

AN EXPERIMENTAL INVESTIGATION ON THE ACTION OF CORAMINE

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(With 14 Figures in the Text)

CONTENTS

	PAGE
I. Introduction	474
II. Chemical and physical properties	476
III. Uses	476
IV. Experiments	477
(1) The effect of Coramine upon the normal animal	477
(a) Small doses	477
(b) Large doses	477
(2) The effects of Coramine upon the cardiovascular system	478
(a) Isolated mammalian heart	478
(b) Heart in the intact animal	479
(c) Blood pressure	481
(d) Right auricular pressure	483
(e) Pulmonary circulation	485
(f) Peripheral vessels	485
Limb volume	485
Splanchnic volume	485
Perfusion of coronary vessels	485
Perfusion of splanchnic vessels	486
Perfusion of limb vessels	487
(3) The effects of Coramine upon the respiratory system	489
(4) The effects of Coramine upon the central nervous system	491
(a) Medulla	491
(b) Pupil	492
(c) Spinal cord	492
(d) Sympathetic ganglion cells	493
(5) The effects of Coramine upon the intestinal movements	493
(a) Isolated intestine	493
(b) Intact animal	494
(6) Experiments on the frog's heart and vessels	494
(a) Heart	494
(b) Vessels	495
V. Discussion	497
VI. Summary	499
References	499

I. INTRODUCTION

MANY reports have appeared in the medical literature drawing attention to the beneficial effects of Coramine in a variety of infective and non-infective diseases. Most of these diseases are associated with definite pathological

lesions of the respiratory and cardiovascular systems, which in many instances are believed to be caused by bacteria or bacterial toxins.

The drug is marketed as an analeptic, and it has been claimed to possess a camphor-like action and to act as a powerful stimulant to the respiratory and cardiovascular systems. Coramine is now widely used by clinicians, both in hospital and in a general practice. In spite of the favourable reports on the use of the drug, which have appeared from time to time, disappointing results have often been reported. In consequence there is a great cleavage in opinion as to the value of the drug in particular pathological conditions. A survey of the literature shows that most of the reports come from clinical sources and in many instances are little more than a collection of case reports, while a few are short laboratory investigations concerning the effects of the drug upon one or other of the various systems of the body.

In view of the widespread use of the drug and the general lack of precise evidence concerning its effects upon the body, it was thought advisable to conduct a lengthy investigation into the action of Coramine upon the healthy systems of the body, and then discuss whether such effects might improve the functional efficiency of these systems when damaged by pathological changes. By approaching the problem in this way it is hoped that the uses of the drug may be clearly defined. A brief outline of the work leading up to the production of Coramine is given.

For many years medical men and research chemists have devoted their attention to the problem of obtaining camphor in a water-soluble form, but their efforts have only been rewarded with partial success. They have succeeded in preparing derivatives of camphor which are soluble in water, but not without changing its molecule in such a way that its pharmacological action became to a great extent altered or, in some instances, completely lost.

In 1924, Uhlmann, working in Switzerland, attacked the problem by discarding the idea of using camphor or camphor derivatives as a starting point in the synthesis of new compounds which might have a camphor-like action. Instead, he turned his attention to finding a water-soluble substance, irrespective of the class of chemical substances to which it belonged, that would have a pharmacological action similar to that of camphor itself. His investigations led him to examine the pyridine carbonic acids and their derivatives. Three monocarbonic acids of pyridine are known:

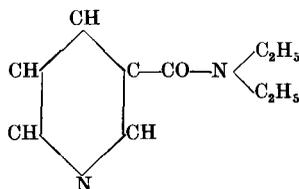
- (1) Pyridine- α -carbonic acid or picolinic acid;
- (2) Pyridine- β -carbonic acid or nicotinic acid;
- (3) Pyridine- γ -carbonic acid or iso-nicotinic acid.

Very little was known of the pharmacological actions of these three compounds until Faust (1924) showed that they were but feebly toxic and that when injected into rabbits they have an action which is sedative and narcotic. He observed the onset of paralysis in cold-blooded animals. A similar but more pronounced action was observed in the case of the alkyl ester of the pyridine carbonic acids, and the hydrogenated derivatives of pyridine β -carbonic acid such as N-methyl-3-tetrahydropyridine- β -carbonic acid and its methyl ester, arecoline. The methyl chloride ester of pyridine- β -carbonic acid has a similar but less powerful action.

All the amines of the aromatic acids have a general narcotic action which is also seen with the amides of the pyridine carbonic acids. In the latter instance the narcotic effects are seen

only when large doses are employed. These substances have a low toxicity and do not affect the respiratory or cardiovascular systems. Nebelthau (1895) has shown that the introduction of alkyl groups into the amide group of benzol derivatives does not, as might be expected, increase the narcotic effects, but produces a new train of effects. The preliminary action is one of slight narcosis which is rapidly followed by general stimulation of the respiration and, later, a strychnine-like action upon the muscles, giving rise to painful cramp. This observation has been confirmed by Harras (1903) and Kionka (1904), who also found a similar effect when aliphatic derivatives were employed. Faust (1924) also confirmed the observations of Nebelthau and extended his studies to the alkyl amides of the pyridine carbonic acids. He found that the use of pyridine in place of a benzol nucleus produced a difference in the effects of the two groups of amides. The mono- and dialkylamides have a similar type of action but differ in intensity. In large doses, both have a narcotic action, lower the blood pressure, have a marked convulsant action on smooth muscle, and do not influence respiration. The dialkylamides were found to be strongly acting substances and pyridine- β -carbonic acid diethylamide was found to resemble camphor in its actions, and to be devoid of narcotic effects. The diallylamide and the isobutylamide have similar but weaker actions than the diethylamide.

The diethylamide of pyridine- β -carbonic acid is now manufactured in various countries under a number of protected trade names. It was first manufactured by the Gesellschaft für Chemische Industrie in Basel, Switzerland, and marketed under the name of Coramine. Since the expiration of the patent rights of this firm, it has been produced by other firms under the names of Nicamide, Anacardone, etc.



Pyridine- β -carbonic acid diethylamide.

II. CHEMICAL AND PHYSICAL PROPERTIES

Coramine is a viscous, pale lemon yellow-coloured liquid which is almost odourless. The formula is given above. It distils at a temperature of 150 °C. at a pressure of 2 mm. Hg. It is soluble in water as well as many organic solvents. In the pure state it has a bitter taste, but is almost tasteless in dilute aqueous solutions. Coramine can be administered by the oral, subcutaneous or intravenous routes.

III. USES

Hirsch (1926) states that it has proved beneficial in the treatment of circulatory troubles associated with pneumonia and empyaema. In a discussion on blood pressure which appeared in the *Lancet* (5 February 1927) this drug was advocated in the treatment of chronic hypopisias. Faust (1925) claims it to be a powerful cardiac stimulant. Other clinicians (Buschmann, 1925; Straumann, 1926; Valéry, 1927; Barriou, 1927; Petschacher, 1928; Paret, 1928; and Rajna, 1928) have claimed beneficial results in conditions of shock, arteriosclerosis, degenerative myocarditis, myocardial insufficiency, acute cardiac distress, and other pathological cardiac conditions. Uhlmann (1924), using rabbits, found the Coramine produced a marked rise in blood pressure which he deduced was due partly to increased cardiac efficiency

and partly to vasoconstriction produced by a stimulating action on the vasomotor centre. Massart (1930) recorded a generalized vasodilatation in the intact dog and believed that Coramine acted peripherally. Using the heart-lung preparation Leyko (1930) found a dilatation of the heart with a diminution in cardiac output in response to Coramine. He also noted an increase in the coronary flow, while Greene (1936) found a prompt increase in coronary flow in dogs with right vagus nerve degeneration and a compensated blood pressure. Lagier (1922), Faust (1925), Asher (1926), and Burgi & Gordonoff (1928) concluded that Coramine acted as a stimulant to the circulation by acting upon the myocardium, or by vasoconstriction. Mezey (1935), using heart-lung preparations, noted an increase in the diastolic excursions of the heart and an increase in coronary flow. Stoland & Ginsberg (1937), using the heart-lung preparation of dogs, reported that small doses of Coramine produced general vasodilatation while large doses dilated the coronary vessels. From this review of the literature it will be seen that widely different results have been obtained by the numerous workers who have investigated the effects of Coramine upon the cardiovascular system.

IV. EXPERIMENTS

This investigation on the action of Coramine was undertaken to determine its precise action on the various systems, and to find, as far as possible, how far the claims made for it in the literature are justified. Cats, rabbits, and frogs were used and diluted Coramine was injected by various methods. In addition, the effects of the drug upon various animal tissues in the isolated state were studied. The Coramine used was supplied in the pure state by Messrs Ciba Ltd., of Horsham, Sussex. The dilutions were made with distilled water, or suitable Ringer's solution immediately before its use.

(1) *The effect of Coramine upon the normal animal*

Four rabbits weighing about 2 kg. were used, and varying doses (0.25–1 c.c. 10% solution) of Coramine were injected into a large ear vein. The results obtained were very constant and best illustrated by the following accounts.

(a) *Small doses.*

Rabbit, male, weighing 2 kg. 2.30 p.m. Intravenous injection of 1 c.c. of 10% Coramine given slowly. The animal showed immediate signs of excitability; it ran and jumped about in an excited manner.

2.32. The respiratory rate and reflexes were markedly increased.

2.35. The animal was still excited and running about, taking a great interest in its surroundings.

2.40. The degree of excitability was slightly lessened. The animal was sitting still eating food. The respiratory rate was still increased.

2.50. The animal appeared quite normal except for some slight increase in respiratory rate.

2.55. The rabbit now appeared normal again. Respiration normal.

(b) *Large doses.*

Rabbit, male, 2.2 kg. 11.0 a.m. 5 c.c. of 10% Coramine were injected slowly intravenously. The animal showed immediate signs of excitability which were so great that it was

only held with great difficulty while the injection was completed. On being freed it jumped around, kicking out its hindlimbs. This increased activity was much greater than could be accounted for by the necessary manipulation required by the technique of injection.

11.04. Condition as before, except that the respiratory rate was enormously increased.

11.06. The animal ceased running about and sat down in the usual sitting posture. The respiratory rate was becoming faster, and the tongue was protruded frequently to lick the nostrils. The pupils were "pin point". Reflexes were still very brisk.

11.07. The forelimbs were spread flat upon the floor at right angles to the body. The rabbit could draw the limbs to its sides but was unable to use them either to lift its body or to walk. Increased salivation was present.

11.11. Voluntary movements of the forelimbs were now abolished and paralysis of the hindlimbs had commenced. From time to time the hindlimbs were moved in an endeavour to raise the body and run, but these efforts were unsuccessful. The respiratory rate was still markedly increased.

11.13. Complete paralysis of all limbs was present and the animal was lying on its side in a helpless condition.

11.20. The condition of the animal was getting worse, although it was quite conscious. Trismus, with grinding of the teeth, was present.

11.25. Violent convulsions developed with arching of the spine, and extension of the hindlimbs. The head was in a position of hyperextension. Respiratory paralysis lasting 90 sec. was seen.

11.27. The tonic rigidity of the whole body had passed off, respiratory movements returned and the muscular spasms recommenced. Marked exhaustion was apparent after this convulsion which appeared to be the end.

11.29. The animal was quiet, but stimulation by stroking or pinching the limbs produced convulsions of great severity. Blowing air upon the body of the animal produced a similar result.

11.35. Another convulsion took place but was much less severe than the previous one. The spasms are both tonic and clonic in type. The respiratory rate was still increased.

12.5. The general condition was greatly improved and the paralysis of the hindlimbs had passed away. The forelimbs were still paralysed, and respiration was nearly normal again.

12.15. The paralysis of the forelimbs was passing off but the twitchings were still present.

12.20. The rabbit now appeared normal except for general muscular weakness and occasional twitching of the limbs. The pupils were still contracted.

12.30. The twitchings had almost disappeared, and the noise of bubbling mucous could be heard in the trachea and bronchi.

There was no incontinence of faeces or urine at any stage of the experiment and the animal was alive and well six weeks later.

Larger doses of Coramine gave rise to a similar train of symptoms but death occurred from respiratory failure during the convulsions. Results similar to those already described were seen when the subcutaneous and intramuscular routes of injection were employed, the only variation being a slight difference in the rate of onset of the effects.

(2) *The effects of Coramine upon the cardiovascular system*

(a) *Isolated mammalian heart.*

The coronary vessels of the rabbit's heart were perfused with Ringer's solution and later with a solution of Coramine in Ringer's solution, using the Langendorff method. The heart movements were recorded upon a kymograph and the coronary flow measured.

The results obtained showed that Coramine in a dilution of 1/40,000 produced no effects upon the isolated heart. In a dilution of 1/20,000 it first caused a small increase in the amplitude and force of systolic contraction. This effect was of short duration and was followed by a progressive but small diminution in amplitude and force of the beat which was at the expense of systole. No change in heart rate was recorded when this dilution was used. When the strength of the perfusing fluid was increased to 1/10,000, or more, the depressant effects became more marked, while the initial phase of increased amplitude, seen when the weaker concentrations were employed, was absent (Fig. 1). Reperfusion with Ringer's solution always abolished this cardiac depression and restored the heart to its former rate and amplitude.

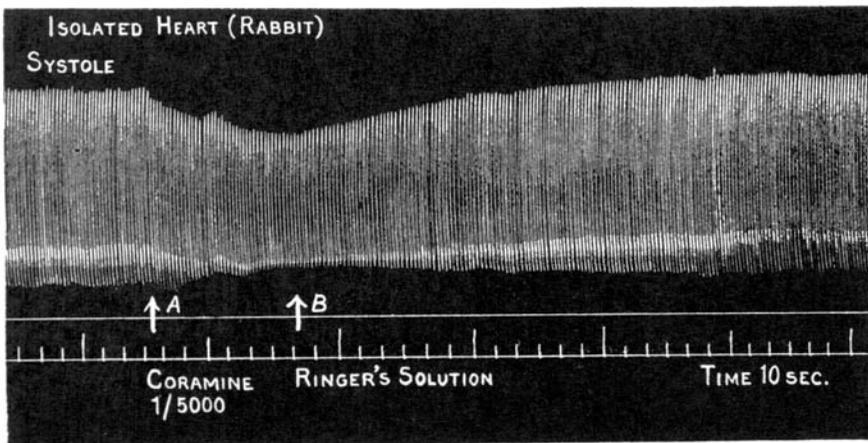


Fig. 1. Isolated heart (rabbit). Perfused with Ringer's solution. At A 1/5000 Coramine in Ringer's solution was substituted. At B the perfusing fluid was changed back to Ringer's solution.

The rate of the isolated heart was slowed. This was more marked when the organ was perfused with the stronger solutions of Coramine, such as 1/5000 or more. The introduction of 0.5 c.c. of atropine sulphate (0.5%) into the perfusing fluid abolished the slowing of the heart rate produced by Coramine. It is clear, therefore, that this drug acts upon the peripheral vagus system.

(b) *Heart in the intact animal.*

Cats anaesthetized with ether and urethane were used and the heart volume recorded by means of a cardiometer technique. The drugs were injected either into the left external jugular vein or the left femoral vein. The injection of 0.5 c.c. of Coramine (5%) into a cat weighing 3 kg. produced no changes in blood pressure or heart volume. Twice this dose (0.5 c.c. 10% sol.; Fig. 2) produced a momentary fall followed by a small rise in blood pressure accompanied by an increase in heart volume which indicated a more complete relaxation of the myocardium. The blood pressure attained its maximum

height 2 min after the injection was made and then declined slowly to normal during the next 12 min. Larger amounts (1 c.c. of a 10% sol ; Fig 3) produced a marked decrease in stroke volume at the expense of both systole and diastole, indicating a less perfect relaxation and less complete contraction of the myocardium. During this phase the blood pressure showed a marked rise in

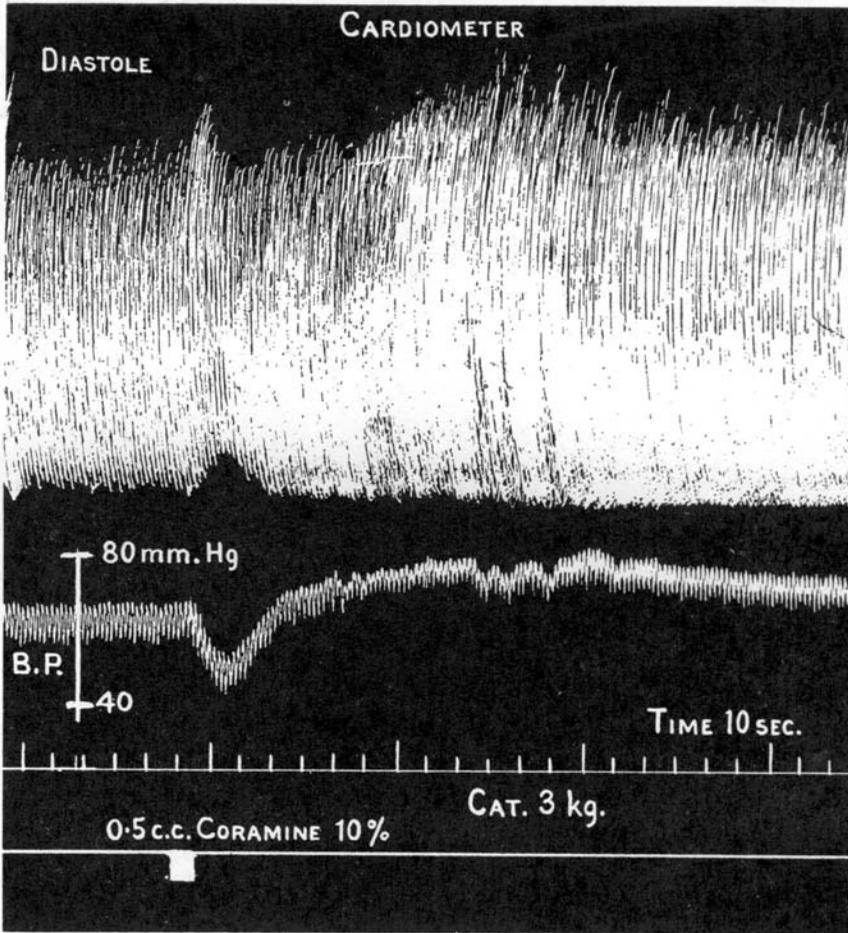


Fig 2

spite of the decreased cardiac output, indicating that peripheral vascular effects were the probable cause of the rise in blood pressure. The maximum rise was recorded within 90 sec., after which it slowly declined to normal during the next 12 min. Larger doses produced similar effects, but the degree of cardiac depression was correspondingly greater. Although this depression was very great when very large amounts of Coramine were injected, it was never found possible to arrest cardiac action. No changes in heart rate, such as were

observed in the isolated heart, were recorded in these experiments on the intact heart.

(c) *Blood pressure.*

Using cats weighing 2.5–3.5 kg., anaesthetized with A.C.E. mixture and urethane, the intravenous injection of 10% Coramine in moderate doses

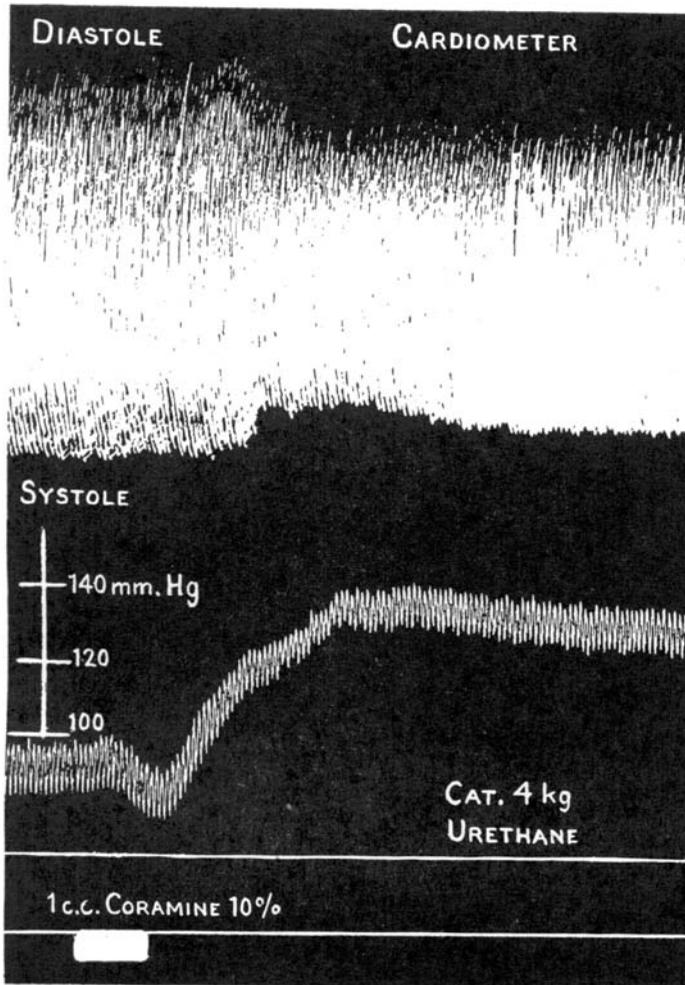


Fig. 3.

(0.25–1 c.c.) always produced a temporary lowering of blood pressure which never lasted longer than about $\frac{1}{2}$ min. This was soon followed by a moderate rise in blood pressure which reached a maximum within 2 min. and then declined slowly to normal during the next 15–30 min. Larger doses (1–2 c.c.) produced a greater rise, while very large doses caused a definite lowering of

blood pressure which took some hours to recover to normal again. In addition to dosage the rise in blood pressure was found to be dependent upon the pressure existing immediately before the Coramine was injected. Small doses produced only a slight rise when the normal blood pressure was high, whereas the same doses produced a much greater increase when the blood pressure was low at the beginning of the experiment.

Repeated small doses usually caused successive rises in pressure. Section of the vagi in the neck did not alter these effects.

Animals with the brain removed, including the medulla, and kept alive with artificial respiration, did not show any marked changes in blood pressure in response to injections of Coramine. Similar results were obtained when the medulla and cord were destroyed. Coramine also failed to produce a rise in blood pressure after the ganglion cells had been paralysed with nicotine. This was well illustrated in the following experiment.

A cat weighing 3.5 kg. was anaesthetized with A.C.E. and urethane; blood pressure was recorded. The intravenous injection of 0.25 c.c. of 10% Coramine produced a rise in blood pressure equivalent to 15 mm. Hg. A second injection of the same amount of the drug given 15 min. later produced a rise of 16 mm. Hg. Repeated injections of nicotine tartrate were then given at suitable intervals until further injections failed to produce a rise in blood pressure, and stimulation of preganglionic fibres of the vagus or splanchnic nerves failed to produce any effect. At this stage the mesenteric and other ganglion cells were considered to be inactive. An injection of 0.25 c.c. of 10% Coramine given 10 min. later failed to produce a rise in blood pressure. Two further injections of 0.5 and 1 c.c. Coramine given at 15 min. interval were also without effect.

From these results it would appear as if the rise in blood pressure is due to an action of Coramine on the central nervous system or ganglion cells. Repeated small doses of Coramine are usually followed by successive increases in the blood pressure producing a "staircase" effect. After a certain amount of the drug has been injected twitchings ensue which may later develop into convulsions. Large doses of the drug always cause a marked lowering of the blood pressure and convulsive movements.

One cat weighing 2 kg. and anaesthetized with chloralose was given repeated injections of a 10% solution of Coramine. At the beginning of the experiment the blood pressure was equivalent to 128 mm. Hg. The first two injections of 0.5 and 0.75 c.c., with an interval of 30 min. between them, raised the blood pressure to 166 and 187 mm. Hg respectively. A third injection of 0.5 c.c., made 15 min. later, lowered the pressure to 130 mm., while a fourth (0.5 c.c.) given after a further delay of 15 min. lowered the blood pressure to 100 mm. Hg. At this stage muscular twitchings became frequent, and within a few minutes were so severe as to embarrass the respiration. Artificial respiration was therefore commenced. An additional 3.75 c.c., given in three separate injections (1, 1.75, and 2 c.c.) at 10 min. intervals, only caused a further fall of 10 mm. Hg. A further 3 c.c. failed to have any effect.

From these results it is evident that, if the detrimental effects of large doses of Coramine upon the respiration are attended to by giving artificial respiration, then it is extremely difficult to cause a failure of the healthy cardiovascular system with a continued high dosage of the drug.

It is interesting to compare the effects of adrenaline HCl and nicotine tartrate upon the blood pressure before and after large doses of Coramine. The effects produced by both of these drugs were definitely diminished when administered after large doses of Coramine, and in some experiments very much larger doses of nicotine were required to produce effects comparable with the small dose administered at the beginning of the experiment. This evidence suggests that large doses of Coramine may depress, not only ganglion cells, but may also interfere with the action of adrenaline at the myoneural junctions of the sympathetic system in such a way as to reduce its normal action.

(d) *Right auricular pressure.*

In these experiments auricular pressure was recorded by passing a long cannula filled with half-saturated sodium sulphate into the right auricle by way of an artificial opening made into the wall of the right external jugular vein. The cannula was connected to a small water manometer, the other end of which was connected to a recording tambour. Right carotid blood pressure and heart volume (cardiometer) were sometimes recorded at the same time. Cats anaesthetized with urethane were used, and the results obtained can be best illustrated by describing a typical protocol.

Two successive injections of 0.1 c.c. of 10% Coramine made into the left femoral vein of a cat weighing 3.6 kg. were entirely without effect upon the carotid pressure, right auricular pressure, or heart volume. 0.5 c.c., however, produced a rise of 30 mm. Hg in carotid pressure, while the right auricular pressure showed a decrease in pressure equivalent to 14 mm. water (Fig. 4). No change in heart volume was recorded until the carotid pressure had reached its maximum rise and the right auricular pressure reached its maximum fall. At this point the heart showed a decrease in the degree of diastolic relaxation without any change in the degree of systolic contraction or heart rate. This indicated that the less complete relaxation of the cardiac muscle during the diastolic phase must have caused a deficient filling of the right heart with a consequent decrease in output from the left heart. Such a condition would lead to a definite fall in carotid pressure were there not peripheral vascular effects at work causing some vasoconstriction which raised the blood pressure. A further injection of 1.0 c.c. of 10% Coramine given 30 min. later (Fig. 5) caused a further fall in right auricular pressure, with a temporary rise and, later, a marked decrease in carotid pressure, while the heart showed some increased relaxation, beyond normal limits, during diastole and a less complete contraction during the systolic phase.

It is evident, therefore, that small doses of Coramine (0.1 c.c.) have no effect upon the right auricular pressure, carotid pressure, or the heart. Medium doses (0.5 c.c.) cause a fall in right auricular pressure which is accompanied by the rise in the pressure of the right carotid artery and some decrease in cardiac output which is partly due to an imperfect filling of the heart during the diastolic pause. Large doses cause a further decrease in right auricular pressure accompanied by a greater rise in carotid pressure. At the same time there is a relaxation of the myocardium beyond normal limits and a decrease in the amplitude of systolic contraction.

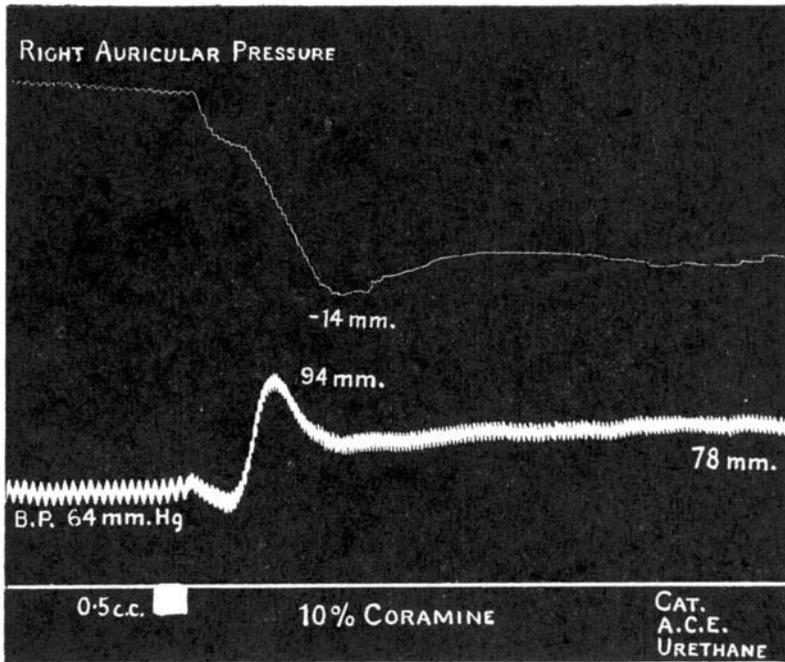


Fig. 4. Cat 3.6 kg. A.C.E. and urethane. Blood pressure and right auricular pressure. Showing the effect of an intravenous injection of Coramine.

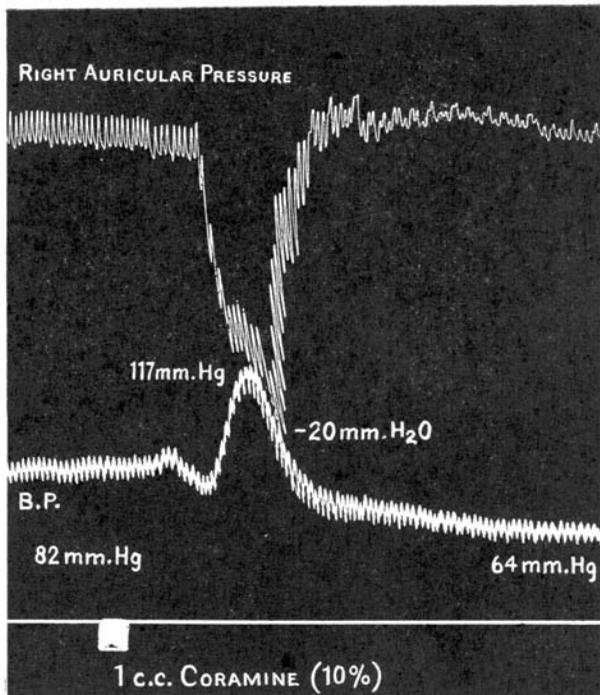


Fig. 5. Cat 3.2 kg. Urethane. Blood pressure and right auricular pressure. Showing the effect of a moderate dose of Coramine injected intravenously.

(e) *Pulmonary circulation.*

Pulmonary artery pressure was recorded by connecting a cannula, which had been previously ligatured into the pulmonary artery, to a manometer filled with half-saturated sodium sulphate solution. The manometer was connected to a recording tambour. Right carotid blood pressure was also recorded. Cats under the influence of urethane were used.

A first dose of 0.25 c.c. of 10% Coramine injected into a 3.2 kg. cat produced a fall in pulmonary pressure equivalent to 5 mm. water which was accompanied by a rise in right carotid pressure. The pulmonary pressure was normal again 20 min. later, while the carotid pressure was still slightly raised. A second injection of 0.75 c.c. given 40 min. later produced a similar result. A third injection of 1.5 c.c. made after an interval of 30 min. produced a fall in the pulmonary artery pressure of 6 mm. of water accompanied by a fall in the carotid pressure. Ten minutes later, while the carotid pressure was still lowered, the pressure in the pulmonary artery rose to +7 mm. of water, after which it slowly returned to normal during the ensuing 20 min.

(f) *Peripheral vessels.*

Limb volume. Experiments made upon urethanized cats weighing 2.5–3.5 kg. showed that the intravenous injection of 0.25–1 c.c. of 10% Coramine produced a marked diminution in limb volume accompanied by a rise in blood pressure. The degree of vasoconstriction increased with the dosage employed. In some experiments, large doses of the drug (1–3 c.c.) produced vasoconstriction even when a fall in blood pressure was recorded, and so the fall in arterial pressure must be assigned to the diminished cardiac output seen in the cardiometer experiments when large doses were employed.

Splanchnic volume. Splanchnic volume was determined by placing a selected portion of the small intestine, complete with vascular connexions, into an oncometer.

Urethanized cats were used. The results obtained showed a well-marked constriction of the splanchnic vessels produced in response to injections of Coramine and are in complete agreement with the results obtained with the limb vessels.

When large doses of Coramine were injected intravenously the carotid blood pressure invariably fell anything from 10 to 50 mm. Hg, depending upon the dosage employed and the level of the blood pressure before the injection was made. The degree of fall was always greatest when the initial blood pressure was high. As the blood pressure fell splanchnic vessels always constricted to a marked degree, while the limb vessels, as recorded by the limb-volume method, showed a slight degree of dilatation (Fig. 6). The pulmonary vessels also showed a small degree of dilatation (Fig. 7).

This evidence suggests that the fall in blood pressure is of cardiac origin and is probably due to a decrease in cardiac output. This view is supported by the results of the heart-volume experiments. The dilatation of the limb vessels is probably passive in nature and may be due to the removal of blood from the visceral area by the intense constriction of the splanchnic vessels.

Perfusion of coronary vessels. These experiments were conducted at the same time as those on the isolated rabbit's heart. The coronary vessels were

perfused with a dilution of Coramine in Ringer's solution. The dilutions used ranged from 1/10,000 to 1/2500, and the results of four experiments are set out in Tables 1 and 2. The figures are a measurement of the coronary outflow and show that Coramine in dilutions of 1/5000, or more, had a dilatatory effect upon the coronary vessels of the myocardium.

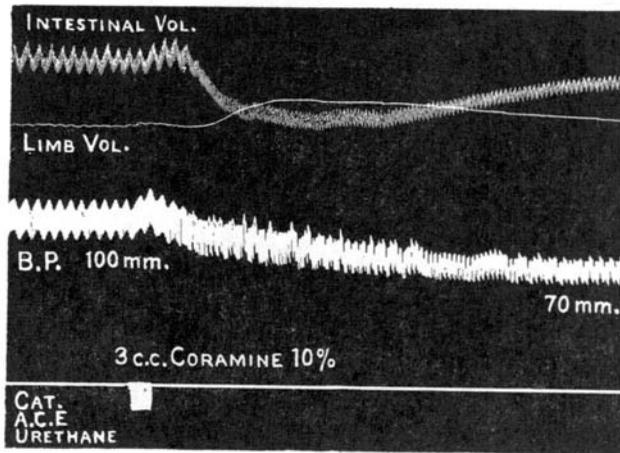


Fig. 6. Cat 3.2 kg. A.C.E. and urethane. Blood pressure, limb volume and intestinal volume. Shows the effect of a large dose of Coramine.

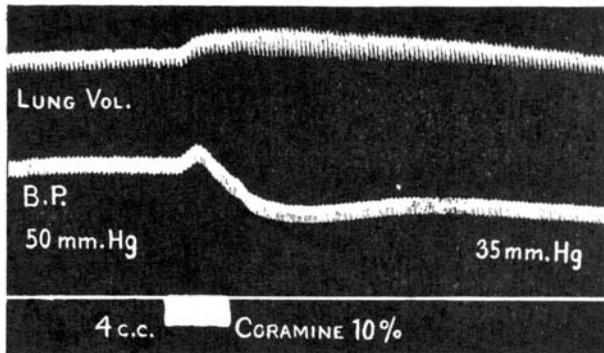


Fig. 7. Cat 3.5 kg. A large dose of Coramine was injected intravenously. Showing the effect on lung volume and blood pressure.

Perfusion of splanchnic vessels. Cats were anaesthetized and a laparotomy performed. The whole of the intestine supplied by the superior mesenteric artery was excised and transferred to the perfusion chamber, and kept at a constant temperature of 37.5°C . The arteries were perfused with a mixture of 40 c.c. defibrinated blood, taken from the animal, and 300 c.c. of Ringer's solution at 37.5°C ., and at a constant pressure of 25 cm. of water. Coramine was injected into

Table 1. *Perfusion of coronary vessels (rabbit's heart)*

Perfusing fluid	Coronary output in c.c./min.		
	Heart no. 1	Heart no. 2	Time (min.)
Ringer's solution	3.9	3.8	1st
	4.0	3.8	3rd
	4.0	4.0	5th
	3.9	3.9	9th
Coramine 1/5000	4.0	4.0	11th
	4.2	4.1	13th
	4.2	4.3	17th
	4.3	4.3	20th
Ringer's solution	4.2	4.2	23rd
	3.8	3.9	25th
	3.8	3.9	29th
	3.7	4.0	31st
	3.8	3.8	35th

Table 2. *Perfusion of coronary vessels (rabbit's heart)*

Perfusing fluid	Coronary output in c.c./min.		
	Heart no. 3	Heart no. 4	Time (min.)
Ringer's solution	3.6	4.0	1st
	3.7	4.1	3rd
	3.7	4.0	5th
	3.7	4.1	9th
Coramine 1/2500	3.6	4.0	11th
	3.8	4.3	13th
	3.9	4.2	17th
	4.0	4.3'	20th
Ringer's solution	4.0	4.3	23rd
	3.6	3.9	25th
	3.6	4.0	29th
	3.7	3.9	31st
	3.7	3.9	35th

the circulation after a suitable interval. Tables 3-5 show the results of some experiments which were typical of the others. From these figures it is evident that Coramine in a dilution of 1/34,000,000 (Table 3) had no effect on the vascular tone, whereas 1/3,500,000 (Table 4) produced a marked vasoconstriction. Higher concentrations (1/360,000; Table 5) produced an even more marked increase in vascular tone than the weaker concentrations. In two experiments a concentration of 1/3,400,000 produced a very slight dilatation of the vessels which could not be explained. Four other similar experiments, using the same concentration, showed a well-marked constriction.

Perfusion of limb vessels. This was carried out using the Dixon perfusion apparatus. The perfusing fluid entered the limbs by way of a cannula ligatured into the abdominal aorta, immediately proximal to the common iliac arteries, while it left the circulation by way of a cannula inserted into the inferior vena cava at the same level. A perfusing fluid consisting of a mixture of 35 c.c. Ringer's solution and 65 c.c. defibrinated blood from the animal was perfused through the vessels at a pressure of 10 mm. Hg.

Table 3. *Perfusion of isolated intestine (vessels)*

Cat 2.5 kg. A.C.E. mixture and urethane. Volume of perfusing fluid 340c.c.

Time p.m.	Perfusing fluid	Output c.c./min.
4.10	Mixture of Ringer's solution and defibrinated blood	9.0
4.11		9.0
4.12		8.8
4.13		9.0
4.14		9.4
4.15	0.5 c.c. Coramine 1/50,000 added	9.4
4.16		9.4
4.17		9.3
4.18		9.2
4.19		8.8
4.20		9.0
4.21		9.0

Table 4. *Perfusion of isolated intestine (vessels)*

Cat 2.8 kg. A.C.E. mixture and urethane. Volume of perfusing fluid 350 c.c.

Time p.m.	Perfusing fluid	Output c.c./min.
2.10	Mixture of Ringer's solution and defibrinated blood	9.2
2.11		9.2
2.12		9.3
2.13		9.2
2.14		9.3
2.15		9.2
2.16	0.5 c.c. Coramine 1/5,000 added	9.3
2.17		8.8
2.18		8.6
2.19		7.6
2.20		7.6
2.21		6.2
2.22		5.0
2.23		5.0
2.24		4.9
2.25		4.9
2.30		4.9
2.31		4.9

Table 5. *Perfusion of isolated intestine (vessels)*

Cat 2.9 kg. A.C.E. and urethane. Volume of perfusing fluid = 360 c.c.

Time a.m.	Perfusing fluid	Output c.c./min.
11.12	Mixture of Ringer's solution and defibrinated blood	9.1
11.13		9.0
11.14		9.2
11.15		9.1
11.16		9.1
11.17		9.0
11.18		9.1
11.19		0.5 c.c. Coramine 1/500 added
11.20	9.0	
11.21	8.5	
11.22	7.6	
11.23	7.2	
11.24	6.3	
11.25	5.0	
11.26	4.6	
11.27	4.1	
11.28	4.0	
11.29	4.0	
11.30	4.0	
11.31	4.1	

Three different concentrations of Coramine were tested. The injection of 1 c.c. Coramine (1/10,000), making a final dilution of 1,000,000, produced only a slight constriction of the limb vessels. A dilution of 1/500,000 caused a small initial dilatation which was rapidly followed by a marked vasoconstriction. These effects were even more marked when a dilution of 1/50,000 was employed (Fig. 8). With this strength the initial dilatation was marked, but recovery to normal was rapid and the following stage of vasoconstriction was well marked.

From these results it is obvious that the initial dilatation of blood vessels produced by Coramine is sufficient to account for the small but short-lived fall in blood pressure which usually precedes the rise in blood pressure seen in the intact animal.

(3) *The effects of Coramine upon the respiratory system*

That Coramine is a powerful respiratory stimulant was observed during the preliminary experiments when the drug was injected into rabbits. It was seen that small doses produced a noticeable increase in the rate and amplitude of the respiratory movements, while large doses caused convulsions, and death sometimes occurred during the convulsive stage. In animal experiments there is, however, a large margin of safety between the therapeutic and lethal doses of the drug. Further experiments on respiration were conducted on cats and rabbits under the influence of urethane.

Injections of small doses (0.5 c.c. 10%) of Coramine produced an immediate increase in the amplitude of the inspiratory phase which lasted only a few seconds. This was quickly followed by a rapid increase in respiratory rate. The amplitude of the movements was increased in such a way as to indicate a more complete filling and emptying of the lungs with each excursion. The maximum effects were usually recorded during the first 5 min. following the administration of the drug by the intravenous route, after which they slowly decreased to normal during the next $\frac{1}{2}$ –2 hr. Similar effects were recorded using large doses (2 c.c. 10%), but there was always a stage of apnoea produced (Fig. 9), first during the expiratory and then in the inspiratory phase. The stage of apnoea lasted 10–45 sec. and was followed by a rapid increase in the rate and amplitude of the respirations during the next 30 min. Very large doses always caused convulsions and a complete failure of respiration leading to death, which is similar to that seen in strychnine poisoning. The effects of repeated small doses were studied. An intravenous injection of 1 c.c. of 10% Coramine was made into a urethanized rabbit weighing 3 kg. The respiratory rate increased from 58 to 136 per min. in 3 min., while the amplitude was doubled. 15 min. later a second injection of 1 c.c. (10%) increased the rate from 98 to 176 per min. and increased the amplitude to three times the normal excursion. This effect was prolonged, and 1 hr. later the amplitude was normal again and the rate 48 per min., which was subnormal.

The effects produced by the injection of morphine HCl during the active phase of previously administered Coramine were of interest. A 3 kg. rabbit, anaesthetized with urethane, was given an intravenous injection of 2 c.c. of 10% Coramine which increased the amplitude threefold and the rate from 50 to 164 per min. Then 1 c.c. of 2% morphine HCl was given intravenously. The effect was an immediate reduction of the respiratory rate to 30 per min. and a marked diminution in amplitude, which was, however, only transitory. The rate quickly recovered to approximately its former rate (152 per min.) and amplitude. Two further injections of 20 and 40 mg. morphine HCl, given with an interval of 15 min. between, were required to depress the respiratory rate to 28 per min. and amplitude to a degree slightly less than normal. This condition was maintained for 14 min. when 1 c.c. of

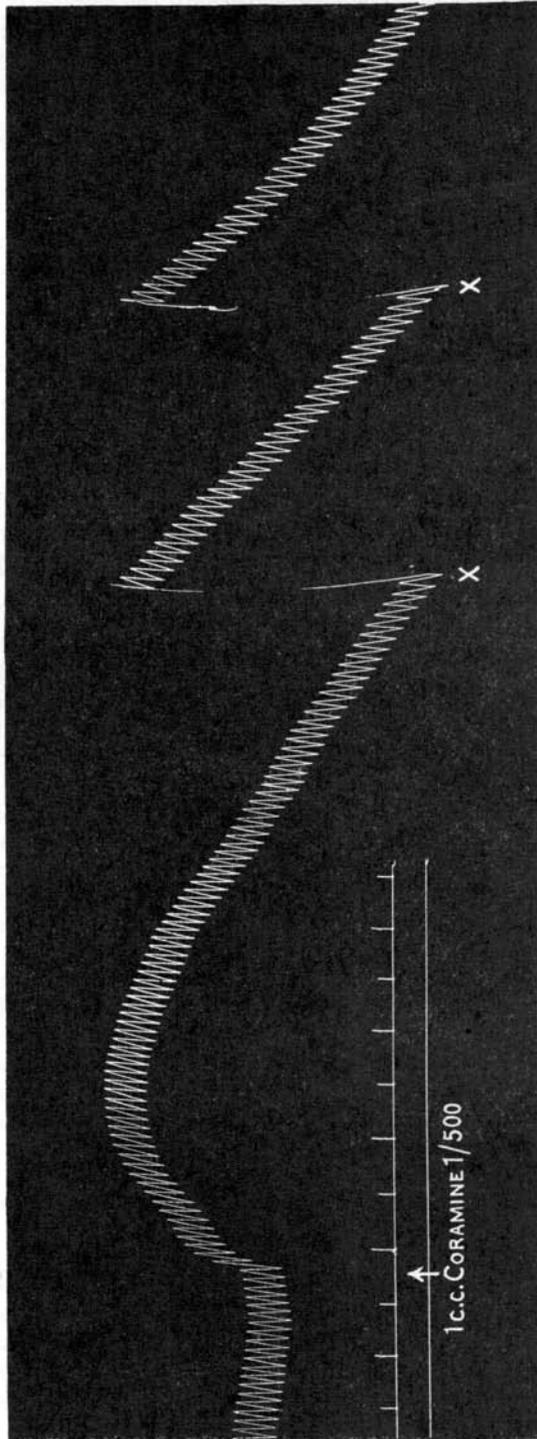


Fig. 8. Cat. Hindlimb perfusion: shows effect of injecting 1 c.c. Coramine 1/500 into perfusion fluid. Final dilution 1/50,000. Time 30 sec. At each X 5 c.c. of perfusion fluid was added to the venous receptacle.

10% Coramine was injected intravenously. The effect was immediate; both the rate and the amplitude began to increase again. The rate 10 min. later was 98 per min., while the amplitude was twice the normal. This condition was maintained for 25 min., after which a slow deterioration followed.

From these results it appears as if Coramine is able to antagonize, to some extent, the depressant effects of morphine upon the respiratory centre. A detailed study of these effects of Coramine in animals suffering from experimental poisoning with narcotic drugs is now in progress and will be published at a later date.

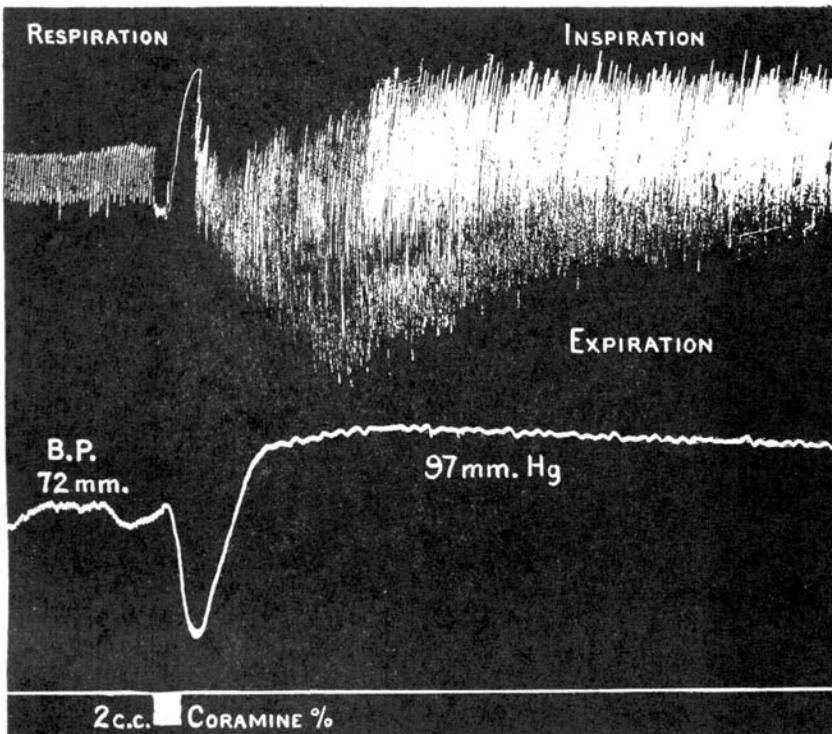


Fig. 9. Rabbit 2.2 kg. Ether and urethane. Respiration. Blood pressure. Shows the effect of 2 c.c. Coramine (10%) on the respiration. The respiratory rate increased from 52 to 184 per min.

(4) *The effects of Coramine upon the central nervous system*

(a) *Medulla.*

These experiments were designed to ascertain whether there was any change in the sensitivity of the medullary centres after the administration of Coramine.

Urethanized rabbits were used and records made of the carotid blood pressure and respiratory movements. The point of minimal response to faradic stimulation of the central end of the severed cervical vagi was determined both before and after administration of Coramine. These experiments showed a general agreement, and the results of one of them are given in Table 6, while Fig. 10 shows a record made in the same experiment.

Table 6. *Stimulation of the central end of the cut vagus nerve*

Rabbit 3.3 kg. Male. Urethane.

	Vagus nerve	Coil position cm.	Result
Normal	Left	80	-
		70	Weak +
	Right	80	-
		70	+
0.1 c.c. of 10% Coramine in left femoral vein	Left	80	-
		70	Strong +
	Right	80	-
		70	Strong +
0.25 c.c. of 10% Coramine in left femoral vein	Left	90	-
		80	Strong +
	Right	100	-
		90	Weak +
		80	Strong +

These results show that the respiratory centre in the medulla is more sensitive to central vagal stimulation after the injection of 0.1 c.c. of 10% Coramine. Smaller doses than this produced no change, while with larger amounts the sensitivity was considerably increased and the drug appeared to facilitate the reflex activity of the centre.

(b) *Pupil.*

The instillation of a few drops of a dilute solution of Coramine into the conjunctival sac of the rabbit produced no changes in the pupil even after 20 min. The dilutions used ranged from 0.001 to 10%. In the intact animal Coramine (0.5 c.c. 10%, or more) usually produced a constriction of the pupil which was more marked when large doses were employed. It appears, therefore, that the drug has some effect upon the third nerve nucleus but not upon the peripheral nerve mechanism.

(c) *Spinal cord.*

Throughout this investigation it was constantly observed that one large dose, or several small doses given within a short space of time, produced twitchings of the limbs and body muscles which sometimes developed into convulsive movements, according to the dose employed. The muscular twitchings were both tonic and clonic in character and could always be produced in the conscious, decerebrate, or anaesthetized animal.

A 3 kg. cat was anaesthetized with A.C.E. mixture and urethane and blood pressure recorded. An intravenous injection of 0.25 c.c. 10% of Coramine was tolerated without twitchings or convulsions. 10 min. later a second injection of the same amount was given with a similar result. A third and similar dose, given after an interval of 10 min., immediately produced twitchings of the muscles of the limbs and body. When the twitching had subsided, about 12 min. later, the pads of the hindlimbs were gently stroked without any reflex movements taking place. Gentle pressure, however, applied to one hindfoot by a nipping movement, at once produced violent twitchings which were limited to both hindlimbs. Similar results, but restricted to both the forelimbs, were observed when one foot of the forelimbs was pressed gently. The animal was then decerebrated in such a way as to leave the medulla intact. After

a lapse of 20 min. a further injection of 0.25 c.c. of 10% Coramine was given; the muscular twitchings at once reappeared. Gentle stroking and pressure applied to the feet elicited the same responses as before. A further injection of the same dose increased the severity of the twitchings and struggles of the animal. After an interval of 15 min., when the muscular movements had ceased, the cord was destroyed by means of a flexible trocar passed from the brain along the path of the cord. 5 min. later, the injection of 0.25, 0.5, 1.0, 2 and 4 c.c. of 10% Coramine in successive doses over a period of 10 min. failed to produce either twitchings or convulsions. In some experiments with the cord and brain intact the twitchings were abolished by curaré.

These experiments show that large doses of Coramine produce muscular twitchings and convulsions which are due to a stimulating action of the drug on the spinal cord. Peripheral action plays no part in the production of these effects.

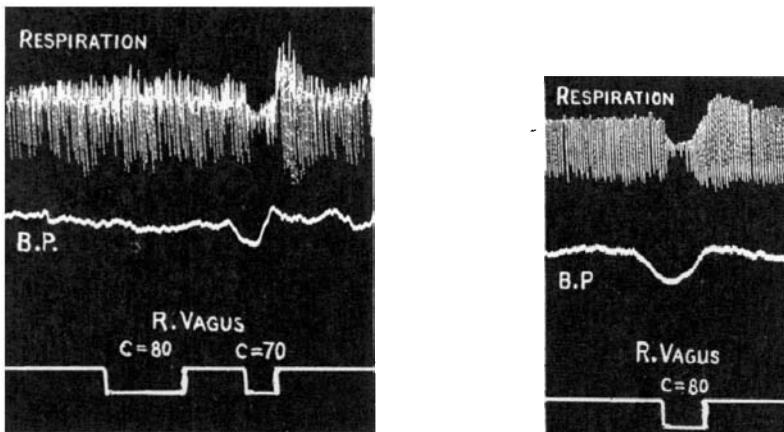


Fig. 10. Rabbit 2 kg. Ether and urethane. Stimulation of the central end of the cut vagi. Respiration. Blood pressure. Showing the increased excitability produced after an intravenous injection of 0.25 c.c. Coramine (10%). Upstroke is inspiration.

(d) *Sympathetic ganglion cells.*

The effects upon the nictitating membrane, produced by faradic stimulation of the cervical sympathetic nerve trunk immediately distal to the superior cervical ganglion were compared before and after painting the ganglion cells with solutions of dilute Coramine. Table 7 shows the results of one experiment. Where a 1% solution was employed there appears to be some increase in the sensitivity of the ganglion cells to faradic stimulation, whereas the 10% solution caused a temporary depression of the ganglion which was followed by a quick recovery.

(5) *The effect of Coramine upon the intestinal movements*

(a) *Isolated intestine.*

The movements of pieces of isolated intestine were studied after suspension in a tyrode bath at 37.5° C. A dilution of 1/40,000 Coramine produced a small degree of relaxation in the intestinal muscle with a slight reduction in the

Table 7. *Stimulation of the sympathetic trunk below the cervical ganglion*

Cat 3.4 kg. A.C.E. and urethane.

	Min. after painting ganglion	Position of coil and result	
Normal	—	33 +	34 -
Coramine 1%	1	35 +	38 -
	8	35 +	38 -
	12	38 +	39 -
Normal	—	38 +	39 -
Coramine 10%	1	25 +	26 -
	8	35 +	36 -
	12	38 +	39 -

amplitude of the movements. No change in the rate of the movements was recorded. Complete recovery to normal did not occur after changing the bath to Tyrode's solution again. Similar effects were produced with dilutions of 1/20,000, 1/10,000 and 1/5000. Solutions of 1/60,000 and 1/80,000 were entirely without effect upon the intestine.

(b) *Intact animal.*

Decerebrate cats were used, and the movements of the small and large intestine were recorded by a balloon method. In these experiments no differences were recorded between the behaviour of the small intestine (duodenum) and large intestine (caecum).

The intravenous injection of 0.25 c.c. of 10% Coramine into a 3.9 kg. cat caused a moderate increase in tone accompanied by a marked increase in the amplitude of the movements, lasting 10–15 min. The injection of sufficient atropine (5 mg.) to inhibit the peripheral vagal mechanism always abolished the increased tone produced by Coramine without any change in the amplitude of the movements. The subsequent injection of the same dose of Coramine, after atropine had been given, never reproduced the effects upon the intestinal tone seen previously.

This suggests that Coramine has some action upon the peripheral vagus system. In other experiments it was found that large doses of Coramine (2 c.c. or more) either produced no effects upon the intestinal movements, or caused a small diminution in the amplitude of the movements without any alteration in the general tone. In every case the intestine of these animals exhibited a normal response to the injection of adrenaline, arecoline, and atropine, thus showing that it was responsive to drugs acting on the vagus and sympathetic systems. It is interesting that the stimulating effects of small or moderate doses of Coramine, seen on the intestine of the intact animal, were never observed in the experiments on the isolated intestine.

(6) *Experiments on the frog's heart and vessels*

(a) *Heart.*

Decerebrate frogs were used and their hearts perfused with a modified Ringer's solution. Heart movements were recorded by a suspension method. A dilution of 1/20,000 Coramine in Ringer's solution (Fig. 11) produced little

effect beyond a very slight diminution in the amplitude of the beat which was on the systolic side. No change in heart rate was recorded.

At a strength of $1/10,000$ (Fig. 12) the depressant effect was marked and effected both the degree of contraction and relaxation of the myocardium. No change in heart rate was observed, and perfusion with Ringer's solution always restored the heart to its normal condition. A dilution of $1/5000$ produced the same effects but in a more marked degree.

The effects of Coramine upon the frog's heart depressed with $1/5000$ chloral were studied. When the depression was well marked the heart was then perfused with a $1/10,000$ solution of Coramine (Fig. 13) which quickly overcame the depression and restored the heart to its former condition of amplitude and rate. Coramine was able to produce this effect in hearts which had been arrested in diastole after perfusion with chloral. Fig. 14 shows the recovery of a heart depressed with chloral when reperfused with Ringer's solution.

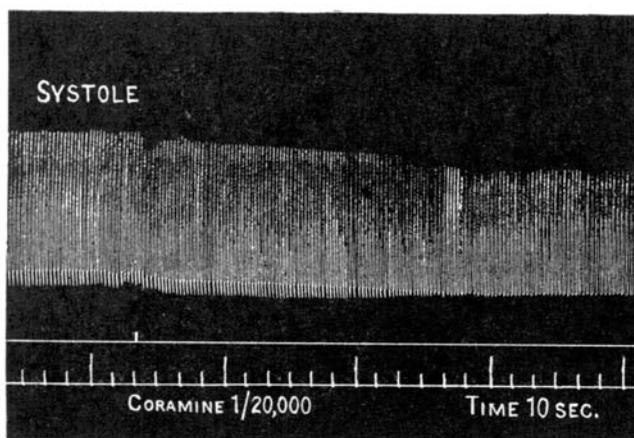


Fig. 11. Frog's heart. Perfused with Ringer's solution. Shows the depressant effects of $1/20,000$ Coramine.

There is no doubt that Coramine in a dilution of $1/10,000$ has a depressant effect upon the frog's heart. Chloral has a similar but more marked effect, and yet Coramine in this dilution is able to abolish the depressant action of chloral upon the myocardium. No explanation of this action of Coramine can be advanced, but it confirms the experiments of Uhlmann (1924) who first drew attention to this peculiarity of Coramine.

(b) *Vessels.*

Perfusion of the vessels with a dilution of $1/20,000$ Coramine in modified Ringer's solution produced no change in the recorded outflow and therefore does not effect the calibre of these vessels. A small degree of vasoconstriction was recorded when a dilution of $1/10,000$ was employed. A more marked vasoconstriction was evident with a dilution of $1/5000$ or more. Reperfusion of the vessels with Ringer's solution always caused the outflow to quicken until normal rate was re-established.

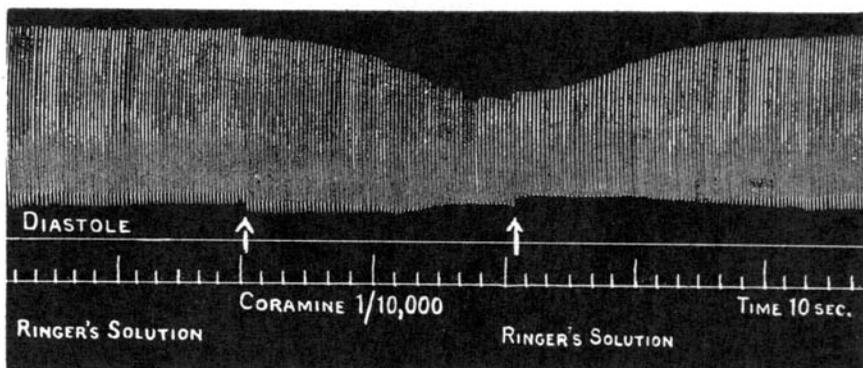


Fig. 12. Frog's heart. Perfused with Ringer's solution. Shows the depression caused by 1/10,000 Coramine.

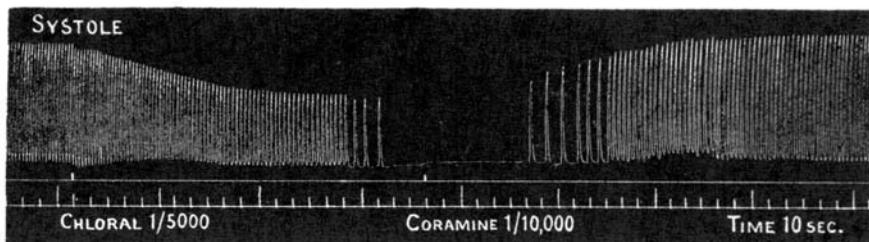


Fig. 13. Frog's heart. Showing the antagonism of Coramine to the myocardial depression produced by chloral.

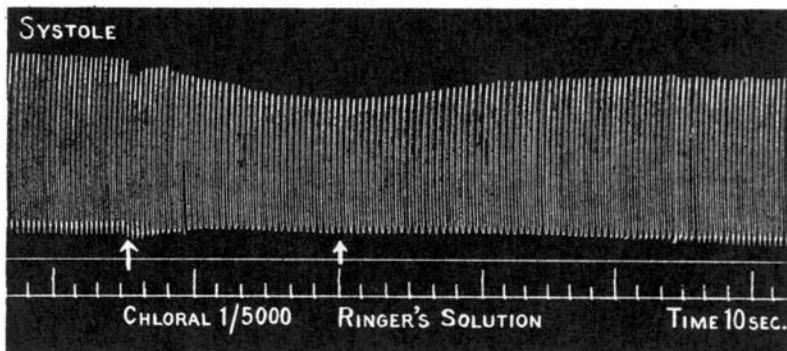


Fig. 14. Frog's heart. Showing recovery from depressant effects of chloral when reperfused with Ringer's solution.

V. DISCUSSION

The results of this investigation have clearly shown that the principal action of Coramine is on the nervous system. When administered in moderate doses it has a stimulating action, which is mainly centred upon the medulla oblongata and spinal cord. In the case of the medulla, the evidence suggests that Coramine increases the sensitivity of the various nerve centres in this region, giving rise to an increased rate and depth of respiration and a peripheral vasoconstriction resulting in a general rise of the systemic blood pressure. The effect of the drug upon respiration is one of its prominent features, and a marked antagonism exists towards the depressant effects of morphine on the respiratory centre. There seems little doubt that it is this action which gives Coramine its usefulness as a therapeutic agent in the treatment of narcotic poisoning. Another feature of the drug is the wide margin of safety between its therapeutic and toxic doses. The administration of large doses is always quickly followed by muscular twitchings of the limbs and body which, at a later stage, may take on the character of severe convulsive movements not unlike those seen in strychnine poisoning. These convulsive movements may involve the muscles of respiration and so cause death from respiratory failure, and to a lesser degree, exhaustion. In so far as the sympathetic nervous system is concerned moderate doses of Coramine appear to increase slightly the sensitivity of ganglion cells to stimuli, whereas larger doses sometimes cause a small degree of depression which is always of short duration and never permanent. It is interesting that the drug has no effect on the pupil when instilled into the conjunctival sac. When given intravenously or subcutaneously it usually causes constriction of the pupil which is suggestive of a central action in the region of the third nerve nucleus. Moderate amounts of Coramine cause blood vessels to constrict with a resultant rise in blood pressure. This is not seen in animals which have had the spinal cord destroyed or have been given nicotine to paralyse ganglion cells. Large doses of Coramine are able to depress the blood pressure but never to a serious extent. This depression may last $\frac{1}{4}$ – $1\frac{1}{2}$ hr. according to the dosage employed.

The results obtained from the perfusion of the blood vessels of the isolated intestine clearly showed that the vasoconstriction produced by Coramine is partly peripheral in origin and not entirely due to the action of the drug on the medulla. That this vasoconstriction may be preceded by a temporary vasodilatation lasting a few seconds was demonstrated in the limb-vessel perfusion experiments. This is particularly interesting because it explains the sudden lowering of blood pressure, lasting only a few seconds, which was commonly seen immediately after the intravenous administration of moderate amounts of Coramine. In small doses Coramine has no action on the coronary vessels of the heart, but with larger doses the coronary flow is increased. Small doses of Coramine have little effect on the normal healthy heart. In a few experiments a slight increase in the amplitude of the heart beat, without any change

in the heart rate, was recorded. Such a result is indicative of an increased cardiac output and would represent a useful action in certain pathological cardiac conditions which lead to heart failure. This effect of Coramine, however, was never constant with any particular dosage, and in most experiments was not seen even when carefully graded dosage was employed. Moderate amounts of the drug cause a decrease in stroke volume without any alteration in the heart rate, and is accompanied by a decreased cardiac output which is partly due to an imperfect filling of the right heart. This is shown by the fall in pressure of the right auricle and pulmonary artery and is a particularly important observation in view of the clinical literature where Coramine is advocated in the treatment of myocarditis, endocarditis, and conditions of acute heart failure, in the belief that it acts as a cardiac stimulant. In heart failure, especially the chronic type, there is usually a marked lowering of the oxygen tension in the blood which further impairs the efficiency of the myocardium and so continues the vicious circle of impairing the function of the myocardium until death ensues. The administration of Coramine in such conditions may produce a beneficial effect, not because of any direct cardiac action, but because of its effects upon respiration leading to a better gaseous exchange at the alveolar interface and later a rise in the oxygen tension of the blood. It is probable that indirectly such an action would improve the function of the myocardium with a consequent increase in cardiac output. One further point is the rise in blood pressure which follows the use of Coramine. This, coupled with the fact that the calibre of the coronary arteries may be increased by the drug, would lead to an increased coronary flow and oxygen supply to the myocardium with beneficial results. On the other hand, such conditions are far from being ideal in establishing an improved circulation of blood in the body.

The role of Coramine in the treatment of pneumonia is to some extent in keeping with the evidence, for it has been shown to act as a powerful respiratory stimulant. This would have a markedly beneficial effect in many cases, but it is important to remember that it is almost generally agreed that in pneumonia death is caused by cardiac failure, and to use a drug, which has been shown to depress cardiac function, in the late stages of pneumonia may not be sound treatment.

The stimulating effects of Coramine on the medulla and its antagonistic action to the depressant effects of chloral, as shown on the frog's heart, suggest its useful employment in cases of poisoning with anaesthetics, barbiturates, and narcotic drugs of the morphine series. An investigation on these lines is now in progress, and the results obtained so far appear very encouraging.

VI. SUMMARY

1. Coramine increases the sensitivity of the central nervous system, particularly the centres situated in the medulla.

2. In large doses, Coramine increases the activity of the spinal cord, producing muscular twitchings of the limbs and body which, when severe, take on the character of convulsive movements.

3. There is a wide margin of safety between the therapeutic and lethal doses.

4. Lethal doses produce convulsions and respiratory failure owing to the involvement of the muscles of respiration.

5. Coramine acts as a powerful respiratory stimulant and is able to overcome the depressant effects of morphine on the respiratory centre in the medulla.

6. Small doses of Coramine raise the blood pressure which is due to a peripheral vasoconstriction. This is partly due to a stimulating effect of the drug on the medulla and to some extent to a peripheral action on either the vasoconstrictor nerves or the arterial muscle. Slightly larger but moderate doses sometimes cause a primary relaxation of the arterioles lasting a few seconds, which may cause a small short-lived fall in blood pressure which is never serious in the normal animal. The rise in blood pressure may last $\frac{1}{4}$ –2 hr., according to the dosage employed.

7. Small amounts of Coramine may increase the amplitude and stroke volume of the heart. This effect was never constant. Larger but moderate doses always produced a diminution in cardiac stroke volume with a decrease in cardiac output. The same effect is seen when large doses are employed. This appears to be the cause of the prolonged lowering of the blood pressure following the administration of large doses of Coramine.

8. Coramine dilates the coronary vessels of the myocardium producing an increase in coronary flow.

9. Coramine lowers the pressure in the right auricle of the heart and the pulmonary artery.

10. Coramine has no effect upon intestinal movements except, when large doses are employed, it causes a slight diminution in the amplitude of the movements with a small increase in muscular tone.

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