THE INTRAPERITONEAL INJECTION OF CERTAIN DRUGS.*

BY W. H. ZEIGLER.[1]

The experiments recorded in this investigation were the result of an attempt by the author to determine the most suitable drug or combination of drugs which, when injected into the peritoneal cavity, would produce both motor and sensory paralysis, with as little depression of the respiration and circulation as possible. The results obtained were more than satisfactory and should be of interest especially to investigators using animals in experimental work. Other drugs having marked effects when injected subcutaneously or intravenously were also studied.

Dandy and Rowntree (1) report a very interesting study of the absorption of phenolsulphonphthalein from the pleural and peritoneal cavities. They found that it appeared in the blood in from two to four minutes; in the urine in from four to six minutes; in the lymph (thoracic duct) in from twenty to sixty minutes. Their conclusions were: "There is very active absorption of fluids from all parts of the normal peritoneal and pleural cavities. This absorption is essentially haemic and not lymphatic. Peritoneal absorption is practically equal in all postures except pelvis down, in which it is fifteen per cent. less than in others. Gravity has a decided influence upon the localization of fluids—rapid in the pleural cavity, much slower in the peritoneal cavity. The intestines delay and influence the gravitation of fluids in the abdominal cavity."

Schmidt and Meyer (2) by means of a trochar, especially constructed by Schmidt, have recorded the intraperitoneal injections into animals and human beings of infusions of salt solutions, sugar, egg-white, oil, oil plus iodipin or iodine in emulsion, also oxygen. Sodium bicarbonate was used in the case of diabetic coma and cocaine in a case of *tabes dorsalis*. The results were negative. They found that infusions of isotonic salt and sugar solutions, while producing a noticeable irritation, was well borne by both animal and man. Oil and oil plus iodipin was quickly absorbed, although the quantity of fat burned up in a day was small. In human beings oil and iodine emulsion seemed to be quickly re-absorbed without irritation of the peritoneum.

Rosenburg (3), experimenting upon rabbits, into which he injected neo-arsphenamin intraperitoneally with the view of determining the practicability of administering it in this manner in the treatment of infants with congenital syphilis found that absorption was complete in twenty-four hours and, after treating a patient with congenital syphilis, came to the conclusion that "the use of the intraperitoneal route for the administration of neo-arsphenamin is a safe procedure and may aid in the treatment of congenital syphilis."

METHOD OF INJECTION.

About one hundred and fifty dogs and about twenty-five rabbits and guinea-pigs were used in these experiments. The solutions were all made up in normal salt. The injections were made with a leur syringe, using a special needle. The needle was made by tempering and curving a long needle. It was then filed off

* Scientific Section, A. Ph. A., Buffalo meeeting, 1924.

[1] Laboratory of Pharmacology of the Medical College of the state of South Carolina.

so that the needle only measured 18 mm. The animal was placed upon his back and the needle inserted into the peritoneal cavity about three inches to the right or left of the umbilicus. In order to ascertain if it was possible to puncture the intestines by this method, several animals were anesthetized and an incision made through the peritoneum in the median line, the needle being thrust through into the peritoneal cavity at the usual place. It was found that by the method outlined for the injection of the drug it was almost impossible to puncture the intestines or the mesentery.

DRUGS USED.

The following drugs were used in the experiments. Each drug will be taken up in order.

Magnesium sulphate
Magnesium sulphate and hyoscine hydrobromide
Magnesium sulphate and caffeine
Magnesium sulphate and atropine sulphate
Magnesium sulphate and alcohol
Magnesium chloride
Magnesium chloride and calcium chloride
Magnesium chloride and caffeine citrate
Magnesium chloride and atropine sulphate
Magnesium chloride and urethane
Magnesium chloride, urethane and caffeine citrate
Paraldehyde in salt solution
Chloral hydrate
Alcohol
Chloretone in alcohol
Chloretone in oil
Urethane
Urethane and caffeine citrate
Urethane and chloretone in alcohol
Cannabis indica
Epinephrine
Nitroglycerin
Potassium cyanide
Strychnine sulphate

MAGNESIUM SULPHATE.

A great deal of time has been devoted to the study of the anesthetic effect of magnesium. Meltzer and Auer (4) have established a subcutaneous dose of 1.5 Gm. of crystalline magnesium sulphate per Kg. of body weight, for the rabbit. They also introduced it by lumbar subdural injection, using 1 cc. of the 25 per cent. solution. Peck and Meltzer (5) using a six and ten per cent. solution of magnesium sulphate, injected slowly into the veins of human subjects a dose of 0.125, 0.200, 0.220 mgs. per Kg. of body weight. The anesthesia was perfect and an operation was performed successfully in each case. Respiratory depression was marked in one case.

D. R. Joseph and S. J. Meltzer (6) found that "The toxicity of magnesium, calcium, potassium and sodium to the entire animal is in inverse proportion to the amounts in which they are present in the serum of that animal; the smaller the amount of the ion is in the serum the more toxic it is in the infusion. Magnesium was found to be twice as toxic as calcium, potassium three times less toxic than the latter, while sodium was many times less toxic than any of the others." Joseph and Meltzer (7) also found that physostigmine was capable of antagonizing some of the toxic effects of magnesium salts. "It improves definitely the respiration in every instance whether the dose of magnesium salt be only toxic or fatal. The beneficial effects are found to be due to the physostigmine stimulating the respiratory center. Physostigmine antagonizes also the magnesium action on the peripheral nerve endings and probably also the action upon muscle tissue."

A 30 per cent. solution of C. P. crystalline magnesium sulphate was used in all of the experiments. The solutions were made in normal salt and were injected intraperitoneally as described. The dose administered was gradually graded by commencing with 0.2 gram and increasing the dose by grams. Two-tenths and 0.3 gram per Kg. of body weight, while producing incoördination in the dog with some sensory paralysis, especially in the abdominal area, was not sufficient. After a number of experiments, the safe dose was found to be 0.6 gram per Kg. of body weight for dogs, rabbits and guinea-pigs. The first effects invariably occurred in from two to four minutes, followed by total sensory and motor paralysis in ten minutes. Vomiting was a common occurrence in the dog and usually occurred one minute after the injection. Magnesium sulphate depresses the respiration, (Matthews and Brooks (8) and causes death by failure of the respiration. Knowing this, an attempt was made to offset this effect by the addition of the following respiratory stimulants: caffeine, atropine and hyoscine hydrobromide; the drugs being dissolved in the 30 per cent. solution of magnesium sulphate.

The effect of caffeine, in doses of twenty milligrams dissolved in the magnesium sulphate solutions, was very noticeable. The respiration was deeper and more rapid. When magnesium sulphate and caffeine citrate in 0.6 and 0.04 gram per Kg. of body weight was injected into rabbits, there was a marked diuresis. The vessels of the ear were widely dilated. Caffeine did not, however, prevent the toxic effect of large doses of the magnesium. It was found that large doses of caffeine would antagonize also some of the motor and sensory effects. Atropine in doses of 1 mg. per Kg. of body weight was disappointing. Hyoscine hydrobromide in $^1/_{100}$ and $^1/_{50}$ grain doses increased the central depression but did not lessen the toxicity of the magnesium. This drug was also administered subcutaneously, followed in one-half hour by the magnesium sulphate. The vomiting occurred as usual. The respiration was slightly improved. Throughout the experiments it was found that the sensory paralysis lasted longer than the motor, and that in most of the experiments the animals appeared to be conscious throughout the anesthesia. Ninety mg. per Kg. of body weight of calcium chloride injected intraperitoneally will antagonize the effect of the magnesium, although the effect is not as spectacular as when injected intravenously. The effect is more gradual.

The most successful combination for guinea-pigs, rabbits and dogs was found to be 0.6 Gm. magnesium sulphate and 0.6 cc. per Kg. of body weight of ethyl alcohol in salt solution, using a 30 per cent. solution of each in combination and administering 2 cc. per Kg. of body weight. This combination produces in two to seven minutes a total paralysis. The anesthesia in dogs lasted from three to four hours. One and one-half cc. per Kg. of body weight of the combination solution was found to be a safe dose for the rabbit, the effect taking place in four minutes and lasting about twenty minutes. This was also found to be a safe dose for guinea-pigs although several pigs survived when injected with 2 cc. of the mixture. Several abdominal operations were performed with success under the anesthesia. We keep as many as 150 dogs on the roof and found it necessary to cut the vocal cords of the animals. The animal man has always used ether. This combination of magnesium sulphate and alcohol has been used for "debarking" the animals, and was found to be an ideal anesthetic, inasmuch as there were no secretions to interfere with the operation.

MAGNESIUM CHLORIDE.

Magnesium chloride in 30 per cent. solution was also used; 0.6 Gm. or 2 cc. of the 30 per cent. solution per Kg. was found to be a safe dose. The effects only differed from the sulphate in producing a more marked emesis. The antagonistic effect of calcium chloride for magnesium is very prettily demonstrated by injecting a combination of 0.6 Gm. of magnesium chloride and 90 mg. calcium chloride per Kg. of body weight. A combination of 0.6 Gm. of magnesium chloride and 40 mg. of caffeine citrate dissolved in 0.9 per cent. salt solution was found to produce an anesthesia that lasted about twenty-five minutes. The objective feature of all magnesium experiments was the vomiting that invariably occurred.

PARALDEHYDE.

A dose of 0.250 of a cc. per Kg. of body weight, dissolved in salt solution, was found to be a safe dose. The animals vomited and struggled a great deal after injections, this, undoubtedly, being due to the irritating action of the drug. The anesthesia was rapid, but not total. The animals were conscious but unable to stand. The effect, however, was not as lasting, the animals returning to consciousness in about twenty minutes.

CHLORAL HYDRATE.

Chloral hydrate was used in a 20 per cent. solution. Two-tenths Gm. or 1 cc. of the 20 per cent. solution per Kg. of body weight, injected intraperitoneally, produced excitation in three minutes, incoördination in four minutes and narcosis in eight minutes. All of the animals recovered.

ALCOHOL.

One cc. of ethyl alcohol in a 25 per cent. solution per Kg. of body weight was found to produce in from four to five minutes incoördination of movements. The animal was unable to stant at the end of one-half hour. As stated under discussion of magnesium sulphate, 0.6 cc. in combination with 0.6 Gm. of magnesium sulphate was found to produce complete anesthesia.

TRICHLOR-TERTIARY BUTYL ALCOHOL. (CHLORETONE).

L. W. Rowe (9), in a series of experiments, established a dose of 0.4 gram per Kg. of body weight, dissolved in forty to forty-five per cent. alcohol; 1 cc. of the solution per Kg. being injected into the peritoneal cavity. He found this produced a rapid and complete anesthesia, lasting from twelve to forty-eight hours, death taking place from one to three days after. He also used oil solutions and found that the absorption was uncertain and slow. The results were confirmed by the author. The lasting effect of this drug and its toxicity makes it objectionable, if the animal is to survive. The most satisfactory combination is mentioned under urethane; the only objection was the vomiting that occurred.

ETHYL CARBONATE. (URETHANE.)

After a number of experiments a safe dose was found to be 0.5 Gm. per Kg. of body weight, in 25 per cent. solution. The first effect occurred in from two to three

minutes. Caffeine citrate in 40 mg. doses per Kg. of body weight was found to antagonize the respiratory effect of the urethane to a large extent. This combination also produced marked diuresis. A combination of one cc. of alcohol, 0.1 Gm. each of urethane and chloretone also produced a total anesthesia in about six minutes, recovery taking place only after several hours (see protocol). We have also used this combination very successfully in a number of operations. Mansfield and Hamburger (10), experimenting with magnesium, urethane and calcium chloride, concluded that magnesium increases the anesthetic action of urethane. Gensler and Issekutz (11 and 12) found additive effects with the aliphatic hypnotics.

CANNABIS.

Using a pilular extract purchased in the open market, a 4 per cent. emulsion was made with a sufficient quantity of 5 per cent. sodium hydroxide. One cc. per Kg. of body weight injected intraperitoneally produced only a slight incoördination. The dose was doubled, 80 mg. per Kg. of body weight being used (2 cc. per Kg. of body weight, of the 4 per cent. emulsion). The first effect occurred on an average of ten minutes, and in twenty minutes there was a marked incoördination. At some future time the author will make further investigation along this line with the hope of demonstrating that the intraperitoneal method for the injection of cannabis into dogs should take the place of the oral administration in the official method which is not only slow but uncertain.

EPINEPHRINE.

One-twentieth cc. per Kg. of body weight of a 1:1000 solution of epinephrine hydrochloride when injected intravenously into a dog, will produce a rapid rise in blood pressure, the pressure returning to normal in a very short time. It was thought, on account of the absorbing surface of the peritoneal cavity and also because of the rapid absorption of the drugs reported elsewhere in this report, that epinephrine would also produce a rapid rise with a return to normal; as seen by the following protocol which is typical of the experiments carried out with this drug, the rise was very gradual. Commencing one minute after the injection, the pressure continued to rise, reaching its highest peak twenty-eight minutes afterwards and returning to normal only after thirty-six minutes. Grehant's anesthesia was used in these experiments.

Protocol.

July, 14, 1924.
Dog, male.
Weight 6.8 Kg.
Grehant's anesthesia.
Dose—$^1/_{20}$ cc. of a 1:1000 solution epinephrine hydrochloride, intraperitoneally.

12:22 Dose administered	Blood-pressure 156 normal.
12:23	Blood-pressure 168
12:50	Blood-pressure 170
12:55	Blood-pressure 160
12:58	Blood-pressure 156
1:15	Blood-pressure 180
1:20	Blood-pressure 200
1:30	Blood-pressure 204

Respiration failed and the animal died.

After returning to normal in thirty-six minutes' time, the pressure commenced to rise again, reaching the high level of 204, when the animal died. The second rise may have been due to the failure of respiration and asphyxia accompanying it. The author hopes in the near future to continue these observations, as it appears that peritoneal injection of this drug is the ideal method to obtain more lasting effects.

Nitrites.

Dog.
Weight 8.7 Kg.
Grehant's anesthesia.
Dose—0.5 cc. of a 1:1000 solution of nitroglycerin per Kg. of body weight injected intraperitoneally.

Protocol.

12:17 Dose administered	Blood-pressure 160 normal.
12:21	Blood-pressure 134
12:30	Blood-pressure 140
12:42	Blood-pressure 160

As will be seen by this protocol, when nitroglycerin is injected intraperitoneally, 0.5 cc. of a 1:1000 solution per Kg. of body weight, a more gradual lowering of blood pressure takes place than by intravenous injection.

POTASSIUM CYANIDE.

A dog weighing 8.9 Kg. was injected intraperitoneally, at 4:30 P.M., with a dose of 5 mg. per Kg. of body weight, a 10 per cent. solution being used. At 4:31½ P.M. the animal vomited and immediately went into convulsions of the medullary type. At 4:34 P.M. the animal vomited again and went into a stage of collapse. The respiration was very rapid. At 4:42 P.M., the convulsions were of the clonic type. At 5:10 P.M. the animal was in a comatose stage, and died at about 7 P.M.

It will be seen by this record that the animal only succumbed after two and one-half hours. This was rather surprising in view of the violent convulsions that occurred.

STRYCHNINE SULPHATE.

Strychnine sulphate was injected intraperitoneally, a 1:1000 solution being used. The rapidity of absorption was determined by the appearance of the first convulsion. After injecting the animals, they were placed in a cage in a quiet room. The first convulsion occurred on an average of about eight minutes. Several animals were injected subcutaneously, with the same dose; the convulsions occurred on an average of five minutes. It therefore appeared that the absorption of strychnine sulphate from the peritoneal cavity is not as rapid as by subcutaneous injection. An attempt was made to prevent the convulsions by administering, intraperitoneally, chloral hydrate or magnesium sulphate. The results were negative. Repeated injections were found to delay and control the convulsions. The failure to prevent death by this method may have been due to the large dose of strychnine administered.

DISCUSSION.

From the experiments recorded here, it is very evident that certain drugs are suitable for peritoneal injection, and that the effect is rapid and lasting. I believe that this method for such drugs as epinephrine, pituitrin, caffeine, atropine, quinine, etc., is more practical than intravenous injections, and is the method to be used when a rapid and lasting effect is desired, as in surgical shock or in the crisis of pneumonia and other infectious diseases. In animal experimentations and student laboratory work, magnesium sulphate in 0.6 Gm. doses per Kg. of body weight or the several combinations of magnesium sulphate, chloride, alcohol, chloretone or urethane, may be used by intraperitoneal injections to produce a general anesthesia. The two combinations, with which I have obtained best results—and is more suitable for operations upon guinea-pigs, rabbits and dogs—were alcohol and magnesium sulphate, of each 0.6 Gm. per Kg. of body weight, or alcohol, urethane and chloretone. The dose is given elsewhere in this article.

CONCLUSIONS.

1. The absorption of drugs is very rapid from the peritoneal cavity of guinea-pigs, rabbits and dogs.

2. Six-tenths gram of magnesium sulphate or chloride per Kg. of body weight, injected intraperitoneally into dogs, rabbits and guinea-pigs, will produce total motor and sensory paralysis in about fifteen minutes.

3. Ninety mg. of calcium chloride per Kg. of body weight, injected intraperitoneally with the anesthetic dose of magnesium chloride or sulphate will antagonize the action of the magnesium.

4. Caffeine citrate in 40 mg. doses per Kg. of body weight, injected intraperitoneally, will antagonize to a certain extent the respiratory depression of magnesium salts.

5. A combination of magnesium sulphate 0.6 Gm. and ethyl alcohol in 0.6 cc. doses per Kg. of body weight, injected intraperitoneally, produces an ideal general anesthesia for guinea-pigs, rabbits or dogs.

6. Forty mg. of caffeine citrate and 90 mg. of calcium chloride per Kg. of body weight, when injected intraperitoneally, will antagonize the effects of the combination of alcohol and magnesium sulphate mentioned as a general anesthetic.

7. A combination of one cc. of ethyl alcohol, chloretone and urethane, of each 0.1 Gm. per Kg. of body weight, injected intraperitoneally, will produce a general anesthesia in guinea-pigs, rabbits and dogs, which lasts for four or five hours and from which the animal will recover.

8. Extract of cannabis emulsified with sodium hydroxide, and injected intraperitoneally, is absorbed and produces marked incoördination in less than one-third of the time when administered by oral injection.

9. The absorption of strychnine sulphate by intraperitoneal injection is not as rapid as by subcutaneous injection.

10. Epinephrine and nitroglycerin, when injected intraperitoneally, is rapidly absorbed, the effect produced being more gradual and lasting than by intravenous injection.

BIBLIOGRAPHY.

(1) Dandy and Rowntree, *Ann. Surg.*, 59, 4 (1914).
(2) Schmidt and Meyer, *Biochem. Centr.*, 4, 465 (1905).
(3) Rosenburg, W., *Jour. A. M. A.*, 82, 682 (1924).
(4) Meltzer and Auer, *Am. Jour. Phys.*, 14, 366 (1905).
(5) Peck and Meltzer, *Jour. A. M. A.*, 67, 1131 (1916).
(6) Joseph and Meltzer, *Jour. Phar. and Exp. Ther.*, 1, 1 (1909).
(7) Joseph and Meltzer, *Jour. Phar. and Exp. Ther.*, 1, 369 (1909).
(8) Mathews and Brooks, *Jour. Pharmacol*, 2, 87 (1910).
(9) Rowe, L. W., *Jour. Phar. and Exp. Ther.*, 9, 2 (1916).
(10) Mansfield and Hamburger, *Arch. ges. Physiol.*, 161, 444 (1915).
(11) Gensler, *Arch. Exp. Path. Pharmacol.*, 78, 317 (1915).
(12) Issekutz, B. *Therap. Monatsh.*, 29, 379 (1915).

ABSTRACT OF DISCUSSION.

J. C. Krantz Jr., inquired whether Dr. Zeigler has used the instrument in standardizing any pharmaceutical preparations and then checked results.

The author replied that he had not done any research work with the administration of drugs, but expected to take this up later.

Dr. H. C. Wood said he was very much interested in the apparatus and wondered whether Dr. Zeigler had attempted to demonstrate the comparative changes under the influence, for example, of drugs by simultaneous comparison with mercury and the oscillometer.

Dr. Zeigler replied that he had not, but hoped to make a report on this phase later.

Dr. A. Schneider said that he would like to try this instrument out to see whether it is more delicate than the so-called lie detector which has been employed by Dr. Larson for some years. He asked the author of the paper where the instrument can be purchased. The reply was made that the instrument was of French manufacture, and that Arthur Thomas and Company, of Philadelphia, were the agents.

Dr. H. C. Wood referred to the paper on "The Intraperitoneal Injection of Certain Drugs," and asked why "it was practically impossible to penetrate the intestines with the needle used?"

Dr. Zeigler replied that the short, curved needle and the position of the subject made it almost impossible to penetrate the intestines; the subject being on its back, there is quite a space between the intestines and the peritoneum. In reply to the request in regard to the technic used in debarking dogs, he replied that a bronchoscope made by using a large piece of brass tubing was used; the vocal chords were clipped with an instrument for this purpose.

A PHARMACODYNAMIC STUDY OF THE ANTHELMINTIC PROPERTIES OF TWO OILS OF CHENOPODIUM.

BY A. RICHARD BLISS, JR.

INTRODUCTION.

These investigations were prompted by the facts that (1) the supply of oil of Chenopodium "American Oil of Wormseed" is inadequate for human and animal medication, and (2) the resulting high price of the "Maryland Oil of Chenopodium" is consequently preventing the extensive use of the drug in the treatment of domestic animals, a field in which it is much needed.[1]

In 1854 an article by Garrigues[2] described the Southern (U. S.) and the Western (U. S.) Chenopodium plants, and accredited the oils distilled from both varieties with equal anthelmintic properties. During the same year, very shortly after the appearance of this article, another paper[3] was published by a second writer protesting