THE COMBINED ACTION OF MORPHINE AND CENTRAL STIMULANTS AND ITS RELATION TO THE TREATMENT OF MORPHINE POISONING *

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THE effect of central stimulants on morphine narcosis was studied as early as 1847 when Tschudi (1) expressed the opinion that picrotoxin may be used as a suitable antagonist to morphine. Kossa (2) disproved this assumption by showing that while picrotoxin stimulated the respiration of morphinized rabbits it decreased rather than increased the average lethal dose of morphine. Several authors (3, 4, 5) have since reported beneficial results following the administration of doses of convulsants in experimental and clinical morphine poisoning, but others (6, 7, 8) have stated that central excitants increased rather than decreased the toxicity of opiates. Koppanyi (9) emphasized that atropine supports the action of both aliphatic narcotics and convulsants, and reiterated a belief in the diphasic action of morphine. [Tatum et al, (10); Schmidt et al, (11).]

Since central stimulants are still used in the treatment of clinical morphine poisoning, it becomes imperative that the effects obtained by a combination of morphine or dilaudid with different types of stimulant drugs be subjected to further experimental analysis.

EXPERIMENTAL

Methods

Adult albino rabbits weighing between 1.5 and 3.0 Kg. were used in these experiments. Morphine sulfate in 1.0 and 4.0 per cent aqueous solutions was administered intramuscularly to circumvent the acute toxic effects of intravenous injections and at the same time to insure rapid, uniform absorption. Metrazol, picrotoxin, coramine and nembutal were administered intravenously; strychnine sulfate was given both intravenously and subcutaneously.

In the experiments requiring continuous records of blood pressure and respiration, the following methods were used. Preliminary surgery, including the cannulation of the trachea and carotid artery, was performed under morphine analgesia (usually 200 mg.†) and in no case was any other anesthetic agent used. A period of about fifteen minutes

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† All doses are expressed in terms of milligrams of the drug per kilogram of body weight. To avoid repetition, the words "per kilogram of body weight" are omitted.

was allowed to elapse after the administration of morphine before instituting surgical manipulations.

The common carotid artery was cannulated and connected with a standard mercury manometer. The minute volume of respiration was recorded from a tracheal cannula connected through a set of valves with a counterbalanced spirometer. The valves were of the ball-seat type connected by a rubber tubing to a glass T-tube and arranged in such a manner that the animal inspired atmospheric air and expired into the spirometer. A writing lever attached to the spirometer traced the vertical excursion of the cylinder on a smoked drum. Readings of the volume from the graduated scale of the spirometer were made and recorded at exact minute intervals. Approximately one-half hour elapsed between the injection of morphine and the beginning of the tracings. Thereafter, tracings were made at frequent intervals, each covering a period of three to five minutes.

COMBINATION OF MORPHINE WITH CONVULSANTS

Following the administration of morphine, a period not less than ten and usually not more than fifteen minutes was allowed to elapse to permit complete absorption of the drug and full development of its effects. By this time the animals showed depressed respiration, cyanosis and complete analgesia. The righting reflexes were present, the placement reactions absent and the animals showed catalepsy. Various types of convulsants were then administered and the responses noted. In order to differentiate between convulsions caused by large doses of morphine and the convulsions produced by central excitants, a number of control experiments were performed using large doses of morphine alone. It was found that convulsions from morphine alone did not occur until about ninety minutes after injection, while convulsions resulting from the combined administration of morphine and central stimulants usually occurred within a few minutes following the injection of the stimulant.

Since the results in each group where morphine and central stimulants were used jointly must be compared with both morphine and central stimulant controls, statistical interpretation was employed for the proper evaluation of the results. The chi-square test was used and due to the small numbers of animals, Yates' correction for continuity was applied. Since the controls for morphine and the central stimulants gave similar results, they were combined and a single chi-square computed for each combined action against the sum of the two controls.

Strychnine

The incidence of convulsions in animals treated with 0.2 mg. of strychnine sulfate (subcutaneously in 0.04 per cent aqueous solution) and 15 or 30 mg. of morphine sulfate was about the same as in the

control group which received 0.2 mg. of strychnine alone. There was a definite synergism, however, between the effects of 0.2 mg. of strychnine and 100 or 150 mg. of morphine. Since the results obtained with subcutaneous administration of strychnine and the smaller doses of morphine were inconclusive, strychnine was also used intravenously.

TABLE 1

DETERMINATION OF THE MAXIMUM SUBCONVULSANT DOSE OF MORPHINE *

No. of Rabbits	Morphine Sulfate mg./Kg.	Convulsions		Died
		Present	Absent	
10	15	0	10	0
10	30	0	10	0
9	100	1	8	0
9	150	2	7	2

* All morphine administered intramuscularly

An intravenous dose of 0.1 mg. of strychnine alone or in combination with 15 mg. of morphine failed to produce convulsions in any of the experimental animals, but following the administration of this dose of strychnine and higher doses of morphine (30 and 100 mg.), convulsions occurred in 50 and 100 per cent of the animals, respectively. (See Tables 1 and 2.)

TABLE 2

THE EFFECT OF COMBINATION OF SUBCONVULSANT DOSES OF MORPHINE AND STRYCHNINE

No. of Rabbits	Morphine Sulfate mg./Kg.	Strychnine Sulfate mg./Kg.	Convulsions		Died	X^2 *
			Present	Absent		
Subcutaneous						
13	—	0.2	2	11	0	—
16	15	0.2	5	11	0	3.20
11	30	0.2	2	9	0	0.83
11	100	0.2	10	1	0	15.25
7	150	0.2	7	0	3	11.82
Intravenous						
8	—	0.1	0	8	0	—
6	15	0.1	0	6	1	—
6	30	0.1	3	3	0	8.05
6	100	0.1	6	0	0	14.37

* Computed for the combined action against the sum of the two controls. For morphine controls see Table 1. Chi square equals 3.84 is the required level for statistical significance.

Picrotoxin

Picrotoxin in doses of 0.5 mg. was administered intravenously in 0.1 per cent aqueous solution. This dose was found to be subconvulsive for all control animals. In three groups of experiments picrotoxin was administered in the above dose to animals receiving 15, 30, and 100 mg. of morphine, respectively. In all these groups picrotoxin produced convulsions in at least 50 per cent of the animals, and in the last group 3 of the 6 animals died. (See Table 3.)

TABLE 3

THE EFFECT OF COMBINATION OF SUBCONVULSANT DOSES OF MORPHINE AND PICROTOXIN

No. of Rabbits	Morphine Sulfate (intramuscular) mg./Kg.	Picrotoxin (intravenous) mg./Kg.	Convulsions		Died	X^2*
			Present	Absent		
8	—	0.5	0	8	0	—
7	15	0.5	4	3	0	8.36
6	30	0.5	3	3	0	8.05
6	100	0.5	4	2	3	6.39

* Computed for the combined action against the sum of the two controls. For morphine controls see Table 1.

Metrazol

Intravenous injections of 7.5 mg. of metrazol were found to be subconvulsive for 80 per cent of the experimental animals. Following the administration of 15, 30, and 100 mg. of morphine, the above dose of metrazol produced convulsions in 18 of 21 animals. Fatalities occurred only in the animals which received 100 mg. of morphine and metrazol. (See Table 4.) In a few experiments in which the animals received 150 and 200 mg. of morphine and were prepared for recording blood pressure and respiration, 3 mg. of metrazol produced immediate and violent convulsions. (See Fig. 2.)

TABLE 4

THE EFFECT OF COMBINATION OF SUBCONVULSANT DOSES OF MORPHINE AND METRAZOL

No. of Rabbits	Morphine Sulfate (intramuscular) mg./Kg.	Metrazol (intravenous) mg./Kg.	Convulsions		Died	X^2*
			Present	Absent		
10	—	7.5	2	8	0	—
6	15	7.5	5	1	0	9.16
9	30	7.5	7	2	0	11.69
6	100	7.5	6	0	2	10.61

* Computed for the combined action against the sum of the two controls. For morphine controls see Table 1.

A series of similar experiments was carried out to test the combined effects of metrazol and dilaudid hydrochloride. Dilaudid was administered intramuscularly in an 0.8 per cent solution in doses of 4, 8 and 20 mg.; these doses are subconvulsive and their pharmacological activity corresponds roughly to 15, 30, and 100 mg. of morphine [Schoen (12)]. Table 5 shows that animals treated with subconvulsive doses of metrazol and dilaudid showed convulsions with but one exception.

TABLE 5

THE EFFECT OF COMBINATION OF SUBCONVULSANT DOSES OF DILAUDID AND METRAZOL

No. of Rabbits	Dilaudid HCl (intramuscular) mg./Kg.	Metrazol (intravenous) mg./Kg.	Convulsions		X^2*
			Present	Absent	
6	—	7.5	0	6	—
5	4	—	0	5	—
5	4	7.5	5	0	11.68
4	8	—	0	4	—
5	8	7.5	5	0	10.83
4	20	—	0	4	—
5	20	7.5	4	1	7.2

* Computed for the combined action against the sum of the two controls. For morphine controls see Table 1.

Coramine

A dose of 50 mg. of coramine was found to be just subconvulsive. This dose of coramine showed doubtful synergism with 15 mg. of morphine, but showed definite synergism with 30 and 100 mg. doses of morphine. Another series of animals was injected with 100 mg. of morphine and 40 mg. of coramine. While there were no controls at this dose level of coramine, the incidence of convulsions in this series was significantly greater than in the 50 mg. coramine controls. It should be noted that none of the coramine-morphine treated animals died. (See Table 6.)

TABLE 6

THE EFFECT OF COMBINATION OF SUBCONVULSANT DOSES OF MORPHINE AND CORAMINE

No. of Rabbits	Morphine Sulfate (intramuscular) mg./Kg.	Coramine (intravenous) mg./Kg.	Convulsions		Died	X^2*
			Present	Absent		
6	—	50.0	1	5	0	—
9	15	50.0	5	4	0	5.21
6	30	50.0	5	1	0	9.47
4	100	50.0	4	0	0	4.28
8	100	40.0	7	1	0	—

* Computed for the combined action against the sum of the two controls. For morphine controls see Table 1.

In addition to the foregoing experiments, a case history of a patient suffering with pain following a minor operation may be referred to at this time. Through an error in compounding a prescription, he was given approximately 200 mg. dilaudid rectally and 10 mg. of morphine subcutaneously. The patient became comatose with a respiratory rate of 10 per minute. He was then given successively small doses of coramine, caffeine and strychnine. Shortly thereafter the respiration became deeper and increased to 50 per minute. The patient showed rigidity with carpopedal spasms, opisthotonus and periodic tetanic convulsions. Shortly before death, which occurred about thirty-six hours after the poisoning, the respiratory rate was still 46 per minute and began to decrease in depth only after the onset of cyanosis. Unfortunately, the periodic blood pressure readings or electrocardiograms were not taken during the progress of the "treatment."

EFFECT OF AN ALIPHATIC NARCOTIC ON MORPHINE-METRAZOL CONVULSIONS

The above results reveal the synergy between central excitants and morphine. It is also generally known that aliphatic narcotics enhance some of the depressant actions of morphine, and that aliphatic narcotics are very effective in antagonizing the convulsant action of central stimulants. Since morphine enhances both convulsant and depressant actions, it was decided to determine which synergism was predominant when morphinized animals were treated with a depressant (nembutal) followed by a convulsant (metrazol).

TABLE 7

THE EFFECT OF NEMBUTAL ON THE MORPHINE-METRAZOL SYNERGISM

No. of Rabbits	Morphine Sulfate (intramuscular) mg./Kg.	Nembutal (intravenous) mg./Kg.	Metrazol (intravenous) mg./Kg.	Convulsions	
				Present	Absent
6	15	—	7.5	5	1
6	100	—	7.5	6	0
6	—	10	40.0	1	5
6	—	10	60.0	4	2
6*	15	10	60.0	4	1
9	100	10	60.0	7	2

* One animal died upon administration of nembutal, no metrazol given.

The results of these experiments are summarized in Table 7. Two control series were necessary to determine (*a*) the minimum amount of metrazol required to produce convulsions in animals which received morphine only (15 and 100 mg.) and (*b*) the minimum amount of metrazol required to produce convulsions in animals receiving 10 mg. of nembutal. The first value was found to be 7.5 mg. and the second 60 mg. of metrazol. After these values were determined a number of

morphinized animals received 10 mg. of nembutal fifteen minutes after injection of morphine. The combination of morphine and this amount of nembutal caused the loss of righting reflexes, complete muscular relaxation, and profound respiratory depression more so than is obtained by either of the above doses of morphine and nembutal alone. The administration of 60 mg. of metrazol to animals thus depressed produced convulsions in about the same number of cases as it did in the controls receiving nembutal but no morphine. Thus morphine neither lowered nor raised the average convulsive dose of metrazol for nembutalized animals; it appeared that the morphine-nembutal and the morphine-convulsant synergism completely offset each other.

THE ALLEGED ANTI-CONVULSANT ACTION OF MORPHINE

The above experiments have clearly demonstrated that morphine in doses of 15 mg. or more has no anti-convulsant action. Since morphine has been used as an anti-convulsant in the clinic, it was endeavored to determine whether smaller doses of this opiate, which would more nearly approximate the amounts used in the clinic, possess any anti-convulsant properties. After the minimum intravenous con-

TABLE 8

THE EFFECT OF SMALL DOSES OF MORPHINE ON CONVULSANT DOSES OF STRYCHNINE

No. of Rabbits	Morphine Sulfate (intramuscular) mg./Kg.	Strychnine Sulfate (intravenous) mg./Kg.	Convulsions		Died
			Present	Absent	
6	—	0.2	4	2	0
6	1.0	0.2	4	2	0
6	5.0	0.2	6	0	2

vulsant dose of strychnine sulfate was determined (about 0.2 mg.) animals premedicated with 1 and 5 mg. of morphine sulfate were given this dose of strychnine. The results summarized in Table 8 show that even in these smaller doses morphine did not increase the minimum convulsant dose of strychnine. With 5 mg. of morphine there is even a trend toward increasing, rather than decreasing, the incidence of convulsions in the strychninized animals.

THE DIPHASIC RESPIRATORY ACTION OF MORPHINE

In this series of experiments 13 rabbits received 200 mg., and 3 additional animals 150 mg. of morphine. These doses usually produced convulsions and proved fatal within two or three hours. The blood pressure and respiratory minute volume of these animals were recorded in the manner previously described. The initial recorded blood pressure (thirty minutes following morphine) ranged from 80 to 135 mm. of

FIG. 1–A. Respiratory minute volume and blood pressure one hour following intramuscular administration of morphine sulfate. Rabbit, 2.85 Kg.; Morphine sulfate, 200 mg./Kg., intramuscularly. *a*, line indicating injection of drugs; *b*, time 1.7 seconds, base line representing zero mm. Hg. pressure; *c*, blood pressure tracing from the common carotid artery; *d*, record of the respiratory minute volume.

Average minute volume ..... 322 cc.
Average blood pressure ..... 108 mm. Hg

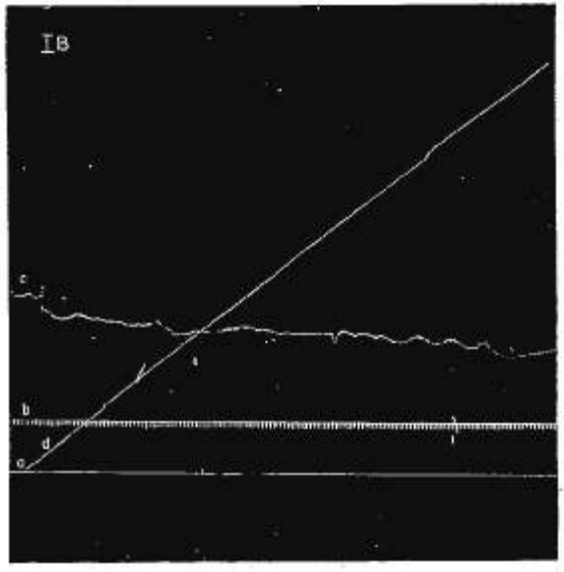

FIG. 1–B. Same rabbit, three and one-half hours following the intramuscular administration of morphine, and one hour after the first convulsion had appeared. Lettering as in Figure 1–A.

Average minute volume	1163 cc.
Average blood pressure	82 mm. Hg

FIG. 1–C. Same rabbit, four hours following the intramuscular administration of morphine. Lettering as in 1–A.

First four minutes of record
Average minute volume ..... 480 cc.
Average blood pressure ..... 24 mm. Hg
Second four minutes of record
Average minute volume ..... 196 cc.
Average blood pressure ..... 14 mm. Hg

FIG. 2. The effect of a small dose of metrazol on respiratory minute volume in a morphinized rabbit. Rabbit, 3.4 Kg.; 150 mg./Kg. morphine sulfate intramuscularly. Lettering as in 1–A. The first continuous respiratory volume recording is taken immediately before, and the second one immediately after the intravenous injection of 3.0 mg./Kg. of metrazol. The steep rise of blood pressure following the metrazol injection occurred during a convulsive seizure.

Before Metrazol
Average minute volume ..... 600 cc.
Average blood pressure ..... 101 mm. Hg
After Metrazol
Average minute volume ..... 1650 cc.
Average blood pressure ..... 110 mm. Hg

mercury. The corresponding minute volume ranged from 200 to 600 cc. with an occasional lower value, as contrasted with normal respiratory volumes for rabbits of about 1000 cc. per minute. Following this initial phase of depression, the respiratory rate and minute volume spontaneously increased before the onset of convulsions. The minute volumes reached levels of 500 to 1900 cc., a threefold increase over the period of depression. This increase in minute volume lasted throughout the convulsant phase of the morphine action. The blood pressure remained fairly constant except for small pressor effects during convulsive seizures. After several severe seizures the blood pressure fell gradually or abruptly, but the respiration remained at higher levels. Even after circulatory collapse had occurred and the blood pressure had reached shock levels, the respiratory minute volume remained fairly high. Death in these animals was thus invariably due to circulatory collapse. Figures 1–A, B, and C show the tracing of a typical experiment, including both the depression and stimulation of respiration by morphine and the gradual fall in blood pressure terminating in circulatory collapse. The respiratory minute volume begins to decline only after the blood pressure has reached critical levels.

In each of three experiments, metrazol was given in doses of 3 mg. at a period when animals receiving 150 or 200 mg. of morphine showed the initial respiratory depression. Following the injection of metrazol, the minute volume increased about threefold with the onset of convulsions. (See Fig. 2.) The usual sequence of respiratory stimulation, convulsions and circulatory collapse was greatly accelerated by metrazol.

The injection of nembutal in doses from 1 to 10 mg. in animals receiving 150 and 200 mg. of morphine slowed the respiration and controlled the convulsions. Nembutal in repeated doses of 1 mg. did not prevent subsequent convulsions and circulatory collapse, and in doses of 7.5 to 10 mg. it usually increased the respiratory depression to such an extent that the animals died of acute respiratory depression shortly after the administration of the barbiturate.

In a few preliminary experiments it was found that drugs such as epinephrine, ephedrine and benzedrine, which temporarily raise the blood pressure, did not prevent the onset of circulatory collapse, nor the death of the animal, if these drugs were given at the time when blood pressure had begun to decline.

DISCUSSION

The results described in the body of this paper prove that the combination of subconvulsant doses of morphine or dilaudid with subconvulsant doses of cortical, medullary and spinal stimulants (coramine, metrazol, picrotoxin and strychnine) causes marked tetanic and clonic convulsions. In addition larger doses of morphine, after an initial depression, stimulate the rate of respiration, increase the respiratory minute volume and produce excitement and convulsions.

In the literature we find the statement of McGuigan and Ross (13) that previous treatment with morphine sensitizes frogs to strychnine tetanus. They believe that this synergism is due to an oxidation product of morphine which supports the action of strychnine. In mammals, Pulewka (14) studied the combination of effects between morphine and picrotoxin (albino mice) and showed that premedication with 40 mg. of morphine lowered the fatal dose of picrotoxin from 2.6 to 2.0 mg. According to Stender (15) one-half of the average subcutaneous convulsant dose of strychnine produced convulsions in white mice which previously or afterwards had received 50 mg. of morphine hydrochloride. The average fatal dose of strychnine was also lowered at least 25 per cent by previous administration of 50 mg. of morphine. Schmitz (16) reported that coramine, metrazol and hexetone did not save the lives of morphine-poisoned white mice, but noted that some of the animals developed convulsions. However, he did not control his experiments by determining the minimum convulsant doses of morphine and the central stimulants for mice. Amantea and Martino (17) found that following local strychninization of a definite area of the sigmoid sensoromotor region of the cerebral cortex, epileptiform convulsions could be produced by stimulation of the corresponding cutaneous zone only in 25 per cent of the experimental animals, whereas following the subcutaneous injection of 10 to 60 mg. of morphine, convulsions could be produced in 100 per cent of the animals under the same conditions.

Mayor (18) found that intracerebral injection of a 0.5 per cent morphine solution caused convulsions. This author has also pointed out that, in rabbits, following morphine the blood pressure falls rapidly and steadily, respiration is slowed and becomes periodic; later the blood pressure rises and the respiration is stimulated. It is at this point that twitches and convulsions occur. Schmidt and Harer (11) also observed that the respiratory effects of large doses of morphine were similar in all respects to those of effective doses of strychnine, and that during the period of the acceleration of respiration there were signs of increased reflex excitability. Filehne (19) made a similar observation in rabbits. We have been able to obtain essentially the same results, but in our series of experiments, pressor effects occurred only when actual convulsions took place and the blood pressure returned to normal or even subnormal levels immediately after the cessation of the individual seizures. Schoen (20) also reported primary depression and subsequent stimulation of respiration by large doses of morphine. He believes that respiratory depression is most prominent in intact rabbits, less so in thalamus animals, and least of all in midbrain rabbits. According to him, the depression of respiration is induced by the effect of morphine on centers proximal to the corpora quadrigemina, and the secondary stimulation of respiration by action on more distal centers.

Death in acute morphine poisoning, provided the drug is not given intravenously, is usually attributed to respiratory paralysis. We have

found in rabbits, however, that as long as the arterial blood pressure is maintained above shock levels, the respiratory stimulant action rather than the depressant action of morphine predominated. Death was due to circulatory collapse.

Schmidt and Livingston (21) observed that intravenous or intra-arterial injection of morphine causes a marked and primary fall in blood pressure in dogs and cats, while in rabbits no fall in pressure occurs even upon intravenous injection of relatively enormous doses (100 mg.). They have also shown that acute tolerance may be established to the intravenous or intra-arterial injection of morphine in cats and dogs. In a dog, for example, small doses of morphine produced vasodilator effects under ether anesthesia, while in the same dog, one hour following the subcutaneous injection of 100 mg. of morphine, similarly small or even larger intravenous doses of morphine produced no vasodilator effects. The work of Schmidt and Livingston indicates that the terminal fall of blood pressure seen in our rabbits before the failure of respiration is an effect quite different from the acute circulatory depression they have described.

In this connection it may be recalled that Kipp (22) reported 6 cases of acute clinical morphine poisoning, each of which was breathing at the rate of 16 to 18 per minute when sudden circulatory collapse and death supervened. The case we reported showed respiratory stimulation enhanced by previous administration of several centrally acting excitants almost to the time of death.

Although in animals the excitant and convulsant action of morphine is becoming increasingly recognized (Eddy, 23) it is still generally held that in the human it produces central depression only. This assumption cannot be universally true since several cases of morphine convulsions have been described in humans. Since these cases terminated fatally, the convulsions were believed to be due to terminal asphyxial processes. Such interpretation cannot apply to the case report of Gordon (24), whose patient took 3 grains of morphine by mouth and subsequently developed clonic contractions of the upper extremities and trismus. When he was forced to take a few steps, spastic paralysis was evident. There was increased knee jerk and marked motor excitement. In seventeen hours these symptoms disappeared and the patient recovered. The author remarked that the clinical picture resembled strychnine poisoning.

Tatum et al (10) state briefly that in acutely poisoned dogs and rabbits prolonged convulsions invariably occur after large doses of morphine. Furthermore, they have reported that the generally fatal doses of 400 mg./Kg. can be tolerated if the animals are symptomatically treated for convulsions by intravenous injections of suitable aliphatic depressants such as soluble barbital and paraldehyde. This, they believe, proves that death is not due to direct depression of the respiratory center, but to exhaustion and asphyxia from tetanic fixation of the re-

spiratory muscles. Tatum et al did not study the combined action of central stimulants and morphine in acute experiments, but they gave dogs, for over a period of months, daily doses of 5.0 mg. of morphine and 100 mg. of caffeine or 1.2 mg. of strychnine. They found that it is possible to hasten the development of tolerance to the depressant action of morphine by the simultaneous use of suitable stimulants.

The practical conclusion to be drawn from these observations is that central excitants which hitherto have been employed rather freely in the treatment of acute morphine poisoning should be used either with extreme care or withheld entirely.

SUMMARY

The maximum average subconvulsive dose of morphine (intramuscular) and of strychnine (hypodermic and intravenous), picrotoxin, metrazol and coramine (intravenous) were determined in rabbits.

The combination of subconvulsant doses of morphine and dilaudid with subconvulsant doses of strychnine, picrotoxin, metrazol and coramine produced convulsions in a statistically significant number of cases.

Morphine shows an evenly balanced diphasic action, i.e., it enhances the action of either an aliphatic narcotic (nembutal) or a central stimulant (metrazol) to approximately the same extent. The dose of nembutal sufficient to antagonize the convulsant action of a given dose of metrazol is neither increased nor decreased by morphine.

Morphine has a primary depressant and a secondary stimulant action on the respiratory minute volume of rabbits. A fair degree of respiratory exchange may still be observed at a time when the animals poisoned by morphine show circulatory collapse. Nembutal enhances the depressant phase, and central excitants enhance the stimulant phase of the respiratory action of morphine.

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A complete list of theses on Anesthesiology and related subjects, together with the universities at which they may be found on file, may be located through the book, "A Guide to Bibliographies of Theses, United States and Canada," Edition 2, Chicago, American Library Association, 1940, compiled by Thomas R. Palfrey and Henry E. Coleman, Jr.