

## Original Communications.

## THE PHYSIOLOGICAL ACTION OF CAFFEIN AND THEIN FROM EXPERIMENTS UPON THE LOWER ANIMALS.

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THE substances, called Thein, discovered by Oudry, and Caffein, discovered by Runge in 1820, are analogous in their chemical and physiological action. These substances are very slightly soluble in cold water, ether or alcohol, and are fusible at a temperature of 377° Fahrenheit. They are more readily soluble in the strong acids, though decomposed by muriatic acid. With regard to their solubility in the fluids of the body, I made the following experiments. I mixed equal parts of warm water and fresh blood, which dissolved a small quantity of caffein, about one quarter of which crystallized out on cooling. Of five grains dissolved in warm gastric juice, mingled with an equal quantity of warm water, about one twentieth crystallized on cooling. I propose to illustrate the therapeutical effects of these drugs by a course of experiments performed by myself, with the assistance of Mr. Fitz, of the City Hospital, during the last five months. To prevent wearying those who may read this account, I have selected a few experiments out of a large number, but always exposing those which are attended with peculiar physiological effects, only omitting those which are repetitions of others. The readiest and most effective method of administration, I found, after much difficulty, was that by gastric fistulæ. The traumatic injury did not apparently affect the action of the drug, nor did the physiological actions differ, in this method, from those in which the natural method of administration was employed.

I obtained, while in Paris last summer, a very pure sample of these two drugs, made by La Fontaine's Pharmacy according to the following process, of which I give the translation from the French:—

“Boil the tea leaves in water, which will

dissolve the thein as well as malic acid and the acid malates. Strain *with expression*, and precipitate the malic acid, &c., by the acetate of lead. Filter and separate the lead by sulphuretted hydrogen. Concentrate this last filtrate over a water-bath after its decolorization by charcoal, and allow the crystals to form slowly, by natural evaporation. Or, treat a decoction of tea-leaves with a slight excess of acetate of lead. Filter and evaporate the liquid to dryness. This extract, distilled cautiously, will give the beautiful crystals of thein perfectly white.”

With the thein thus obtained, I made the following experiments. The rectal temperature of a small guinea-pig was 38°.90 Centigrade.

At 4.30, I placed in the mouth of this animal a bolus of thein rubbed together in water, and kept it there until the animal had swallowed the broken-up fragments. This was repeated until about 1 gramme (15 grains) had been swallowed, and none rejected. I added water to assist in the deglutition.

4.45.—Sensibility preserved, and not exaggerated. Has had several evacuations of the contents of the intestines, of a hard and normal consistency.

4.51.—Several evacuations from rectum since last record.

5.00.—One fifth gramme was now given in the same manner.

5.10.—Holds himself erect by the fore-legs, while the posterior extremities remain stretched out. Sensibility preserved.

5.45.—The fore-legs are now extended, so that the animal lies on his belly. Cannot hold himself upright when placed in the proper position. When he moves, he crawls on the belly. Pulsations of heart increased in frequency. Respiration noisy, somewhat as in anæsthesia by ether; movements as if to vomit.

6.24.—Rectal temperature is 39.20 Centigrade. The animal vomits and dies, without convulsion or other premonitory symptoms, except slight trembling in maxillary muscles.

*Autopsy* (immediately after death). Stopped  
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mach filled with partially digested food and thein. A lump of thein is found in the pharynx, plugging the tracheal opening, being thus asphyxiated during the act of vomiting. Lungs collapsed; absence of crepitation under digital pressure. The left cavities of heart empty; the right partially filled with blood. In the lining membrane of the brain, vessels somewhat injected; also, some slight injection in vessels of the cerebellum.

After several unsuccessful attempts to induce rabbits to swallow thein in small doses, or mixed with Indian meal, I attempted fistulous openings of the stomach in some dogs and a cat, three of which recovered from the effects of the operation. I experimented first with the cat, by introducing 73 grains of thein, rubbed up with glycerine, into the canula.

Exp. 2.—Four minutes after—rigidity of muscles, frothing at the mouth, crying as if in distress, respiration hurried and distressed, discharge of fæces, running wildly round the room. Five minutes after—champing of jaws, increased respiration, tonic spasms, followed by a convulsion, the animal rising up slowly and falling suddenly backwards, with a forced discharge of urine; then lying quiet, with her muscles stiffly contracted, and legs shaking, occasionally champing her jaws, and frothing at the mouth. Twenty minutes after—death.

*Autopsy* (immediately after death). Reveals nothing abnormal, with this exception: the abdominal tissue in vicinity of the spleen was deeply injected; the canula was found imbedded and extending half way into this organ. About two thirds of the thein was found undissolved, lying in and around the canula.

From this experiment, it would be difficult to judge what disturbance may have been caused by the presence of the thein in the spleen, interfering with its functions, and what by the action of the drug itself upon the system. However, after a careful investigation with regard to the effects of an interference of the splenic functions upon the economy, I can find no reasons to attribute the serious disturbance above described to an interruption to the functions of this organ *merely*. (I would here state that the canula had been inserted three weeks before the administration of this drug.) I am, moreover, disposed to consider these various physiological phenomena as due to the drug, as can be seen from my next experiment.

Exp. 3.—A dog, upon whom I had successfully operated for gastric fistula six

days before, was muzzled, bound, and placed upon the table; 90 grains of thein, mixed with one fourth of its weight of glycerine, as in the preceding experiment, was then introduced through the tin canula into the stomach in divided doses (the stomach was previously empty, and could be seen in its interior). The vermicular motion was now apparent, and the gastric juice soon began to flow. At a quarter to four, the animal was unbound and placed upon the floor of my laboratory, with the muzzle still on. He walked to his box in the corner, and lay down for a few moments; then arose and began tearing at his muzzle, champing with his jaws, respiring frequently and noisily. Soon he became violent, staggered out of his box through the open door and on to the hay, falling occasionally on to his head, tearing furiously at the muzzle and frothing at his mouth. At ten minutes before five, he fell over in a convulsion on to his back and side, frothing all the time, and champing his jaws. He now lay with his legs extended and stiff, then moving his legs as if walking rapidly. These spasms grew gradually less violent; only, however, to be succeeded by another at five o'clock, which was less violent, and terminated in the same manner as in the first. Other spasms occurred at varying intervals, the animal growing with each more feeble, until he succumbed at fifteen minutes past five. The heart continued its pulsations for three minutes longer. The forelegs were rigid; the posterior relaxed.

*Autopsy* (18 hours after death). Lungs normal, crepitating under pressure of the fingers. Heart—left ventricle, though almost empty, distended and firm; right ventricle flaccid, partially filled with coagula, half red and half white, the line of demarcation being quite distinct. Right auricle and superior vena cava filled with clots of dark blood. Stomach filled with a very frothy, grumous fluid, giving no purple color according to a test recommended by Beale,\* viz., to “put a small quantity of a deposit of suspected urea, or of an urate, and then drop a drop or two of fuming nitric acid. Evaporate to dryness under gentle heat, then add a drop of ammonia or expose to ammoniacal fumes. A violet color (murexide) is seen, and indicates uric acid or an urate.” He goes on to say that caffeine gives this same test, and with the same result. I have often tried this with thein and caffeine, both pure and mixed, or dissolved in some drug or acid. The mucous

\* I translate his words from a French translation of his work, as I have not a copy in English at hand.

coat of the stomach was pale, except near insertion of the canula. The duodenum was also pale, filled in its upper portion with the same fluid as the stomach, but lower down with a yellowish fluid resembling chyle. The gall-bladder was full. The encephalon was then exposed. The sinuses were turgid with dark blood, but there was no extravasation. The cerebellum was slightly injected. The spinal axis from the cerebellum had no abnormal appearance or congestion.

The pathological phenomena point to no particular lesion in this case, except, perhaps, the slight congestion of the cerebellum. When there can be found no lesion of striking importance in the *post-mortem* appearance, after poisoning by some drug, the French call it death by intoxication. This might be thus classed.

Exp. 4.—The crop of a pigeon was opened, and some thein (20 grs.) inserted. In a short time there was discharge from the rectum, and every few minutes afterwards until its death. Locomotion was much impeded, and in an hour and a half convulsions occurred, and the bird was dead the next morning. I was called away at the end of an hour and three quarters, leaving the pigeon in a dying state. I made no *post-mortem* examination.

Exp. 5.—I made an incision through the abdominal walls into the stomach of a rabbit, placed in the stomach 20 grains of thein, and sewed up the wound.

10 minutes after—the animal walks with its legs stiff and back slightly arched. Respiration quite hurried.

17 minutes after—convulsions, preceded by twitchings of the facial muscles. The animal raises herself up, lifting her forefeet off the ground, and falling over backwards. Then she lies quiet on her right side.

20 minutes after—another convulsion, less violent than the preceding, and still lying on her side. No frothing at the mouth. Several times has discharged large quantity of fæces.

23 minutes after—another still less violent convulsion. Closes her eyes when an object is placed near them.

25 minutes after—convulsive movements, though now very feeble, still continue, the head always thrown back. Respiration very slow. Pulsation of heart scarcely to be distinguished. Twitching about mouth and orbital region the only signs of life.

30 minutes after—posterior limbs rigid, the anterior relaxed.

*Autopsy* (made 20 hours after death). All the viscera were in a normal state, with

the exception of one white spot in the liver, resembling a small abscess (probably *not* an effect of the drug). No congestion anywhere, except in the region of the incision. Lungs contained some air. Stomach filled with food (as is always the case with the rabbit, even when starvation has been the cause of death); the mucous coat involving the undigested mass was detached from this organ, not an infrequent occurrence when the stomach has been undisturbed for a short time after death. A very slight injection of the lining membranes of the brain, especially in the vicinity of the cerebellum, but none in the brain substance.

Exp. 6.—Twenty grains of caffein was placed by the same process into the stomach of a rabbit.

10 minutes after—moves about restlessly, with legs stiffened and back slightly arched.

15 minutes after—champing her jaws, but does not froth at the mouth. No convulsions for an hour and a half, at which time I was obliged to leave her. Several profuse discharges from the bowels.

12 hours after—the animal was dead and stiff.

Exp. 7.—Ten grains of thein was wrapped in a piece of meat and given to a fast-ing dog. In three quarters of an hour she got up and paced the room, panting and holding out her tongue, respiration being much hurried. This continued, with intermissions of about a quarter of an hour, for two or three hours, and then ceased. The next day the animal was as well as usual. This, then, was not a poisonous dose.

Exp. 8.—At 3.10, I gave 30 grains of caffein, wrapped in a piece of meat, to a terrier dog.

3.45.—Pants, with tongue extended, walking restlessly; hind legs stiff.

3.53.—Drinks large quantities of water.

3.58.—More uneasy, jumps into a coal-box, rolling round and rubbing his nose and ears in the coal.

4.10.—Respiration much hurried. Is forced out of the box, and then drinks another large quantity of water; he soon vomits up the meat and a large amount of liquid, which leaves, on cooling, a white residue resembling caffein.

At 5.20 was obliged to leave him, still uneasy and restless, and the next morning early found him dead and stiff.

Exp. 9.—To a spaniel of twice the weight of preceding dog, I administered 40 grains of caffein at the same hour and in the same manner as the preceding. He was not as restless as the other dog, but I left them both panting hard. This last dog neither drank

water nor vomited. He was also dead the next morning. Neither had a discharge from the bowels.

Exp. 10.—Mr. Fitz opened the crop of a pigeon, and introduced 20 grains of thein.

In ten minutes—several discharges from the bowels occurred.

In half an hour—cannot balance herself.

In thirty-five minutes—cannot walk, but lies flat on table and flapping her wings. Has apparently lost the power of moving her legs. Respiration accelerated.

In forty minutes—dead. Legs rigid, wings relaxed.

Having proceeded thus far in the course of my experiments, I accidentally came across an article, published in the *Archives de Physiologie*, under the direction of Prof. Brown-Séquard and other distinguished physiologists, concerning *Caffein*, wherein the author affirms that this drug exhausts muscular contractility. My own impression is, that death ensues from an exhaustion of the muscular power, that of the heart occurring last.

Exp. 11.—I therefore placed some thein on an exposed muscle of the leg in a rabbit, and moistened with a drop of acetic acid to dissolve the thein. After an interval of ten minutes, I applied the poles of a bichromate-of-potash battery, and obtained little or no response compared with that before the experiment. I then isolated a nerve on glass rods, placed thereon some thein, and applied the two poles above and below the drug to the nerve, and the muscle did not contract.

Exp. 12.—I was then induced to try the following experiment (the importance of the object justifying the apparent cruelty of the operation). I severed the spinal cord between two lumbar vertebræ in a rabbit of three months' age, producing complete paralysis of the posterior train; reflex action was still intact. I then introduced into the stomach, by an artificial opening, 30 grains of thein, and closed the wound. In half an hour, muscular quiverings commenced in the upper and anterior part of the body, and none in the lower portion. These quiverings increased in strength till feeble spasms occurred in upper portion of the body, especially in the facial muscles, and life was soon suspended. I now applied from an induction coil of sufficient power (giving a spark one quarter of an inch long) the two poles to an anterior limb, the muscles being exposed, which returned a very feeble response. I then applied them to the posterior extremities in the same manner, and the muscles

contracted forcibly, extending and retracting both limbs. These results were manifested for several minutes. It is worth mentioning that I had tried the muscular contractility of both regions before the administration of the drug, with no difference in the power of contraction.

I repeated this last experiment upon two full-grown rabbits, with the same results; and the last time the animal lost much blood during the operation, an artery being pricked and the flow of blood with difficulty being staunched. The convulsive quiverings commenced in half an hour after the introduction of the drug, and were very feeble, occurring at intervals of ten minutes. The heart beat only for a few seconds after apparent cessation of life.

These animals lived six times as long after the exhibition of the drug as in my other experiments, and perhaps because the muscular spasms were more feeble, and not so soon exhausting their power of contraction.

This experiment points to two important effects of this drug:—

1. That this drug poisons by exhausting the muscular contractility throughout the body, and affecting last of all the muscles of the heart.

2. That the spinal cord is that part of the nervous system principally affected, as shown by the convulsions in all the experiments, and, most conclusively, in these last experiments where the posterior train was not convulsed.

To these I might add another effect: that the involuntary as well as the voluntary muscles were stimulated and exhausted till their death or loss of power, as shown by the continued discharges from the bowels and bladder, as well as the quickening and, secondarily, impairment of circulation and respiration.

With regard to its use as a therapeutic agent, there is much to say. It can be used where we wish to stimulate muscular and nervous action. So powerful an agent must also be used cautiously, and the abuse of coffee and tea should be guarded against. I should hope, from its peculiar action, that it may be useful in opium poisoning, and it is known that coffee after a dose of opium is very refreshing. But it must be remembered that though the primary action is excitant, the secondary action is depressant. It should also be borne in mind that coffee little roasted is soothing, and when over-roasted exciting to the nervous system. The dose of caffein, as used by Prof. Oppolzer in cases of nervous headache and hemi-

crania, is one grain combined with an equal weight of quinine, as Dr. F. B. Greenough lately informed me.

*April 10, 1868.*

### THE REGISTRATION OF DEATHS.

By GEORGE DERBY, M.D.

I wish to say a few words on this subject in reply to Dr. Buckingham's article in your last number. Dr. Buckingham regards all death returns under the registration law as without value because certain returns are known to him to be incorrect in a greater or less degree. These inaccuracies are of two kinds: 1st, errors of diagnosis; 2d, statements of fact relating to age, duration of disease, &c., which could not have been within the certain cognizance of the physician signing the certificate of death.

I think Dr. Buckingham does not see the spirit, although he does the strict letter, of the registration laws. Their object seems to me to be to get at the most essential facts relating to deaths in the simplest possible way, and in putting the responsibility of signing certificates upon medical attendants it is placed where, upon the whole, it is most probable that correct information can be obtained. If the relatives or undertakers were relied upon they would be compelled to apply to the physicians, who would have just reason to complain that they were not directly asked by the proper authorities. That all medical attendants upon the dying are not well educated persons is much to be regretted, but well educated physicians are sometimes unable to make a positive diagnosis during life, or even to state with absolute precision the cause of death with the body exposed to post-mortem examination. These are facts which we must accept as evidence of the difficulties of our art, and of the complex organism with which it deals; but to reject on this account all death returns as valueless would be to take away one of our most important aids to a knowledge of disease. A patient with doubtful signs of phthisis comes to us for advice. The question is at once asked concerning the deaths of blood relations. If the reply is that they have died from consumption, we feel a probability amounting to conviction that we have to deal with the same disease. Registration gives us from the community at large, and with the probability of error diminished by the magnitude of the returns, just this kind of information, which we are no more justified in rejecting in the one case than the other. The weekly

returns of the City Registrar are indications of the prevalence of epidemics, pointing steadily at the essential facts, practically noted by us all, and as much to be relied on as the thermometer or the wind vane. I cannot think that any physician would be willing to give them up because of errors of diagnosis which medical attendants may have made.

Were registration returns not essentially correct, how can we account for the nearly persistent percentage of deaths from phthisis extending through a quarter of a century, and the constant slight excess of deaths from this cause in the seaboard counties in every year, or the gradual increase of diphtheria through a series of years and then its equally gradual decline, or the small mortality from zymotic diseases in all parts of Massachusetts in certain years? The operation of general laws like those to which we have referred is abundantly evident on examination of our death returns for a series of years, and these laws could not be demonstrated in any other way. The ignorance of a certain number of persons who sign death certificates cannot obscure the working of these laws, which it is certainly of the greatest importance to our profession to become familiar with. It is to be remembered also that in the collation of death returns it is possible to extinguish inevitable errors and to retain important truths by classing together kindred diseases, and placing in contrast affections of different regions or systems little liable to be confounded by the most unenlightened.

To reject all information concerning disease except what is capable of rigid demonstration is what no one can do in the individual case, and why is it more expedient when dealing with large numbers, derived from the observation of many persons having no common interest to suppress the truth as they saw and believed it?

With regard to the question of age, duration of disease, parentage, &c., although for the sake of simplicity of form they are all embraced in the same certificate signed by the physician, they are practically filled up by the relations or friends, and I think no physician need hesitate to affix his name through fear of being held accountable for errors on these points. Who knows of his own knowledge when he himself was born, and who for the want of this personal knowledge would be unwilling to swear to the date? Archbishop Whateley's argument concerning the existence of Napoleon Bonaparte will show what I mean. We must take the evidence of others as perfectly con-