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# CONTRADICTORY ACTIONS OF CAFFEINE, CORAMINE, AND METRAZOL.

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In 1929, while engaged in the study which revealed the reciprocal antagonism of picrotoxin and the barbiturates, we observed that under certain conditions such stimulants as strychnine and coramine [Maloney, Fitch, and Tatum, 1931] seemed to hasten the fatal termination of the animal poisoned with a lethal dose of one of the barbiturates. Since strychnine is known to exert both a stimulant and a depressant action the question arose as to whether other convulsants might not also be possessed of contradictory actions. In the following experiments we have subjected coramine, metrazol, and caffeine to certain tests for this possible dualism.

*Method of Approach.*—A surely lethal dose of caffeine administered subcutaneously to a normal rat elicits a state of severe apprehensiveness, grossly exaggerated tremors, a staggering gait, and distressed breathing. These phenomena may endure for an hour or more and the animal passes gradually into a state of depression in which he lingers until death finally ensues. Coramine and metrazol, on the other hand, when administered in surely lethal doses are followed by genuine convulsions. The terminal event, usually respiratory in character, is generally described as an asphyxia due to one or more of the following causes : tetany of the muscles of respiration, paralysis of the respiratory centre, and general exhaustion—a state which when protracted may present the appearance of a genuine condition of depression. When the animal is in an initial state of depression the role of a stimulant agent can more decisively be determined as to its antagonistic or its possible potentiative action. Since, in medical practice, stimulatory action is the prime desideratum in depressed states, laboratory investigation of the role played by stimulant drugs is best made upon animals in an experimentally-induced state of depression.

In our experiments the animals were narcotised with a sub-lethal dose of barbital sodium (medinal). Mature stock rats and rabbits were employed.

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Our method was to administer a sub-lethal but narcotising dose of barbital [Fitch and Tatum, 1932, found the M.L.D. of barbital to be 300 mg./kg. for the rat and 225 mg./kg. for the rabbit, both intraperitoneally], and follow this with doses of the stimulant ranging from a stimulating to a lethal amount at the onset of narcosis. Preliminary experiments were therefore formulated to determine the M.L.D. of the stimulants used.

If the stimulant is a clear antagonist it would be reasonable to expect a reversal of narcosis or some evidences of stimulation at dosage levels slightly below or above the normal lethal figure.

Theoretically, the barbitalised animals ought to tolerate dosages of the stimulant agent in excess of the normal lethal figure; the extent being a definite function of the degree of reciprocal antagonism. This was found to be the case in previous studies made on the comparative effectiveness of picrotoxin, strychnine, and cocaine in barbiturate intoxication [Maloney, 1933 *a*; Maloney, 1933 *b*]. An animal poisoned with a barbiturate can tolerate, and recover from, a dose of picrotoxin, for example, which is many times lethal to a normal animal of the same species. Should death occur in such a case it is unmistakably a death from convulsions due to overdosage. If on the other hand the stimulant in question should happen to possess depressant properties, these properties would be expected to manifest themselves at some dosage level(s) short of their normal lethality by contributing to the death of the animal through addition, potentiation, or synergism to the depressant. Barring this latter assumption a sub-lethal dose of the stimulant administered to a depressed animal should not kill, and a lethal dose, if it proves fatal, should cause death in convulsions, or death as a sequel to convulsions.

## Rats.

*Experiments with Caffeine.*—In determining the M.L.D. of caffeine for our rats, forty animals were employed. Doses of 200 mg. killed two out of ten. (All dosage figures in this paper represent milligrams per kilogram.) Doses of 300 mg., 400 mg., and 500 mg. proved 100 per cent. fatal in each series. Caffeine in toxic doses does not cause death by convulsions but depression. The M.L.D. is about 250 mg.

Forty-eight rats were divided into four groups and the members of each group were given 200 mg. each of barbital subcutaneously. As soon as narcosis occurred caffeine was administered to the members of each group in series ranging from 100 mg. to 300 mg. Doses of 100 mg. were void of physiological effect. Optimal stimulation with temporary arousal was observed with doses of 150 mg. With a 200 mg. dosage 100 per cent. became depressed after a brief period of stimulation; however, 60 per cent. recovered as against 80 per cent. which recovered from the same dose of caffeine alone. Doses of 300 mg. gave no evidences

of stimulation whatever; on the contrary 100 per cent. died in profound depression. Ten controls, all recovered from 200 mg. of barbital alone, and each animal was awake and apparently well earlier than those in the same group treated with caffeine. See Table I.

TABLE I.—CAFFEINE ON RATS.

| Series. | | Barbital, mg./kg. | Caffeine, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|
| No. | Animals. | | | | |
| 1 | 8 | 200 | 100 | 8 | Caffeine had no apparent effect on awakening time; no arousal. |
| 2 | 20 | ,, | 150 | 20 | Transitory arousal (five minutes ±). One remained twenty-four hours in deep depression. |
| 3 | 10 | ,, | 200 | 6 | Majority were aroused temporarily, gross tremors, all depressed; four died in depression. |
| 4 | 10 | ,, | 300 | 0 | No arousals, five died within five hours; two were dead next A.M.; three died during the second night. All deaths occurred in profound depression. |
| 1 | 10 | None | M.L.D. 200 | 8 | Apprehensive, gross tremors; staggering gait; difficult breathing. Two died in depression on the following day. |
| 2 | 10 | ,, | 300 | 0 | Apprehensive, gross tremors; staggering gait; difficult breathing. Between one hour and twenty-four hours after injection all died in depression. |
| 3 | 10 | ,, | 400 | 0 | Practically same. |
| 4 | 10 | ,, | 500 | 0 | Practically same. |
| | 10 | 200 | Controls | 10 | Four controls used in series No. 1 and two in each of the three others. All recovered. Recovery time was earlier than that of treated animals in all series. |

*Experiments with Coramine.*—In determining the M.L.D. of coramine normal rats in series of ten each were given varying doses of the compound. Those in series No. 1 received 200 mg. None showed con-

vulsions, all suffered from fluid in the air passages, but all recovered. The members of series No. 2 received 300 mg. each. All went into severe convulsions and four died. Of the six that survived two developed respiratory disturbances following the accumulation of fluid in the air passages, and had to be sacrificed. Ten each in series No. 4 and 5 received 400 and 500 mg. respectively. All died promptly in severe convulsions. We therefore place the M.L.D. for coramine at 350 mg.

Fifty-one rats each injected with 200 mg. of barbital were employed in studies on the effects of coramine. These were divided into five series, and given doses ranging from 150 to 500 mg. of coramine. The optimal dosage was 200 mg. This produced temporary arousal (average one hour) with no fatalities. Beyond this level temporary awakening occurred, but there were also convulsions of varying degrees of severity; 60 per cent. died from 300 mg. Doses of 400 mg. and 500 mg. respectively caused convulsions without arousal, followed by prolonged depression and 100 per cent. fatality.

With 300 mg. 60 per cent. of the rats used in the toxicity studies on coramine survived, whereas with the same dose administered to the previously barbitalised animals only 37·5 per cent. survived. See Table II.

The presence of fluid in the air passages following coramine alone, or in combination with the other pharmacodynamic agents here employed, was a constantly observed phenomenon in the rat. Mention of this has been made elsewhere [Maloney, 1934]. This appears to be a peculiar species reaction to coramine.

*Experiments with Metrazol.*—In determining the M.L.D. of metrazol ten normal rats were given 100 mg. doses of the compound subcutaneously. Convulsions came on in a few minutes; six died. As a check ten were given 150 mg.; severe convulsions followed, and all were dead within fifteen minutes. The M.L.D. is about 100 mg.

Seventy rats grouped in eight series in our experiments with metrazol were given doses of 100, 150, 200, 300, 400, 500, 600, and 750 mg. respectively in each series following the usual depressant doses of barbital. In series No. 1 with eight rats, and series No. 2 with five, the results were similar. No convulsions followed the administration of the metrazol doses, and all the animals were aroused and remained awake. In series No. 3 eight animals were employed. Metrazol (200 mg.) caused arousal followed by mild convulsions of brief duration, but all the animals survived and were apparently well after several minutes. Nine animals in series No. 6 received 500 mg. each. There were no clear convulsions, all animals were aroused, and seven remained awake while two reverted to a state of depression and died. Those that survived were rather listless, and showed a tardy recovery by comparison with the members of series No. 3. In series No. 8 each of ten animals received 750 mg. of metrazol. All immediately went into severe convulsions. Two

TABLE II.—CORAMINE ON RATS.

| Series. | | Barbital, mg./kg. | Coramine, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|
| No. | Animals. | | | | |
| 1 | 8 | 200 | 150 | 8 | No effect as compared with two controls. |
| 2 | 7 | ,, | 200 | 7 | Transitory arousal averaging one hour; no convulsions; fluid in air passages; complete recovery after a few days. |
| 3 | 16 | ,, | 300 | 6 | Transitory arousal averaging one hour; some had mild convulsions; ten died in depression; those surviving remained in prolonged depression; fluid in air passages. |
| 4 | 10 | ,, | 400 | 0 | All had mild convulsions; no arousals; after convulsions subsided all passed into prolonged and profound depression. |
| 5 | 10 | ,, | 500 | 0 | Same. |
| 1 | 10 | None | M.L.D. 200 | 10 | Hyperexcitable; fluid in air passages; complete recovery after a few days. |
| 2 | 10 | ,, | 300 | 6 | All had severe convulsions; fluid in air passages and two developed respiratory disturbances; four died. |
| 3 | 10 | ,, | 400 | 0 | All died in two hours from convulsions. |
| 4 | 10 | ,, | 500 | 0 | Convulsions came on in twelve minutes; seven dead in fifteen minutes; all dead in twenty-five minutes. |
| | 10 | 200 | Controls | 10 | Two controls used in each series. All recovered. |

survived, but were sickly for two days before they were purposely sacrificed. See Table III.

This group of experiments supports Tartler's [1929] conclusion that metrazol acts as a clear antagonist to barbital in the rat. The results of preliminary experiments, not reported, show that convulsions are

TABLE III.—METRAZOL ON RATS.

| Series. | Animals. | Barbital, mg./kg. | Metrazol, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|
| 1 | 8 | 200 | 100 | 8 | No convulsions; all animals were aroused and all remained awake. |
| 2 | 5 | ,, | 150 | 5 | Same. |
| 3 | 8 | ,, | 200 | 8 | Arousal; hypersensitivity of brief duration; all well after several minutes. |
| 4 | 10 | ,, | 300 | 10 | All aroused; hypersensitive; mild convulsion; drowsy in two hours; 9.00 A.M. next day all awake and well. |
| 5 | 10 | ,, | 400 | 1 | All aroused; hypersensitive; mild convulsion; shivers fourth hour; remain awake but inactive; 9.00 A.M. next day all awake and well. |
| 6 | 9 | ,, | 500 | 7 | Hypersensitive; mild convulsions; all were aroused; seven stayed awake, two went into depression and died; those remaining awake were listless. |
| 7 | 10 | ,, | 600 | 4 | All aroused; hyperexcitable; one and one-half hours drowsy and losing equilibrium; two hours narcosis returned; five hours, one dead, nine in deep depression; 9.00 A.M. next day, five dead, four awake but sickly. |
| 8 | 10 | ,, | 750 | 2 | All were aroused; all convulsed severely; two survived but were sickly and weak for two days; purposely sacrificed. |
| 1 | 10 | None | M.L.D. 100 | 4 | Convulsions—severe; six died. This was the M.L.D. |
| 2 | 10 | ,, | 150 | 0 | Convulsions—severe; all ten were dead in fifteen minutes. |
| | 16 | 200 | Controls | 16 | Two controls used in each series. All recovered. |

produced by doses of 30 mg. with an optimal of 50 mg. in the normal rat. But the animal previously depressed with barbital is able to tolerate 100, 150, and even 200 mg. without (or with but very slight)

convulsive seizures and be aroused from depression. From such studies on the rat, therefore, one would conclude with Tartler [1929] that metrazol in contradistinction to coramine and caffeine is unequivocally stimulatory in action. It will be shown, however, that this conclusion does not hold true in studies on the rabbit.

## Rabbits.

*Experiments with Metrazol.*—While the M.L.D. of metrazol for the rabbit was not determined we note from a previous study [Maloney and Tatum, 1932] that the dosages here employed are within the

Table IV.—Metrazol on Rabbits.

| No. | Series. | Weight, g. | Barbital, mg./kg. | Metrazol, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|---|
| 1 | 1 | 1290 | 150 | 25–I | – | Metrazol caused immediate arousal from narcosis; on foot; gradually begins to lose balance; returns to narcosis. Dead next morning. |
| 2 | ,, | 1320 | 150 | 25–I | + | Same. |
| 3 | 2 | 2100 | 170 | 25–S | + | Metrazol caused immediate arousal; narcosis returns; awake next day. Diarrhoea and sniffles. Apparently well the third day. |
| 4 | ,, | 1400 | ,, | 25–S | + | Same. |
| 5 | ,, | 1650 | ,, | 25–S | + | Same. |
| 6 | 3 | 2390 | 200 | 25, 12·5 –I | + | Two fractional injections. Arousal follows each, but narcosis returns. Asleep next morning. Awoke during the day. |
| 7 | ,, | 2420 | ,, | 25, 20 –I | + | Same. |
| 8 | ,, | 2160 | ,, | 25–I | + | Same. |
| 9 | ,, | 2420 | ,, | 25–I | + | Same. |
| 10 | ,, | 1795 | 200 | 14, 14 –I | – | Died during the night. |

I = Intravenous; S = Subcutaneous.

sublethal range. Ten rabbits averaging 1900 g. were given barbital intraperitoneally in serial doses of 150, 170, or 200 mg. Upon the onset of narcosis metrazol in a 10 per cent. solution was administered.

TABLE V.—CORAMINE ON RABBITS.

| No. | Series. | Weight, g. | Barbital, mg./kg. | Coramine, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|---|
| 1 | 1 | 1090 | 150 | 80–I | – | Immediate increase in rate of respiration. Stands on feet but gradually returns to the narcotic state. Remains in narcosis. Dead next morning. |
| 2 | ,, | 1100 | ,, | 80–I | + | Barbital depression was profound. Coramine caused mild convulsions. Temporary arousal. Narcosis. Awoke next day. |
| 3 | 2 | 2000 | 170 | 80–S | + | Coramine caused temporary arousal. Narcosis returned. Awoke next day. Sniffles and diarrhea, weak. Apparently well on second day. |
| 4 | ,, | 2100 | ,, | 80–S | + | Temporary arousal with return to sleep. Awake and well next morning. |
| 5 | ,, | 1500 | ,, | 80–S | + | Same. |
| 6 | 3 | 2460 | 200 | 50, 16, 25 –I | + | Temporary arousal following each injection of coramine. Narcosis returns. Awoke next day. Well. |
| 7 | ,, | 2850 | ,, | 50, 16, 25 –I | + | Same. |
| 8 | ,, | 2310 | ,, | 50, 16, 25 –I | + | Same. |
| 9 | ,, | 1560 | ,, | 53, 53, 53 –I | + | Same. |

I = Intravenous; S = Subcutaneous.

The animals in the 150 mg. series each received 25 mg. intravenously as a single dose. Their response was an immediate arousal, followed by a return to narcosis after a few minutes. Those in the 170 mg. series received 25 mg. of metrazol subcutaneously. The same type of

response was observed; but in addition the animals had diarrhoea and sniffles on the second day after permanent awakening. In the 200 mg. series two rabbits received 25 mg. intravenously as a single dose, and the phenomenon of temporary arousal was again observed. Thinking

TABLE VI.—RABBIT CONTROLS.

| No. | Series. | Weight. | Barbital, mg./kg. | Recovery. | Remarks. |
|---|---|---|---|---|---|
| 1 | 1 | 1200 | 150 | + | Barbital 5 per cent. solution injected intraperitoneally. Narcosis. Awakening occurred during the night. Awake and well next morning. |
| 2 | 2 | 3100 | 170 | + | Same. |
| 3 | ,, | 2100 | ,, | + | Same. |
| 4 | 3 | 2375 | 200 | + | Same. |
| 5 | ,, | 1755 | ,, | + | Same. |
| 6 | ,, | 1560 | ,, | + | Same. |
| 7 | ,, | 1725 | ,, | + | Same. |
| 8 | Check | 2700 | Metrazol 25 mg.–I | + | Normal animal injected with the stimulant intravenously as check on toxicity. Convulsions—not severe; well within one hour. |
| 9 | ,, | 3500 | Coramine 80 mg.–I | + | Same. |

I = Intravenous.

that arousal might be made continuous by broken doses we gave one animal in the series two fractional injections of 14 mg. each, a second 25 mg., and 12·5 mg. each, and a third 25 mg. and 20 mg. each. Arousal occurred immediately after each injection, the second lasting several hours. However, all the animals reverted to the state of narcosis, and were still asleep the next morning. Two animals died in depression the following day, one from the 150 mg. and one from the 200 mg. series. As an added check, one normal rabbit was given 25 mg. of metrazol intravenously. Recovery followed the convulsive seizures. See Table IV.

*Experiments with Coramine.*—Nine rabbits were used in our study on coramine. The dosages of barbital were the same as those administered in the metrazol group. Two animals in the 150 mg. series received 80 mg. of coramine intravenously as a single dose; one

recovered. The three in the 170 mg. series received each 80 mg. subcutaneously; all recovered. The four animals in the 200 series received three fractional doses aggregating 91 mg., 91 mg., 91 mg., and 150 mg. respectively; all recovered. With each single or fractional injection in each group there was an immediate but transitory arousal. As an added check, one rabbit was given 80 mg. of coramine intravenously. Recovery followed the convulsive seizures. See Table V.

Seven animals were used as controls against the animals treated with coramine and metrazol respectively. These animals were given corresponding quantities of the standard doses of barbital alone. See Table VI. There were no fatalities as against two deaths in ten with barbital and metrazol, and one in nine with barbital and coramine.

It was interesting to observe that without a single exception the control animals all recovered from narcosis and were well earlier than every animal treated either with coramine or metrazol. Both coramine and metrazol, either as single sub-lethal doses or as fractional doses were effective in producing a transitory awakening; however, both retarded the time of final awakening and complete recovery, and both caused a few fatalities as against 100 per cent. recoveries with the untreated controls.

## Discussion.

The fact that certain pharmacodynamic agents exert contradictory actions is generally recognised. Claude Bernard [1864] was the first to attribute excitatory as well as soporific properties to morphine, having noted signs of increased irritability in animals subjected to large subcutaneous doses of the alkaloid. Since that time several investigators, notably Tatum, Seevers, and Collins [1929] have convincingly demonstrated this phenomenon. Heubner and Loewe [1913] were among the first to note the stimulant-depressant properties of strychnine. They attributed strychnine paralysis to the action of its constituent depressant principle. Several hypnotics—paraldehyde, chloral hydrate, barbiturates, etc.—under suitable conditions, manifest the contradictory phenomena of narcosis and motor hyperexcitability. Silver [1930] divided this motor excitability into two components (*a*) response to pain, and (*b*) somatic irritability. Using the pernoctonised rabbit, he found that caffeine, coramine, metrazol, and other cortical stimulants acted similar to morphine in abolishing the reflex response to pain, but whereas morphine at the same time abolished somatic excitability the stimulant drugs accentuated it. Tartler [1929], using small doses of medinal (barbital-sodium) on the rat, noted varying degrees of reversal as well as accentuation of its narcotic action with caffeine, hexetone, and coramine.

The results of these experiments confirm us in the view that, in addition to their stimulatory properties, caffeine, coramine, and metrazol

are possessed of subsidiary depressant properties which serve to accentuate an already existing state of depression under certain disturbed physico-chemical conditions. As such they are contraindicated in conditions of profound barbiturate intoxication. These compounds, like strychnine [Barlow, 1932; Maloney, Fitch, and Tatum, 1931], may hasten respiratory paralysis.

A simple case of mild hyposensitivity may respond to any ordinary primary stimulant, but deep depression such as would result from the taking of large doses of a barbiturate with suicidal intent calls for a therapeutic agent possessing unequivocal antidotal potentiality. For such a state we have found picrotoxin the antidote of first choice.

## Summary.

The results of experiments on rats and rabbits narcotised with barbital and treated with caffeine, coramine, or metrazol reveal the fact that these substances are capable of accentuating the depressant action of the barbiturate under certain conditions.

The barbiturate was administered in single sub-lethal doses. The other substances were given in varying quantities, each dosage unit being slightly below or above the lethal level for normal controls.

Sub-lethal doses of caffeine and coramine administered to the barbitalised rat caused transient arousals, with tremors or mild convulsions at certain dosage levels and the same effects, followed by delayed death in depression, at higher levels. The percentage of recoveries from the combined substances was less than that from caffeine and coramine alone.

Lethal doses of metrazol caused permanent arousal without convulsions at lower dosage levels, permanent arousal with convulsions at higher levels, and convulsions followed by death at still higher levels. The barbitalised rat was able to tolerate large lethal doses of metrazol, indicating a high degree of reciprocal antagonism between barbital and metrazol in that species.

A depressant effect was more in evidence than a stimulatory action with caffeine.

The rat manifests a distinct species intolerance to coramine. It is not a suitable animal on which to make generalisations in comparative studies on coramine.

Normally stimulating doses of coramine and metrazol, administered in single or fractional portions to barbitalised rabbits, caused transitory arousal at certain dosage levels, with death in depression in others; but in every instance coramine or metrazol, when combined with barbital, increased the duration of narcosis over that of the controls, and caused some fatalities.

These studies point to possible danger in the use of these substances

indiscriminately in barbiturate depression and emphasise their contra-indication in deep barbiturate depression.

We interpret these phenomena as due to a secondary depressant action of caffeine, coramine, and metrazol elicited at certain levels of depression initiated by the barbiturates.

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