52		Defecation; feces of soft consistency.
1.55		Defecation; feces of soft consistency.
2.00	120	
2.05		Micturition.
2.10	102	
2.20	108	
2.30	102	
2.35		Defecation; liquid feces, scanty and repeated.
2.44	144	
2.50	108	
2.59		Defecation; liquid feces, scanty and repeated.

Dog No. 38 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.00 P.M.	120	Mucus expelled from anus.
3.10	132	
3.19		Defecation accompanied by mucus.
3.20	120	
3.30	126	
3.40	120	

Dog No. 40

May 7, 1945

Male

12.5 kgm. body weight

Temperature: 101.2 F

Drug: nemural in powder

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 109.6 mgm. of nemural (equivalent to 60 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.35 A.M.	96	
10.37		Administration of nemural in so- lution given by stomach tube.
10.43		Emesis.
10.44		Defecation; feces of soft consistency.
10.45	102	
10.47		Defecation; semi-liquid consistency.
10.48		Emesis; foamy material.
10.55	72	
10.59		Micturition.
11.05	90	
11.15	90	
11.20		Copious mucus expelled from anus.
11.25	120	
11.35	108	
11.45	90	
11.50		Mucus blood tinged.

Dog No. 43

May 7, 1945

Male

6.5 kgm. body weight

Temperature: 102.4 F

Drug: nemural in powder

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 56.6 mgm. of nemural (equivalent to 31.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.25 A.M.	84	
10.35		Administration of nemural in solution given by stomach tube.
10.45	102	
10.46		Defecation; feces of soft consistency.
10.55	72	
11.05	84	
11.15	78	
11.25	78	
11.35	78	
11.45	78	

Dog No. 45

May 9, 1945

Male

8.5 kgm. body weight

Temperature: 100.3 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.14 tablets of nemural (equivalent to 40.5 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.25 A.M.	84	
10.39		Administration of nemural in solution given by stomach tube.
10.48		Defecation; feces of soft consistency.
10.50	96	
11.00	54	
11.10	66	
11.20	98	
11.22		Defecation; liquid feces, scanty and repeated.
11.25		Emesis.
11.30	72	
11.40	140	
11.50	156	

Dog No. 48

June 13, 1945

Male

12.5 kgm. body weight

Temperature: 102.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 6.09 tablets of nemural (equivalent to 60 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
9.15 A.M.	114	
9.18		Administration of nemural in so-
		lution given by stomach tube.
9.24		Defecation; feces of soft consistency.
9.25		Micturition.
9.28	90	
9.38	72	
9.44		Defecation; somewhat liquid.
9.48	72	
9.58	78	
10.08	72	
10.09		Defecation; liquid feces, scanty
		and repeated, accompanied by mucus.
10.18	72	
10.28	60	
10.38	66	
10.51	84	
11.00	84	

Dog No. 55

June 15, 1945

Female

5 kgm. body weight

Temperature: 101.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 2.44 tablets of nemural (equivalent to 24 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.45 P.M.	90	
2.53		Administration of nemural in so- lution given by stomach tube.
3.01		Defecation; feces of soft consistency.
3.03	90	
3.13	78	
3.20		Emesis.
3.23	90	
3.33	66	
3.43	78	
3.53	66	
4.03	66	
4.17	72	
4.35	84	

Dog No. 57

July 2, 1945

Female

8.5 kgm. body weight

Temperature: 102.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 4.14 tablets of nemural (equivalent to 40.8 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
1.55 P.M.	144	
2.00		Administration of nemural in so- lution given by stomach tube.
2.10	132	
2.12		Defecation; feces of liquid consistency.
2.20	132	Animal is restless.
2.28		Defecation; liquid feces, scanty and repeated.
2.30	130	
2.38		Emesis.
2.40	108	
2.50	102	
3.00	114	
3.10	96	
3.20	102	
3.30	108	Mucus material expelled from anus.

Dog No. 57 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.40 P.M.	108	
3.50	102	
4.00	120	Mucus

Dog No. 58

July 2, 1945

Female

7.5 kgm. body weight

Temperature: 101.2 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.65 tablets of nemural (equivalent to 36 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.10 P.M.	120	
2.13		Administration of nemural in so- lution given by stomach tube.
2.20		Defecation; feces of soft consistency.
2.22		Emesis.
2.24		Defecation; somewhat liquid.
2.25	84	
2.26		Defecation; liquid feces, scanty and repeated.
2.35	78	
2.38		Defecation; liquid feces, scanty and repeated.
2.45	84	
2.55	84	
3.01		Defecation; feces blood tinged and accompanied by copious mucus.
3.05	90	

Dog No. 58 (cont'd.)

TIME	PULSE	OBSERVATIONS
3.15 P.M.	72	
3.25	72	
3.35	78	
3.45	84	
3.55	78	Mucus expelled from anus.
4.05	84	

Dog No. 59

September 18, 1945

Female

10.5 kgm. body weight

Temperature: 100.4 F

Drug: nemural in powder

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 92.3 mgm. of nemural (equivalent to 50.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.15 A.M.	96	
10.20		Administration of nemural in so- lution given by stomach tube.
10.30	90	
10.33		Defecation; feces of soft consistency.
10.35		Defecation; somewhat liquid.
10.40	90	
10.43		Emesis.
10.50	72	
11.00	78	Copious mucus expelled.
11.10	84	
11.20	84	
11.28		Emesis; liquid and foamy material.
11.30	84	
11.40	90	Mucus expelled from anus.

Dog No. 60

August 23, 1945

Female

8 kgm. body weight

Temperature: 103.2 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.89 tablets of nemural (equivalent to 38.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.38 P.M.	138	
2.41		Administration of nemural in solution given by stomach tube.
2.48		Defecation and micturition.
2.50		Defecation; feces of soft consistency.
2.51	162	
3.01	120	
3.11	144	Mucus material expelled from anus.
3.21	150	
3.31	180	
3.41	150	

Dog No. 61

June 18, 1945

Female

6.5 kgm. body weight

Temperature: 101.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 3.26 tablets of nemural (equivalent to 31.2 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.25 P.M.	96	
2.30		Administration of nemural in so- lution given by stomach tube.
2.40	84	
2.46		Defecation; feces of soft consistency.
2.50	78	
3.00	72	
3.07		Defecation and micturition.
3.10	84	
3.20	102	
3.30	114	
3.40	102	
3.50	90	
4.00	84	
4.15	90	

Dog No. 63

June 18, 1945

Female

15.5 kgm. body weight

Temperature: 102.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 7.55 tablets of nemural (equivalent to 74.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.35 P.M.	120	
2.51		Administration of nemural in so- lution given by stomach tube.
3.01	108	
3.09		Defecation and micturition.
3.11	96	
3.20		Defecation; feces of soft consistency.
3.21	120	
3.31	102	
3.41	126	Defecation; liquid feces and repeated.
3.44		Copious mucus expelled from anus.
3.51	114	
4.01	90	Mucus expelled.
4.15	96	

Dog No. 64

June 18, 1945

Female

10.5 kgm. body weight

Temperature: 102.4 F

Drug: nemural in tablets

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 5.11 tablets of nemural (equivalent to 50.4 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
2.30 P.M.	96	
2.35		Administration of nemural in solution given by stomach tube.
2.45	102	
2.47		Defecation; feces of soft consistency.
2.55	84	Animal seems to be depressed.
2.56		Micturition.
3.01		Emesis.
3.03		Defecation followed by expulsion of mucus.
3.05	90	Animal is quite depressed.
3.15	90	Copious mucus expelled.
3.25	102	
3.35	78	
3.45	84	Copious mucus expelled.
3.55	96	
4.15	108	

Dog No. 65

July 11, 1945

Female

10 kgm. body weight

Temperature: 102.4 F

Drug: nemural in powder

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 82.2 mgm. of nemural (equivalent to 45 mgm. of
arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.15 A.M.	96	
10.19		Administration of nemural in solution given by stomach tube.
10.29	108	
10.31		Emesis.
10.35		Defecation; liquid feces.
10.39	84	
10.45		Animal is depressed. Respiration accelerated. Trembling.
10.48		Defecation; liquid feces repeated and followed by copious mucus.
10.49	90	
10.59	78	
11.09	78	
11.19	108	
11.29	120	
11.39	120	
11.49	108	

Dog No. 66

July 11, 1945

Female

7.5 kgm. body weight

Temperature: 100.9 F

Drug: nemural in powder

Dose: equivalent to 4.8 mgm. of arecoline hydrobromide per
kgm. body weight

Total dose: 65.8 mgm. of nemural (equivalent to 36 mgm.
of arecoline hydrobromide)

Results:

TIME	PULSE	OBSERVATIONS
10.15 A.M.	126	
10.21		Administration of nemural in solution given by stomach tube.
10.25		Defecation; feces of soft consistency.
10.27		Defecation; feces of liquid consistency.
10.31	126	
10.32		Defecation; liquid feces, scanty and repeated.
10.41	120	
10.51	126	
11.01	102	
11.04		Emesis; liquid material and foamy.
11.05		Micturition.
11.09		Emesis; foamy material.
11.11	78	Animal is depressed.
11.21	84	
11.31	96	
11.41	96	
11.51	100	

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