Experimental inquiry into the physiological actions of theine, caffeine, guaranine, cocaine, and theobromine / by Alexander Bennett, M.D.

EXPERIMENTAL INQUIRY

INTO THE

PHYSIOLOGICAL ACTIONS

OF

THEINE, CAFFEINE, GUARANINE, COCAINE, AND THEOBROMINE.

BY

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Diagrams showing the Effects of Theine on the Respiration, Pulsation of the Heart, and Temperature.

Diagram I.

Showing the Effects of Theine upon the Respiration, as ascertained in a Rabbit.

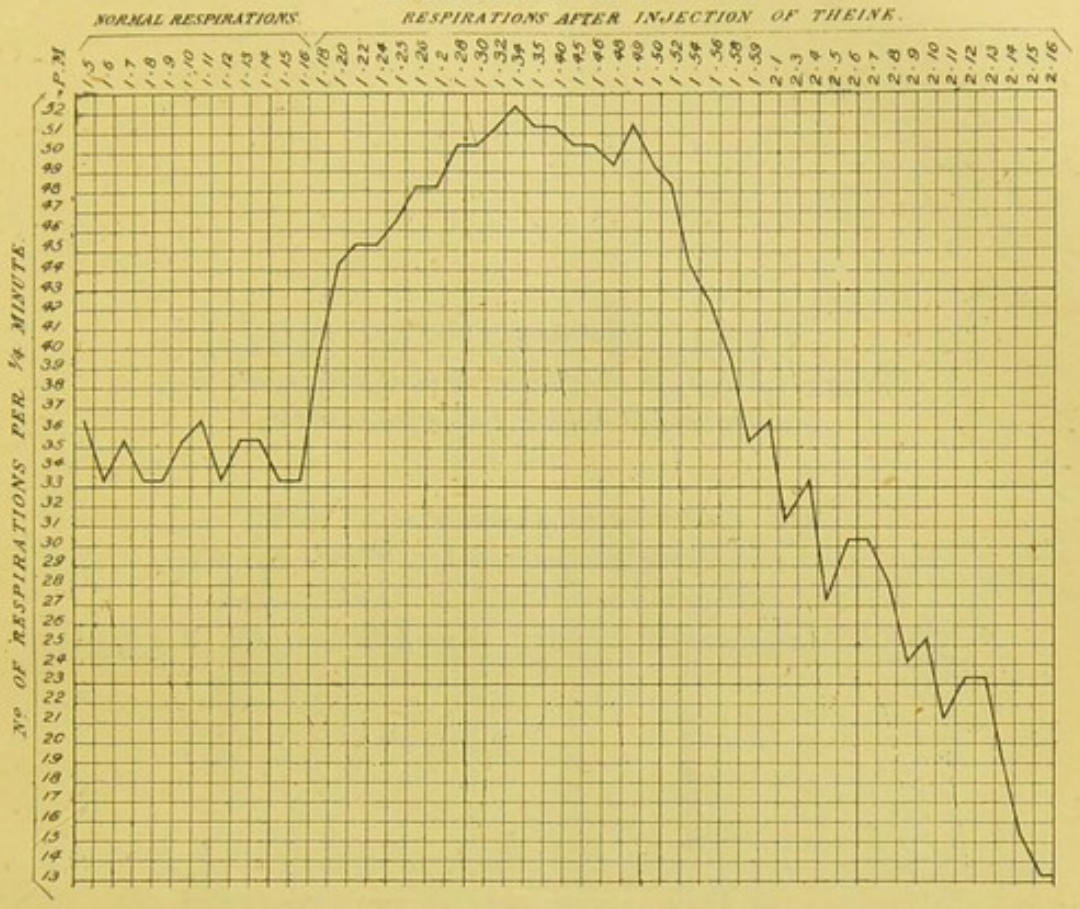


Diagram II.

Showing the Effects of Theine upon the Pulsations of the Heart, as ascertained in a Rabbit.

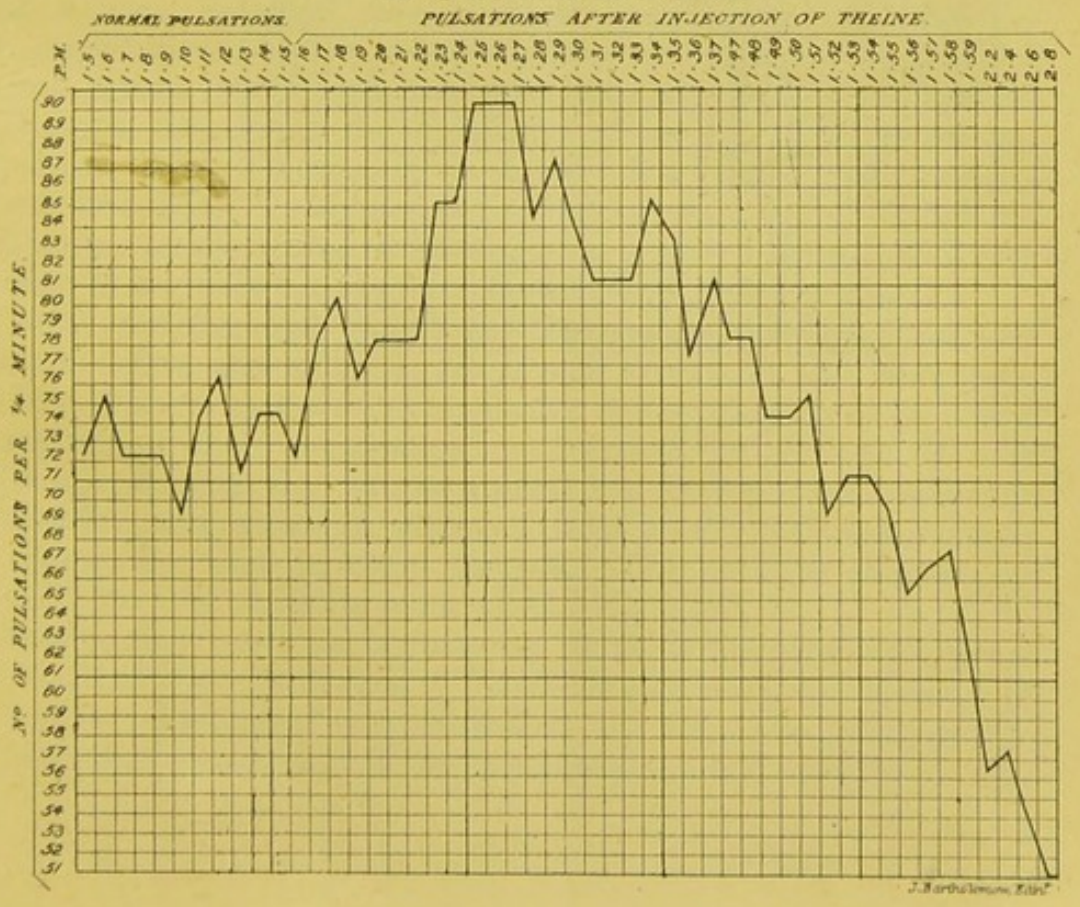
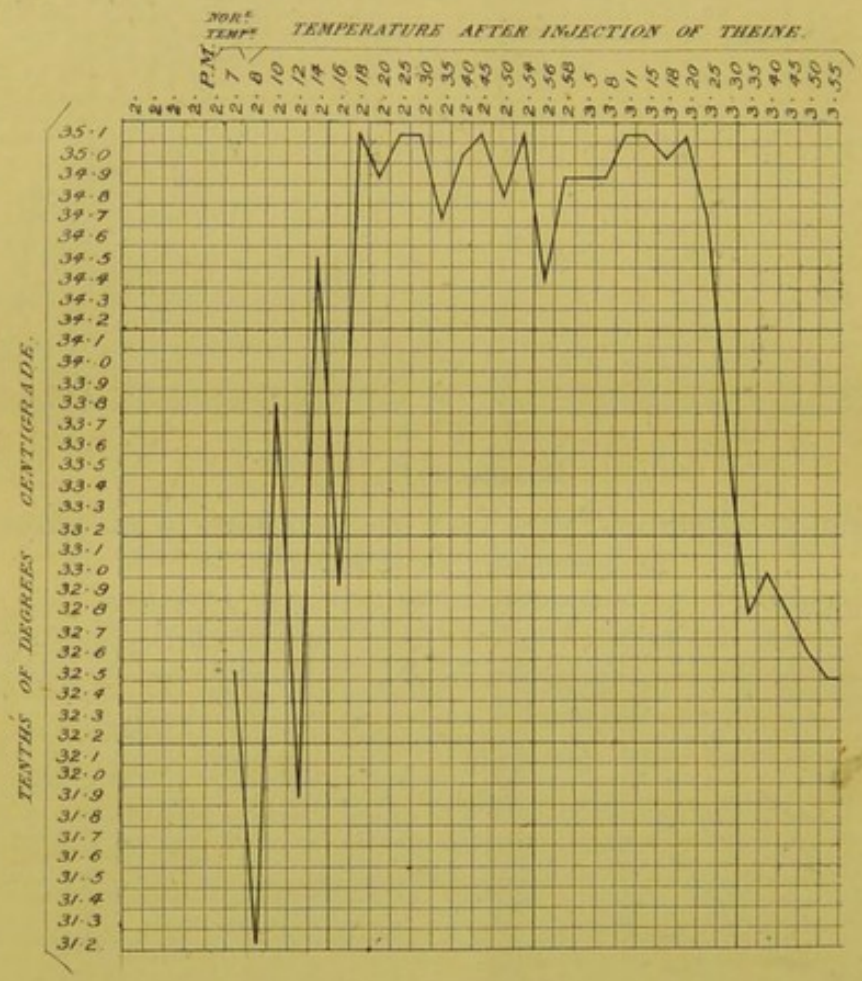


Diagram III.

Showing the Effects of Theine upon the Temperature, as ascertained in the Ear of a Rabbit.



EXPERIMENTAL INQUIRY

INTO THE

PHYSIOLOGICAL ACTIONS OF THEINE, CAFFEINE, GUARANINE, COCAINE, AND THEOBROMINE.

THE following inquiry was conducted in the Physiological Laboratory of the University of Edinburgh, and I have gratefully to acknowledge much kind assistance from Dr M'Kendrick.

Upwards of one hundred experiments were conducted on different living animals, chiefly frogs, mice, rabbits, and cats; and from these I have obtained results which seem to me of considerable importance. In the present paper, as brevity is desirable, I propose, after a few introductory remarks,—1*st*, To give my general conclusions concerning the physiological actions of these neutral principles; 2*dly*, To describe in detail a few characteristic experiments; and, 3*dly*, To append a diagram showing the effects on the circulation, temperature, and respiration; also a series of tables showing at a glance the result of seventy-two experiments.

Theine, *caffeine*, and *guaranine*, the neutral principles derived from tea, coffee, and guarana, are so well known in the laboratory and in commerce that I do not consider it necessary to enter into a description of their preparation or chemical properties. It will suffice to state, that they are now proved to have the same ultimate composition, and, although procured from totally different sources, are chemically alike in every respect. The notation adopted by the most eminent chemists is for all $C_{16}\ H_{10}\ N_4\ O_4$.

Cocaine, discovered by Neimann in 1859, is the proximate principle derived from the leaves of Erythroxylon coca, the narcotic of the Andes. This plant is employed in the form of a beverage by the natives of Bolivia and Peru as a stimulant and antitriptic. In

this country the coca leaves are rare, and even in Paris where they can be obtained they are very expensive. Having, however, procured a supply from the last-named city, I placed it in the hands of Messrs Macfarlan and Co., of this town, who, after overcoming considerable difficulties, have with great care succeeded in obtaining a few grains of cocaine. When we compare this cocaine with theine, caffeine, and guaranine, we find that, if it is not identical, it is intimately related to them in chemical composition, its notation being represented by C_{16} H_{19} N O_4 (Neimann).

Theobromine is the neutral principle of Theobroma cocao, from which the well-known beverage chocolate is obtained. The result of its analysis is C_7 H_8 N_4 O_2.

These five substances, although derived from totally different sources, closely resemble one another in chemical composition; it is therefore a question of the greatest interest to ascertain whether or not they also produce similar physiological effects. This would be all the more important to establish, as all these bases are the proximate principles derived from the beverages of different nations. It has hitherto been supposed and stated by many authors, that theine and caffeine are inert substances, and that the physiological effects of tea and coffee are not due to these neutral principles, at all events in a state of isolation. For example, Schleiden says in his lectures, that "the experiments hitherto instituted by physicians and chemists have as yet furnished no evidence of special actions resulting from the administration of large quantities of pure theine; the substance therefore appears devoid of any striking action on the animal economy."[1]

In recent times, the therapeutical action of some of these substances has attracted the attention of the profession, and guaranine more especially has been employed by physicians as a stimulant and tonic, and in the treatment of sick headache, with, it is said, good results. But I am not aware that until now any series of observations have been instituted to demonstrate the exact physiological actions of these drugs, either upon man or the lower animals.[2]

From the experiments conducted by myself I have arrived at the following conclusions:—

1. The physiological actions of tea, coffee, guarana, coca, and cocoa are mainly, if not entirely, due to their proximate principles.

2. Theine, caffeine, guaranine, cocaine, and theobromine are powerful poisons, inducing a series of symptoms affecting the nervous, respiratory, circulatory, vaso-motor, and glandular systems, which terminate, if the dose be large enough, in death.

[1] The Plant. M. J. Schleiden, M.D., translated by A. Henfrey. London, 1848, page 144.

[2] I am aware that recently Drs Cogswell, Prichard Davies, and others, have administered theine to animals. Their experiments, however, are too few in number, and their conclusions, therefore, too imperfect, to warrant us accepting them as anything like a complete investigation of the subject.

3. These five principles are to all appearances identical in physiological action.

Note.—It is to be noted, that owing to the extreme scarcity of cocaine, and the very small quantity obtainable, the observations with this substance were confined almost entirely to frogs and mice, and only in one instance was it administered to a rabbit; accordingly the experiments were not so extensive as in the case of theine, caffeine, and guaranine. For this reason also, the phenomena connected with the temperature and the glandular secretions were not so completely demonstrated. In every other respect, cocaine had similar actions. The same may be said of theobromine, of which I was unable to obtain a large quantity.

4. In small doses, not ending fatally, these five substances produce, 1*st*, cerebral excitement, not succeeded by coma; and, 2*d*, partial loss of sensibility.

5. In large doses they produce, 1*st*, cerebral excitement; 2*d*, complete paralysis of sensibility; 3*d*, tetanic spasms and convulsions; and, 4*th*, death.

6. They paralyze the entire posterior columns of the spinal cord, also the entire system of peripheral sensory nerves; but the anterior columns of the cord and the peripheral motor nerves are not paralyzed.

7. They frequently produce convulsions of a clonic character, but occasionally they cause tetanic spasms, which latter are sometimes so severe as to cause opisthotonos. There is at first sight a resemblance between these spasms and those following the administration of strychnia. But in the case of strychnia, the action of the poison is limited to the spinal cord, the reflex function of which is so much excited that the slightest touch causes powerful spasms. A poisonous dose of theine, caffeine, etc., on the other hand, paralyzes the sensory nerves so that external irritations do not affect the cord; but, notwithstanding, there are strong spasms which are probably caused by a stimulant action of the drug on the anterior columns, and which spasms are not to be considered as reflex in their nature.

8. They do not produce muscular paralysis.

9. They at first increase, then impede, and lastly stop the respirations. (See Diagram I.)

10. They at first increase, and finally diminish, both the force and frequency of the heart's contractions. (See Diagram II.)

11. They produce at first contraction, and afterwards dilatation, of the capillaries and small bloodvessels, with stasis of the blood, indicating first irritation and subsequently paralysis of the vasomotor nerves.

12. They affect the temperature by, 1*st*, slightly lowering; and, 2*d*, increasing it. (See Diagram III.)

13. They usually produce contraction of the pupil.

14. They produce an increase of the salivary secretion.

15. They induce a peculiar form of tenesmus, accompanied by a copious discharge of clear mucus from the bowels.

The above are the conclusions I have arrived at, from a large series of carefully-conducted observations. In this paper it would be impossible for me to describe in detail an account of all of these, but appended will be found in tabular form seventy-two experiments, showing a characteristic specimen of the effects produced by each of the different doses, with the results of post-mortem examinations, etc. I shall content myself at present by giving in detail, as an illustration, a sample of some of the leading experiments, with the reasoning thereupon. As it has been already stated that theine, caffeine, guaranine, cocaine, and theobromine are to all appearances similar in physiological action, in the following cases I shall take theine as an example of the whole.

EXPERIMENT I.—$\frac{1}{16}$ *gr. Theine. Frog. Recovery.*

The $\frac{1}{16}$ gr. of theine, dissolved in 20 minims of water, was injected under the skin over the back of a healthy middle-sized frog. Almost immediately afterwards the respirations, which normally had been 80, were increased to 120 per minute. Seven minutes afterwards the respirations had diminished to 80 per minute. The frog was now distinctly sluggish in its movements. It made attempts to leap, but did so feebly. When placed on its back it recovered its normal position with difficulty. When its toe was pinched with a pair of forceps it drew up its leg. If its limbs were pulled out they were drawn up slowly. Two minutes after, these symptoms were increased, and in three minutes more the limbs were very weak, and the animal lay on its belly without their support. When placed on its back the frog was unable to recover its position, but lay there with its limbs drawn up; and when the skin or toes were pinched the limbs were moved, but sluggishly. The respirations had diminished to 40 per minute. Five minutes later the frog still lay motionless on its back with its limbs extended. All four legs were completely paralyzed, and they remained in whatever position they were placed. When any portion of the skin was pinched the animal made no movements. On touching the eyeball the eyelids did not close. The respirations had diminished to 26 per minute, and they were very irregular, some being deep and others superficial. There was marked congestion of the under cutaneous surface, which was of a reddish-purple colour. The mucous membrane of the mouth and tongue was also deeply congested. When the web of the foot was examined under the microscope (25 diam.), the capillaries and small bloodvessels were found enlarged and engorged with blood, and there was in them complete stasis of the circulation. The heart was beating, but respiration had stopped. The frog remained in this prostrate condition for eleven minutes, when slight spasmodic movements were observed in the limbs. Four minutes

later, it made feeble attempts to move its legs, and when its toe was pinched, it drew them up. Four minutes afterwards, the animal gave a very feeble leap, and tried to crawl along the table. It sat on all-fours, and when any portion of its skin was pinched it made attempts to move. The respirations, although still irregular, had risen to 20 per minute. Eighteen minutes afterwards, the frog jumped readily, especially if it was irritated. It croaked vigorously when touched, and in half an hour it was apparently in its natural state, with the exception of looking feeble. Next morning it was found in its normal condition.

Commentary on Experiment I.—In this experiment we find that shortly after the administration of the theine, the frog gradually lost motor power and all evidences of reflex action, the animal being reduced to a state of complete prostration. The number of the respirations was first increased and subsequently diminished, congestion of the cutaneous and mucous surfaces was produced, with enlargement of the small vessels, and engorgement of blood in the capillaries, with stasis of blood in their interior. From all these effects, the frog recovered gradually, after remaining under the influence of the drug for more than an hour.

This dose of theine may be considered as the largest that may be given to a frog without proving fatal, and the above description may be taken as the characteristic phenomena occurring in that animal after the administration of the poison. If smaller doses be given, similar symptoms ensue, but they are less violent and less rapid, in proportion to the amount.

It is now to be determined what portion of the nervous system is affected by theine, to account for the loss of motor power and reflex action:—

EXPERIMENT II.—$\frac{1}{12}$ *gr. Theine. Frog. Death. Post-mortem.*

The $\frac{1}{12}$ gr. of theine, dissolved in 30 minims of water, was injected under the skin over the back of a healthy middle-sized frog. A series of symptoms ensued, almost exactly similar to those in the preceding experiment, only somewhat more rapidly, and ultimately causing the death of the animal. On post-mortem examination, the limbs and body generally were flaccid. The skin, especially on its under surface, was congested, of a reddish-purple colour. On pinching with a pair of forceps any portion of the integument, no contractions of the muscles followed; but on the application of the electrodes of a Faradic current, there were strong muscular contractions. A flap of the skin was reflected about one inch square from the back, and when the electrodes were applied to the extremity of it, there were no movements; but when applied to the skin near the muscles, these contracted feebly. When one of the limbs was removed from the rest of the body, and a reflected portion of the skin was treated in a similar manner, the same phenomena ensued.

The head was amputated, and on thrusting the point of a needle

into the brain, the muscles of the face and eye contracted. The exposed part of the spinal cord was also irritated with the electrodes of a weak Faradic current, and strong muscular contractions of the body and limbs ensued. The cervical portion of the spinal cord, about a quarter of an inch in length, was then isolated by carefully removing with a pair of scissors the bodies of the vertebræ. On applying the electrodes of the weak current to the anterior columns of the cord, there were powerful contractions of the lower limbs; on irritating the posterior columns in a similar manner, these contractions were very feeble. On dissecting out the sciatic nerves, and pinching them with a pair of forceps, or applying the electrodes to the lower portions of them, strong contractions of the posterior limbs ensued; when to the upper portion, there were powerful contractions of the upper part of the body. On applying the electrodes to the gastrocnemius and other muscles, they contracted strongly. On opening the cavities of the thorax and abdomen, the heart was found beating feebly, at the rate of 64 per minute. All the internal viscera, especially the liver and bowels, with the mesentery, were deeply congested, and their vessels engorged with blood.

Commentary on Experiment II.—We find in this experiment not only enlargement of the small bloodvessels and capillaries, with engorgement and stasis of blood during life, as proved by inspection of the web of the foot under the microscope, but that, after death from a fatal dose of theine, there was a similar condition of the skin and internal viscera, showing that the drug paralyzes the capillary system, probably by its action on the vaso-motor system. This effect will subsequently be proved by experiments on mammals. It is also shown that the motor filaments of the brain and upper part of the spinal cord, the anterior columns of the cord, the motor nerves, and the muscles, were apparently in a normal condition; but that the posterior columns of the cord were partially paralyzed. To ascertain if the peripheral sensory nerves of the skin were also affected, a large flap of the integument was reflected. On applying the electrodes of a Faradic current to its extremity, no muscular contractions ensued, proving that the sensory nerves of that portion had been paralyzed. If the electrodes were placed on the reflected skin, close to the muscles, they contracted feebly; probably, however, owing to direct action of the electricity on the motor nerves of the muscles, which was proved not to be reflex by the same phenomena occurring when a limb was removed from the body. Whether the sensory nerves of the muscles also are affected or not, will be shown in a succeeding experiment.

EXPERIMENT III.—$\frac{1}{12}$ *gr. Theine. Mouse. Death. Post-mortem.*

The $\frac{1}{12}$ gr. of theine, dissolved in 10 minims of water, was injected under the skin over the back of a white mouse weighing 3 drs. For fifteen minutes no effects were observed. When its tail was pinched, it uttered a cry, which it did before the drug was ad-

ministered. At the end of this time it became sluggish in its movements, being weakened in all four limbs, but especially in the posterior ones. It could only crawl along the table, but could not run. Five minutes later, when placed on its back, the animal lay there with limbs occasionally kicking; and it turned over on its belly with great difficulty. On pinching its tail it did not cry, but struggled and attempted to get out of the way. Five minutes after, the mouse lay helpless on its side. The under surface of the body, the feet, legs, and mouth, were much congested and very red, the ears not markedly so. When the foot was pinched, the animal pulled away its leg. Five minutes later, when placed on its back, it lay there with limbs occasionally moving, and scratching itself with its toes. When its tail or skin was pinched, the animal made very slight efforts to move. When its toe was pinched, it drew its leg out of the way. It did not seem to feel a pinch of the ear. When the eyeball was touched, the eyelid did not close. When its face was touched, the muscles did not move. Congestion of the skin was still considerable. Twenty minutes afterwards, the animal had gradually become prostrate. When any portion of the body was pinched except the toe, there were no signs given of sensation. When the toe was pinched, there were slight muscular contractions of the limb. Congestion of the cutaneous surface had nearly disappeared, and the animal lay helpless and immovable. Respiration had stopped, and ten minutes later the mouse was dead.

Immediately after death, an examination of the body was made. The heart was still beating feebly; the integument, the thoracic and abdominal viscera, were all deeply congested, and their bloodvessels engorged with blood. On amputating the head and irritating the upper portion of the spinal cord with the point of a needle, there were feeble contractions of the muscles of the body generally, which were much increased on applying to the same place the electrodes of a weak Faradic current. On thrusting the needle into the brain, the muscles of the face contracted powerfully. About a quarter of an inch of the cord was carefully dissected out by removing with a pair of scissors the bodies of the vertebræ. On applying the electrodes very gently to the posterior columns, there were slight contractions of the muscles of the lower limbs. On touching the anterior columns, there were strong contractions. On exposing the sciatic nerves, and pinching, or applying the electrodes to them, the limbs were powerfully contracted. On irritating the muscles, they contracted strongly under electrical stimulus. The membranes of the brain were found much congested, but its substance appeared healthy. The spinal cord was not congested, and seemed in its normal condition.

Commentary on Experiment III.—In this experiment, it is seen that the effects of theine on a mammal are similar to those produced on a frog. The mouse lost its motor power. When irritated or pinched, it seemed to have lost its sensibility. Respiration was

stopped, and complete prostration and death ensued. There was great congestion of the skin and internal organs, pointing to the influence the drug has upon the vaso-motor system. There was congestion of the membranes of the brain, which explains the cerebral excitement which is occasionally, although not in this instance, met with after the administration of theine. As in the preceding experiment, the motor filaments of the brain, cord, nerves, and muscles were intact, while the sensory filaments of at least the spinal cord were paralyzed. The slight movements produced by irritating the posterior columns were probably due to transmitted electricity, owing to the small size of the cord of a mouse. This was afterwards proved to be the case by experiments on larger animals. All these facts prove that the loss of motor power of the animal during life was not due to paralysis, either of the motor columns of the spinal cord, the motor nerves, or the muscles. They show, however, that there is at least paralysis of the sensory columns of the cord, and whether the peripheral sensory nerves are affected or not, will be shown in a following experiment. Death probably resulted from paralysis of the nerves connected with the respiratory processes. In this experiment, the mouse died quietly, without convulsions; but in many instances the animal has tetanic spasms and opisthotonos immediately preceding death, having symptoms somewhat allied to those produced by strychnia. Theine differs from strychnia in this respect:—In the latter there is increased reflex action of the cord, so that the slightest touch induces a tetanic spasm. In the former, there is no such excitability, as the posterior columns being paralyzed, and the animal not feeling any irritation, no spasm is induced, but convulsions occur without a stimulant.

EXPERIMENT IV.—$\frac{1}{12}$ *gr. Theine. Frog. Ligature of Femoral Artery. Death. P.M.*

The left femoral artery of a healthy middle-sized frog was tied, and $\frac{1}{12}$ gr. of theine, dissolved in 35 minims of water, was injected under the skin over the back. In ten minutes the animal was almost prostrate. It lay on its back, but was still able to contract its limbs when they were pinched, which both did with equal strength, the left leg perhaps being somewhat more sluggish than the right. Fifteen minutes later the frog was apparently dead. The head was amputated. On irritating the upper portion of the cord with the electrodes of a weak Faradic current, the two limbs contracted powerfully, and apparently with equal strength. When the sciatic nerves were dissected out and irritated or pinched, similar muscular contractions took place in both legs. The other symptoms and post-mortem phenomena were similar to those described in Experiment II.

Commentary on Experiment IV.—This experiment supports former observations in proving that the peripheral motor nerves are unaffected by theine. In tying the artery of the limb, the poisoned blood is prevented from circulating through it; consequently, while

the rest of the body is affected, it remains in comparatively a healthy condition. After the introduction of the drug, the animal gradually became prostrate; but at no stage of the symptoms was there any special or marked difference between the two legs. (It may be mentioned, that cutting off the supply of blood to the limb produced slight weakness of that leg.) On irritating the spinal cord or the sciatic nerves, no difference was observed in the contractile powers of either of the posterior extremities. This proves that the peripheral motor nerves are not paralyzed; otherwise, the leg which had been poisoned would on irritation have been more sluggish in its movements than the limb from which the theine had been excluded by the ligature of the artery. In reality, the latter leg was the feebler of the two. This experiment shows nothing with regard to the sensory peripheral nerves, as, the posterior columns of the cord being affected, reflex action is destroyed.

EXPERIMENT V.—$\frac{1}{12}$ *gr. Theine. Frog. Ligature of the Heart.*

The heart of a healthy middle-sized frog was exposed by carefully dividing the sternum with a pair of scissors, and a ligature passed round its base, and tied so as to interrupt the circulation. The $\frac{1}{12}$th grain of theine, dissolved in 10 minims of water, was then injected under the skin of the calf of the right leg. In four minutes both of the posterior extremities were partially paralyzed. On pinching the skin over the right calf with a pair of forceps, no muscular contractions of any kind followed. On pinching the skin over the left calf there were contractions of all the muscles of the body, including the right leg. On pinching any other portion of the skin, except the right leg below the knee, the animal struggled. A $\frac{1}{12}$th grain theine, in 10 minims of water, was then injected under the skin of the calf of the left leg. Three minutes afterwards, when the toe of this limb was pinched, the muscles did not contract; but on pinching either of the anterior extremities, all four legs contracted.

Commentary on Experiment V.—In the former experiments it has been pointed out that theine paralyzes the posterior or sensory columns of the cord, but that it does not affect the motor filaments of the brain or cord, the motor nerves, or the muscles. The object of this experiment was to determine the local effect of theine upon the peripheral sensory nerves. The heart was tied so as to prevent any circulation of blood in the body. The operation produced partial paralysis of the limbs, probably owing to the want of proper blood supply. When the drug was injected into the calf of the right leg, subsequent irritation of the foot did not induce muscular contraction of that limb, but on irritating the toe of the left leg, there were distinct contractions of all the limbs, including the poisoned one, showing that reflex action was unimpaired, and that the motor nerves of the poisoned leg were unaffected.

This supports the preceding experiment in proving that the nerves

of the motor system are not paralyzed by theine, otherwise a pinch of the left leg (unpoisoned) would not have produced contraction of the right (poisoned). It also proves that the peripheral sensory nerves are paralyzed, as, in this instance, the cord not being under the influence of the drug, the loss of motion of the right leg was due to the local effect on the sensory nerves. This was further shown by injecting theine into the left or hitherto unpoisoned limb. A few minutes afterwards, when it was pinched, the previous muscular contractions were found to have disappeared. The sensory peripheral nerves had been paralyzed. When either of the anterior extremities were pinched, the muscles of the entire body, including both poisoned legs, contracted, showing that, although the sensory nerves of both limbs were paralyzed, the motor nerves were intact. Thus, theine paralyzes the posterior columns of the cord and the peripheral sensory nerves, but it does not affect the anterior columns or motor nerves.

EXPERIMENT V.—6 *grains Theine. Rabbit. Death. Post-mortem.*

Six grains of theine, dissolved in 2 drachms of water, were injected under the skin over the back of a healthy white rabbit, weighing 2 lbs. 3 oz. Almost immediately afterwards the ears were observed to become paler than before, then suddenly they appeared of a bright red colour, all the vessels being enlarged and congested. After remaining in this condition for half a minute, they again became pale and anæmic. These sudden changes from extreme pallor to intense congestion alternated for about five minutes, each stage being about a quarter of a minute in length, after which time the ears became permanently red, hot, and congested. The animal then became restless and somewhat excited, but not hyperæsthetic, and it trembled slightly. When its toe or ear was pinched, it struggled. The force of the heart's pulsations was stronger, and the rapidity of the beats, as well as the respiratory acts, quicker than before. Pupils were unaffected. Three minutes later, the hind legs straggled slightly, and they seemed to have lost power. Two minutes after, all four extremities were considerably weaker, and the rabbit was unable to stand upright, but lay flat on its belly, with all its limbs stretched out on the table. When its toe was pinched it did not struggle so much as formerly, still it pulled away its leg and attempted to crawl along, which it did in a shaky and laboured manner. The breathing was laboured and slow, the heart's pulsations were feeble, and the animal trembled. The ears were still intensely hot to the touch, and congested. Eight minutes later the animal could not make the slightest effort to stand, or move its body by means of its legs. All excitement had disappeared, and it lay quiet on its side. On pinching its toe very hard, it did not give any evidence of feeling pain, and did not move. The ears were still congested and hot, and the pupils were somewhat contracted. For twenty minutes the animal lay in this prostrate condition,

breathing in a laboured manner, when it suddenly took a tetanic spasm, with slight opisthotonos, which lasted for about a quarter of a minute. The congestion of the ears had now almost entirely disappeared. For the next seven minutes the animal took tetanic spasms at intervals, occurring spontaneously, and not brought on by pinching or other external irritations. Evidence of sensibility had disappeared from all parts of the body except the head, where it seemed to be normal. The eyelids winked when the eyeballs were touched, and even when the hands were clapped before them. When any portion of the face was touched, its muscles contracted. The animal, although completely paralyzed in its limbs, looked intelligent, as if sensation was unaffected. Ten minutes later the pupils were considerably contracted, the breathing slow and irregular, and the heart-beats not palpable. It died after a tetanic spasm.

An examination of the body was made as soon after death as possible. On applying the electrodes of a weak Faradic current to the exposed spinal cord, the muscles of the lower limbs contracted. On removing with a pair of scissors the bodies of the vertebræ, and isolating about half an inch of the cord, in the dorsal region it was observed that, although muscular contractions followed irritation of both the anterior and posterior columns, these were much more marked in the case of the former. On thrusting a needle into the brain, the muscles of the face and eye contracted. The sciatic nerves and muscles were found apparently in normal condition. The membranes of the brain were much congested, but its substance appeared healthy, as was also the spinal cord. All the internal viscera were deeply congested, their vessels being engorged with blood.

Commentary on Experiment V.—In this experiment, the loss of motor power and other symptoms, already described in the mouse, ensued. The early stage was indicated by cerebral excitement, irritation, and restlessness of the animal, which subsequently disappeared, and was followed by depression and insensibility to irritation. It is to be observed, however, that the animal never seemed to lose its intelligence. It was watchful, followed every motion of the experimenter, although it was unable to make any movement. From the effects observed in the bloodvessels of the ear, it is evident that theine affects the vaso-motor nerves, first by irritating and afterwards by paralyzing them, as evidenced by the change in the action of the heart and the frequency of its beats, also in the tonicity of the smaller vessels by first contracting and lastly by relaxing them. This same action also explains the increase and subsequent diminution of the respirations which ultimately caused the death of the animal.

EXPERIMENT VI.—6 *grs. Theine. Cat. Death. Post-mortem.*

Six grains of theine, dissolved in 1½ drs. of water, were injected under the skin over the back of a healthy cat, weighing 4 lbs. 1 oz. In ten minutes, the animal became very angry and irritable.

Fifteen minutes later, this excitement had increased, the animal had a watchful anxious appearance, prowled about, and when touched with a stick, bit at it and growled. If any noise or motion was made, it put up its back and made a hissing noise. The legs appeared weakened, and although it could still walk about, it preferred sitting in a corner of the room. Its mouth and tongue were very red, and there was an abundant secretion of saliva, which constantly trickled out of its mouth. The cat defæcated and micturated several times. Forty minutes later, it continued in much the same condition. Salivation was profuse. Animal suffered from tenesmus, and it had a constant straining from the bowel of a clear fluid, like mucus. The limbs, especially the posterior ones, were much weakened, but the animal could still run with difficulty. It could not jump; it made attempts to do so over a bench about two feet high, but failed. The breathing was laboured and irregular. The redness of the tongue and mouth, as well as the excessive irritability of the animal, had disappeared. It was quiet, lay in a corner, stupid and drowsy. It drank freely of water. Twenty minutes later, it was prostrate and lay on its side, its limbs quite helpless. It paid no attention to a pinch of the toe or a blow on the tail with a stick. It seemed, however, to be intelligent, as its eyes watched every movement of the observer, and when the hands were clapped before its face it growled. The salivation and discharge from the bowel were excessive. Pupils were contracted, and the breathing was laboured. Five minutes later, the cat took a series of tetanic spasms, and shortly afterwards died.

The post-mortem examination and phenonema were similar to those in the preceding experiment.

Commentary on Experiment VI.—In the cat the general nervous symptoms are much the same as in the rabbit, with this exception, that the cerebral excitment and subsequent depression are much more marked. There was no evidence of hyperæsthesia, but rather a gradual loss of sensibility. In addition, there was excessive increase of the salivary secretion, and straining from the bowels of a profuse mucous discharge. The cat died after a severe tetanic spasm.

EXPERIMENT VII.—12 *grs. Theine. Rabbit. Spinal Cord exposed during life.*

A healthy white rabbit, weighing 2 lbs. 2 oz., was carefully fastened down on its belly. An incision was made through the skin along the upper part of the spine, about two inches in length, and the vertebral column exposed. By means of bone-forceps and scissors, portions of the vertebræ were removed so as to expose a piece of the spinal cord about a quarter of an inch in length. On touching the posterior columns with the point of a blunt needle, the animal struggled violently and uttered loud cries. Twelve grains of theine, dissolved in two drachms of water, were then injected under the skin of the belly. In ten minutes, the symptoms already described in preceding experiments commenced—congestion of the

ears, etc. On pinching the toe, the animal did not appear to feel it. On touching with the point of a blunt needle the posterior columns of the cord, the animal struggled, but not nearly so violently as before, and it did not cry out. When the anterior columns were touched, there were violent convulsions of the body. Five minutes later the animal was completely paralyzed in all its limbs, and presented all the usual symptoms of prostration. A fresh portion of the cord was exposed by cutting away some of the vertebræ below the original wound. On touching as before the posterior columns, the rabbit only quivered slightly. On touching the anterior columns, marked muscular contractions of the limbs followed. The animal was shortly afterwards killed, and similar phenonema were observed after death as have been already described.

Commentary on Experiment VII.—The object of this experiment was to confirm, during life, what had already been concluded from post-mortem examinations, viz., that theine paralyzes the posterior columns of the spinal cord, while the anterior columns remain apparently unaffected.

These, and other experiments, have frequently been repeated, with various modifications and with different doses of the drug, so as to secure accuracy. Special observations were made to determine the effects of theine, caffeine, etc., upon the heart's action, the respirations, and the temperature, 1*st*, by observing and noting the normal condition; and, 2*dly*, by poisoning the animal, and ascertaining any changes in these functions which ensued. As a result of the whole inquiry, the conclusions already given at a former part of this paper have been arrived at.

I have only to add, that these actions of theine, caffeine, guaranine, cocaine, and theobromine are important as well as instructive. It is extremely interesting to learn, that those agents which the different nations of the world have found by experience to produce refreshing and stimulating beverages, although unlike one another, and procured from totally different sources, possess in common, proximate principles, which not only are almost identical in chemical composition, but also appear similar in physiological action.

That the effects of the beverages themselves are mainly if not entirely due to the neutral principles they contain, is highly probable, and there is every reason to believe that these concentrated forms of the different drugs will prove powerful and useful agents in the hands of the physician for the treatment of disease. The research, however, is yet in its infancy; and this contribution, I trust, may be looked upon as a stepping-stone to further inquiry. I venture to hope that my conclusions will not be found deficient in interest and importance to those who desire to establish a sound system of therapeutics upon careful physiological experiment.

Tables showing the Result of Seventy-two Experiments with Theine, Caffeine, Guaranine, and Cocaine.

TABLE I.—*Experiments with Theine.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post-mortem Examination.
1.	Frog	$\frac{1}{120}$	Slight weakness of posterior extremities.	Recovery	
2.	Frog	$\frac{1}{64}$	Weakness of posterior extremities.	Recovery	
3.	Frog	$\frac{1}{32}$	Paralysis of limbs; loss of reflex action; respiration impeded.	Recovery	
4.	Frog	$\frac{1}{16}$	Complete paralysis of limbs; loss of reflex action; respiration impeded; cutaneous congestion.	Recovery	
5.	Frog	$\frac{1}{12}$	Gradual prostration; paralysis of all the muscles; loss of reflex action; respiration stopped; congestion of cutaneous surface, mucous membrane of mouth, and tongue.	Recovery	
6.	Frog	$\frac{1}{12}$	Femoral artery tied; same effect as in No. 5; no difference between two legs.	Recovery	
7.	Frog	$\frac{1}{12}$	Complete prostration; loss of reflex action; stoppage of respiration; cutaneous congestion; stasis of blood in capillaries.	Death	Heart still beats; congestion of viscera; muscles contract when electricity is applied; when spinal cord, nerves, or brain are irritated, muscular contractions occur.
8.	Frog	$\frac{1}{10}$	Complete prostration; loss of reflex action; stoppage of respiration; congestion of cutaneous surface.	Recovery	
9.	Frog	$\frac{1}{10}$	The same as No. 8.	Death	Same as No. 7. Spinal cord exposed; anterior column irritated, contraction of muscles ensue; posterior column irritated, no contractions.
10.	Frog	$\frac{1}{8}$	Same as No. 8, but more rapid.	Death	Same as No. 7.
11.	Frog	$\frac{1}{8}$	Femoral artery tied; symptoms same as No. 8, but tetanic spasms in addition; no difference between two legs.	Death	Same as No. 7. No difference between two legs when electricity is applied.
12.	Frog	$\frac{1}{4}$	Rapid prostration, with tetanic symptoms.	Death	Same as No. 7.
13.	Frog	$\frac{1}{3}$	Upper part of spinal cord exposed during life; rapid prostration; after death, on touching anterior columns of cord, contraction of all the muscles; on touching posterior columns, no contractions; before death, muscular contractions followed irritation of the posterior columns.	Death	Same as No. 7.
14.	Frog	$\frac{1}{3}$	Lower portion of cord exposed during life; same as No. 13.	Death	Same as No. 7.
15.	Frog	$\frac{1}{2}$	Very rapid prostration and loss of reflex action, with usual effects.	Death	Same as No. 7.
16.	Frog	1	Almost instantaneous prostration.	Death	Same as No. 7.
17.	Rabbit	1+1	No effects from first grain. Slight weakness of posterior extremities from second grain.	Recovery	

TABLE I.—*Experiments with Theine—continued.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post-mortem Examination.
18.	Rabbit	1	Femoral artery tied; contraction of pupil very slight; no other effect; leg of animal was paralyzed by operation.	Recovery	
19.	Rabbit	2+2 +2+2	From first and second dose, no effects. From third dose, ears hot and congested; no other effect. From fourth dose, animal paralyzed and prostrate; tetanic spasms; contraction of pupil.	Death	Membranes of brain congested; substance of brain and spinal cord healthy; internal viscera congested; muscles contract when electrodes of Faradic current are applied; when applied to nerves or spinal cord, muscular contractions ensued.
20.	Cat	4+4	From first dose, great irritation and cerebral excitement; depression afterwards. After second dose, excessive salivation; partial paralysis of posterior limbs; tetanic spasms; tongue and mouth congested; mucous discharge from bowel.	Death	Nerves found sensitive to pinching. The same as No. 19.
21.	Rabbit	6	Observations on respiration—number, 1st increased, and 2d diminished. Complete paralysis of all four limbs; laboured breathing; loss of reflex action; congestion and heat of ears; pupils contracted; tetanic convulsions.	Death	Same as No. 19.
22.	Rabbit	6	Observations on heart's pulsation—number, 1st increased, and 2d diminished; otherwise same as No. 21.	Death	Same as No. 19.
23.	Cat	6	Irritable at first; staggering gait; excessive salivation; discharge of mucus from bowel; subsequent depression.	Recovery	
24.	Cat	6+3	From first dose irritation and cerebral excitement; embarassed respiration; subsequent depression; profuse salivation; staggering gait; animal stupid and drowsy. From second dose, mucous discharge from bowel; mouth and tongue congested; vomiting.	Death	Same as No. 19.
25.	Rabbit	8	Ears congested; staggering gait; pupils contracted; laboured breathing.	Recovery	
26.	Rabbit	8	Ears congested; pupils contracted; paralysis of legs; reflex action lost except in head; tetanic spasms; opisthotonos.	Death	Same as No. 19.
27	Cat	12	Spinal cord exposed during life; posterior column touched, animal cries and struggles. After injection of theine, complete prostration and loss of reflex action; on touching posterior column it does not move away or cry; on touching anterior column, muscles are contracted.	Death	Same as No. 19.

TABLE II.—*Experiments with Caffeine.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post-mortem Examination.
28.	Frog	$\frac{1}{128}$	Very slight weakness of posterior extremities.	Recovery	
29.	Frog	$\frac{1}{64}$	Slight weakness of posterior extremities.	Recovery	
30.	Frog	$\frac{1}{32}$	Considerable weakness of limbs; respiration impaired; reflex action diminished.	Recovery	
31.	Frog	$\frac{1}{16}$	Almost complete paralysis; respiration stopped; almost complete loss of reflex action; prostration; cutaneous surface congested.	Recovery	
32.	Frog	$\frac{1}{12}$	Complete prostration; respiration stopped; reflex action lost; under surface of skin, tongue and mouth congested; stasis of blood in capillaries.	Death	Heart beats feebly; great congestion of viscera. When brain is irritated, muscles of face contract; on irritating spinal cord, nerves, or muscles, there are muscular contractions.
33.	Frog	$\frac{1}{12}$	Ligature of femoral artery. Symptoms same as No. 32. No difference between the two limbs.	Death	Same as No. 32. No difference between the two legs.
34.	Frog	$\frac{1}{10}$	Spinal cord exposed during life. Symptoms the same as No. 32. On touching anterior or posterior columns with point of needle, strong muscular contractions followed. After caffeine was injected, no contractions followed touching the posterior column, while anterior column remained as before.	Death	Same as No. 32.
35.	Frog	$\frac{1}{8}$	Prostration and loss of reflex action; congestion of skin; stoppage of respiration.	Death	Same as No. 32.
36.	Frog	$\frac{1}{3}$	Rapid prostration and loss of reflex action, with usual symptoms.	Death	Same as No. 32.
37.	Frog	1	Ligature of femoral artery; very rapid prostration and loss of reflex action. No difference between the two limbs.	Death	Same as No. 32. No difference between the two legs.
38.	Rabbit	1+1 +1+1	From first and second dose, no effects. From third dose, congestion of ears, cerebral excitement, contraction of pupil, staggering gait. From fourth dose, partial paralysis of limbs, reflex action diminished.	Recovery	
39.	Rabbit	4	Numbers of the respirations and pulsations of the heart—1st increased, and 2d diminished. Temperature of the ear—1st diminished, and 2d increased. Ears at first anæmic, subsequently hyperæmic; breathing laboured; pupils contracted; paralysis of limbs; loss of reflex action; tetanic spasms; opisthotonos.	Death	Membranes of brain and internal viscera congested; substance of brain and spinal cord healthy; electrodes of current applied to cord, nerves, brain, or muscles, produced muscular contractions.
40.	Cat	6	Irritation and cerebral excitement; mouth and tongue congested; staggering gait; tenesmus and mucous discharge from bowel; salivation excessive; subsequent depression.	Recovery	

TABLE II.—*Experiments with Caffeine—continued.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post-mortem Examination.
41.	Cat	8	Same as No. 40; in addition, prostration, loss of reflex action, and tetanic spasms.	Death	Heart beats feebly. The same as No. 39.
42.	Cat	8	No marked effect for about half an hour. Death from sudden tetanic spasm.	Death	Same as No. 39.
43.	Rabbit	12	Spinal cord exposed during life; posterior columns, when touched with point of needle, animal struggles and cries out; anterior columns touched, animal struggles. After injection of caffeine, when posterier columns are touched, animal does not cry out, but struggles slightly; when anterior columns are touched, strong muscular contractions ensue. Symptoms same as No. 39.	Death	Same as No. 39.

TABLE III.—*Experiments with Guaranine.*

44.	Frog	$\frac{1}{128}$	No apparent effects.	Recovery	
45.	Frog	$\frac{1}{64}$	Animal sickly; slight weakness of posterior extremities.	Recovery	
46.	Frog	$\frac{1}{32}$	Weakness of limbs.	Recovery	
47.	Frog	$\frac{1}{16}$	Partial paralysis of limbs; reflex action impaired; respiration impeded; congestion of cutaneous surface.	Recovery	
48.	Frog	$\frac{1}{12}$	Prostration; almost entire loss of reflex action; respiration stopped; congestion of cutaneous surface.	Recovery	
49.	Frog	$\frac{1}{8}$	Complete prostration and loss of reflex action; respiration stopped; cutaneous congestion also of mucous membrane of tongue and mouth; stasis of blood in capillaries.	Death	Heart beats feebly; congestion of skin and internal viscera. On irritating brain, spinal cord, nerves, or muscles, there are muscular contractions; anterior columns of cord irritated, strong contractions of limbs; posterior columns irritated, no contractions.
50.	Frog	$\frac{1}{4}$	Rapid prostration and loss of reflex action; otherwise the same as No. 49.	Death	Same as No. 49.
51.	Rabbit	4	Number of the respirations and pulsations of the heart—1st increased, and 2d diminished. Temperature of the ear—1st diminished, and 2d increased. Ears—1st anæmic, and 2d hyperæmic. 1st cerebral excitement, and 2d depression; paralysis of limbs; subsequently apparent recovery, but afterwards died in sudden tetanic convulsion.	Death	Membranes of brain and internal viscera congested. Substance of brain and spinal cord healthy. Electricity applied to brain, cord, nerves, or muscles, produces muscular contractions.
52.	Rabbit	4+2	From first dose, ears congested, and cerebral excitement. From second dose, complete paralysis of limbs; loss of reflex action; contraction of pupil; tetanic spasms, with opisthotonos.	Death	Same as No. 51.

TABLE III.—*Experiments with Guaranine—continued.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post-mortem Examination.
53.	Cat	6	Irritability and cerebral excitement; subsequent depression; partial paralysis of limbs; respiration impeded; tongue and mouth congested; tenesmus and discharge of mucus from bowel.	Recovery	
54.	Cat	6	Same as No. 53; in addition, tetanic spasms and opisthotonos.	Death	Same as No. 51.
55.	Rabbit	8	Exposure of spinal cord during life. On touching posterior columns with point of needle, animal struggles and cries out; on touching anterior columns animal struggles. Guaranine produced effects as in No. 51. On touching posterior columns animal does not struggle or cry out; on touching anterior columns muscular contractions of limbs ensue.	Death	Same as No. 51.

TABLE IV.—*Experiments with Cocaine.*

56.	Frog	$\frac{1}{128}$	Slight weakness of limbs.	Recovery	
57.	Frog	$\frac{1}{64}$	Weakness of limbs.	Recovery	
58.	Mouse	$\frac{1}{32}$	Weakness of limbs; slight congestion of cutaneous surface.	Recovery	
59.	Frog	$\frac{1}{32}$	Considerable weakness of limbs; respiration impeded.	Recovery	
60.	Mouse	$\frac{1}{32}$	Gradual weakness of limbs, ending in complete paralysis; cutaneous congestion; loss of reflex action; prostration.	Death	Congestion of membranes of brain, skin, and viscera. When brain, spinal cord, nerves, or muscles are irritated with electricity, muscular contractions ensue. Posterior columns irritated, no contractions; anterior columns irritated, strong contractions.
61.	Frog	$\frac{1}{32}$	Ligature of the heart; right calf of leg injected. After no movement on irritation, on pinching left calf movements of entire body, including right leg.	Death	
62.	Mouse	$\frac{1}{32}$	Same as No. 60; in addition, tetanic spasms.	Death	Same as No. 60.
63.	Frog	$\frac{1}{16}$	Gradual prostration; paralysis of limbs and loss of reflex action; subsequent recovery.	Recovery	
64.	Frog	$\frac{1}{12}$	Weakness of limbs at first; paralysis of limbs after. Loss of reflex action; stoppage of respiration; congestion of skin; stasis of blood in capillaries.	Death	Same as No. 60.
65.	Frog	$\frac{1}{10}$	Ligature of femoral artery; symptoms same as No. 64. No difference in two legs.	Death	Same as No. 60. No difference between two legs.
66.	Frog	$\frac{1}{10}$	Observation on lower part of spinal cord, which was exposed. Same as No. 64.	Death	Same as No. 60.

TABLE IV.—*Experiments with Cocaine—continued.*

No. of Experiment.	Animal.	Dose in grs.	General Effects.	Result.	Post mortem Examination.
67.	Frog	$\frac{1}{10}$	Observations on upper part of spinal cord, which was exposed. Same as No. 64.	Death	Same as No. 60.
68.	Frog	$\frac{1}{10}$	Spinal cord exposed during life. Any part of cord touched with needle, strong muscular contractions. Other symptoms same as No. 60.	Death	Same as No. 60. When posterior columns are irritated with point of needle no muscular contractions; when anterior columns are irritated contractions ensue.
69.	Frog	$\frac{1}{8}$	Same as No. 64, but more rapid.	Death	Same as No. 60.
70.	Rabbit	3+2+2+2+3	From first dose, congestion of ears; from second dose, slight cerebral excitement; from third dose, great irritability, no loss of sensibility; from fourth dose, congestion of ears increased; from fifth dose, depression, staggering gait. Numbers of respirations and pulsations of the heart—1st increased, and 2d diminished. Temperature — 1st diminished, and 2d increased.	Recovery	
71.	Frog	$\frac{1}{32}$	Same as No. 60. Number of respirations—1st increased, 2d diminished, and 3d stopped.	Death	Sam as No. 60.
72.	Frog	$\frac{1}{32}$	Same as 60. Pulsations of the heart— 1st increased, 2d diminished, and 3d stopped.	Death	as No. 60.

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