Experimental researches on the physiological action of nitrite of amyl : (memoir to which was awarded the Warren Prize, for 1871, of the Massachusetts General Hospital) / by Horatio C. Wood, Jr., M.D.

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EXPERIMENTAL RESEARCHES

ON THE

PHYSIOLOGICAL ACTION OF NITRITE OF AMYL.

(MEMOIR TO WHICH WAS AWARDED THE WARREN PRIZE, FOR 1871, OF THE MASSACHUSETTS GENERAL HOSPITAL.)

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Nitrite of amyl is a somewhat oily liquid, of a light yellowish colour, and a peculiar, very penetrating and persistent, fruity odour, which has been compared to that of over-ripe pears. It is very volatile and inflammable, and, as far as I know, insoluble in all pharmaceutical menstrua. Mr. Storer, in his *Dictionary of Solubilities*, mentions it, but gives no solvent for it, nor has experimentation afforded me any positive result. This essay is of course not the place to discuss its chemistry, but it is proper to state that my experiments have been made with two distinct parcels or specimens of the drug, which entirely resemble one another both in their physical characters and their action upon animals. One of these samples was imported by Mr. Spangenburg, of New York city, but from whom he obtained it I do not know. The other was manufactured by Prof. Maisch, of the Philadelphia College of Pharmacy, by Ballard's process as modified by Hoffmann, and accords in all respects with the description of the pure article given in Gmelin's *Handbook of Chemistry*.

In 1859 Guthrie called attention to the flushing of the face and throbbing of the carotids caused by inhalation of nitrite of amyl, but it was not until 1864 that any notice was taken of his remarks.

In that year Dr. B. W. Richardson made a detailed report to the British Association for the Advancement of Science, in which he arrived at the following conclusions:—

1. It is absorbed by the bodies of animals, however introduced into the organism, by the skin, by the stomach, by the lungs, or by the cellular tissue.

2. After its absorption, its effects are seen immediately on the heart and circulation; there is in the first instance violent action of the heart, with dilatation of the capillaries, followed by diminished but not extinguished power of the heart, and contraction of the extreme vessels. As an excitant of vascular action, the nitrite of amyl may be considered the most powerful agent as yet physiologically discovered.

3. On animals, such as frogs, whose bodies admit of its removal spontaneously, and whose circulatory and respiratory systems are simple, the nitrite suspends animation; and when the animals are placed under favourable conditions for the process of recovery, they may recover after considerable periods of time. There is no other known substance that suspends animation in these animals for so long a period. On warm-blooded animals which are clothed in thick and less penetrable skins, and in whose bodies the circulatory and respiratory systems are more complicated, the nitrite cannot actually stop the movements of respiration and circulation without destroying life. But even in these animals it can, without destroying life, reduce the forces of respiration and circulation so extremely that a condition precisely analogous to what is known as trance or catalepsy in the human subject can be brought on and sustained for many hours.

4. The nitrite of amyl is not anæsthetic; by it consciousness is never destroyed, unless a condition approaching death be produced.

5. The effects of the nitrite on the organism are directed to the motor force, which it first wildly excites and then subdues.

6. The *modus operandi* of the nitrite appears to be by arresting the process of oxidation in the tissues.

7. Physically the nitrite holds a place between the volatile bodies, such as chloroform, and the solid bodies, such as opium and woorara. Hence its effects are less evanescent than those of very volatile substances, and less certainly destructive than the solid substances. In this lies the secret of its prolonged action.

Dr. Richardson also concludes that the nitrite paralyzes the nerves from the periphery to the centre, lessening the contractile power of the arteries.

The experiments of Dr. Richardson were shortly afterwards repeated by Drs. Gamgee and Rutherford, with somewhat different results. I believe their experiments are as yet unpublished. The only record of them known to myself is contained in a paper by Dr. Brunton, who states that Drs. Gamgee and Rutherford found

"No action on the nerves, either sensory or motor, and rarely on the capillaries of the frog. . . . . And the pulse-rate and pressure in a manometer connected with the carotid of a rabbit fall when the vapour of the nitrite is inhaled."

Dr. Brunton's own experiments were mainly, if not entirely, directed to the effect of the substance on the circulation. They were made in the laboratory of Prof. Ludwig, at Leipzig.

"With the exception of one or two on dogs, they were made upon rabbits; and, instead of allowing the animals simply to inhale the vapour, artificial respiration was employed, the apparatus being so arranged that the air could be either sent directly from the bellows, through a tube in the trachea, to the lungs, or passed through a vessel containing the vapour of the nitrite. The advantages of this arrangement were, that the bellows being worked by an engine with great regularity, the disturbing influences of unequal respiration on the blood-pressure were to a great extent avoided. When air charged with the vapour was passed directly into the trachea of a rabbit, the blood-pressure almost immediately sank very much, but the pulse-rate remained nearly unchanged. As the pressure sank, general convulsions took place, and the pressure immediately rose notwithstanding the continued inhalation of the vapour. When, however, convulsions were prevented by the use of curara, the blood-pressure diminished at first as above, but did not regain its normal amount so long as the inhalation was continued."

I believe the results thus given comprise almost all that is known of the action of the nitrite of amyl. It is very plain that they are, in a measure, contradictory, but they are amply sufficient to show that the substance has some very peculiar physiological powers, and to call for a thorough investigation of the subject. This demand is strengthened by the asserted good results that have been obtained abroad by its use in several cases of angina pectoris and of tetanus; enough experience to give ground for hope that practical therapeutics may be benefited by the inquiry.

My first series of experiments were directed simply to the study of the general, apparent symptoms induced by the drug, the mode in which it usually kills, and the post-mortem appearances. The experiments are as follows:—

Expt. 1.—October 20. A kitten two or three months old. Twenty or thirty drops of the nitrite were given by inhalation. Died in a few minutes, without struggling.

Autopsy immediate.—Heart beating vigorously, and continuing to do so for ten minutes after the cessation of respiration. Blood everywhere dark, no distinction between arterial and venous. Bowels quiescent, but vermicular motion easily aroused by electricity.

Expt. 2.—A very strong terrier, of moderate size. 3.45. Two drops of the nitrite inhaled from a chip, and then the bottle held close to the nostrils for two minutes; directly the dog gave a tremendous bound, very suddenly breaking from his fastenings. 4.4. Injected one drop. 4.7. Injected between three and four minims. 4.33. Injected ten minims into peritoneal cavity. Had been howling before this, but at the time of injection was quiet; immediately afterwards commenced to howl again. 4.34. Very violent struggles, coming on suddenly, accompanied by forcible urination. 4.37. No material change; the breathing diaphragmatic, noisy, spasmodic, laboured. 5.10. Dog let up, able to walk. Following day (10 mo. 4), seems pretty well, except the leg into which a cardiometer nozzle had been inserted. 10 mo. 5. Very much weakened by secondary hemorrhage. Twenty minims of nitrite inhaled. Death in a few minutes, without struggling.

Autopsy immediate.—Lungs whitish. Heart presents curious vermicular waves of superficial motion running through it, the wave commencing apparently at base of the heart, running through auricles and ventricles to apex, and then back again to base. No distinction between arterial and venous blood.

Expt. 4.—4.34 P.M. Injected eight drops into peritoneal cavity of a young rabbit, and in 11 minutes twelve drops more. 4.48. Breathing very hurried; panting. 4.52. Rabbit still perfectly quiet. 5.07. Anæsthesia of cornea marked. Occasional convulsive startings. 5.10. Respiration ceased before heart.
Autopsy.—Everywhere quantities of dark blood. Spinal canal filled with it. Peristaltic action of the intestines very active.

Expt. 5.—Killed a large female cat by twenty-two drops of nitrite inhaled. Death without convulsions. Autopsy exactly as in last.

Expt. 6.—Pigeon. Four drops of nitrite inhaled. 5 min. Perfectly conscious, but respiration very much disturbed. 9 min. Five drops more administered. 11 min. Perfectly conscious; struggling violently. 15 min. Died in violent convulsions.

Expt. 7.—Adult pigeon. 8.56 P.M. Injected a mucilaginous mixture containing nitrite into peritoneal cavity. 9.3. Begins to breathe deeply and labouredly. 9.9. Breathing not now laboured. 9.15. Has been quiet; let up; seems very active; walks about lively.

These experiments show that, as stated by Richardson, the nitrite of amyl, when taken into the system in any way in warm-blooded animals, produces its constitutional effects. The train of symptoms that it gives origin to is somewhat peculiar, the most constant and prominent results of its presence being the rapid, deep, hurried breathing, and the steadily progressive loss of muscular power. Dr. Richardson states that the motive forces of the system are at first wildly excited, and then subdued. My experience does not at all coincide with this. In only one instance have I witnessed any early manifestations of motor activity. In this case (Experiment 2) the sudden effort to break away was apparently voluntary, and was very probably due to the natural repugnance of the dog to having a bottle filled with suffocative vapour placed close to his nostrils. In pigeons, convulsions are very frequently produced, but they come as a late symptom, only appearing when the bird is profoundly affected. Possibly the total absence of early convulsions in my experiments was in a measure due to their being chiefly made upon dogs, cats, and pigeons, since Dr. Brunton states, in one of his papers, that in rabbits the nitrite very frequently produces convulsions. That in the few trials I have made upon rabbits spasms have not been prominent, may be owing to the drug having been employed hypodermically, as the authority just quoted states that the convulsions are very probably suffocative. Convulsions are, however, almost as certainly produced by spinal depressants as by spinal stimulants. Thus they are a very constant phenomenon after the administration of veratria, viridia, &c. The frequency of their absence after the use of the nitrite of amyl is somewhat peculiar; but their association, when present, with a steadily progressive paresis is unmistakable evidence that they are

not owing to an excitement of the motor system. They never appear to be produced in a reflex manner by external excitants, but seem to be always centric in their origin.

One of the most interesting results of such experiments as those already described is to indicate the general method of death after the administration of lethal doses. My experience clearly shows that, in warm-blooded animals, the respiratory system is more profoundly affected by the amyl salt than the circulatory, respiration in all cases ceasing before the heart's action. Of course the continuance of the heart-throb in adult warm-blooded animals can endure only two or three minutes after respiration ceases. It is well known, however, that in this respect young mammals resemble the reptiles rather than old warm-blooded animals, and accordingly, in Experiment 1, the heart of a kitten continued its rhythmic motions ten minutes after the nitrite of amyl had put a stop to all respiration whatever. The action of the heart, however, although not stopped, is, as shall be shown in detail hereafter, always greatly affected.

The post-mortem appearances are peculiar in one respect only, namely, the coloration of the blood. There are no lesions of the solids, nor have I been able to find anywhere any indications of active congestion. The arterial and venous blood are nearly or entirely indistinguishable. The colour approximates that of normal deoxygenated blood, but is very distinct from it. The bluish tint is wanting, being replaced by a brownish, so that tobacco-spittle is suggested, although the tint is again quite distinct from that of that disgusting compound. The coagulability of the blood seems not to be impaired. The red corpuscles under the microscope do not show anything peculiar, unless it be that they are not quite so eager to adhere, and become crenated under less provocation than normal. It is quite probable that very careful use of the medicine might induce a trance-like condition of the animal, as spoken of by Dr. Richardson; but I have never seen, except in one case, anything resembling it. In this experiment, which will be detailed when the effects of the drug on animal temperature are discussed, a pigeon was thrown into the condition which I suppose Dr. Richardson refers to, yet, after all, it was much such as is seen when anæsthetics are administered. Consciousness, however, is always lost very late, instead of very early.

On cold-blooded animals, as represented by frogs, the nitrite acts very much as upon mammals. Dr. Richardson states that he has suspended animation for a very long time in frogs, the batrachians eventually recovering entirely. I have made no experiments bearing upon this point. The investigations of Dr. Fraser upon atropia, however, have shown that apparent death from that drug may occur in the frog, and last many hours, or even days, when it yields to a state of greatly augmented reflex excitability, from which the frog may or may not finally recover. There is, therefore, nothing so unique in this action of the nitrite as was at first

supposed. The following experiments will serve to illustrate the symptoms that the nitrite of amyl has produced in my hands when administered to frogs. It will be seen that the only prominent symptom was constantly increasing loss of muscular power. While studying the action of the poison upon the nervous system, hereafter, there will be detailed a number of other experiments upon frogs, which agree well with the one about to be noted. In no case have vigorous general convulsions been produced, but in some instances there would be sudden, electric-like motions, resembling those of jumping, but evincing great loss of power.

Expt. 8.—5.22 P.M. Injected a drop of nitrite into the thigh of a moderate-sized frog. 5.52 Apparently as before injection; threw two minims into the belly. 5.54. Lying perfectly quiet; hardly able to turn from back to belly. 5.58. Respirations irregular; heart still beating. 6.5. Respiratory movements almost ceased. 6.17. Heart now beating regularly and strongly.

Having now studied sufficiently the gross symptoms produced by nitrite of amyl, it remains to investigate its action more in detail upon the various parts of the economy, and finally to discuss the method of its action.

Under the first of these heads is comprised its action: 1. On the nervous system; 2. On the muscular system; 3. On the circulation—including the heart, arteries, and vaso-motor nerves; 4. Its influence on tissues when applied locally. These points I shall discuss in the order in which they stand. It is evident that the first two can be most readily discussed together.

That nitrite of amyl usually produces, when taken into an animal, progressive loss of muscular power, has already been shown, and the experiments hereafter detailed corroborate entirely those already given. There are but four ways in which the drug can cause paralysis: 1. Impairment of the will power to arouse the motor ganglia of the spine; 2. Impairment of the power of said ganglia; 3. Impairment of the conducting power of the nerves; 4. Impairment of the contractile power of the muscles.

The first of these methods is conceivable, rather than practical, for there is at present no known substance which will, without suspending consciousness, so influence the cerebral ganglia as to forbid their acting upon the spinal cord. I know of no proof that the nitrite of amyl possesses any such peculiar power, and its action can be traced to other parts of the nervous system, so that it seems pardonable to take for granted that it has not such power, and to limit the discussion to the other points.

The next series of experiments will be directed to determine whether fatal doses of the nitrite destroy, or not, the conducting power of the nerves or the contractility of the muscles.

Expt. 9.—5.22. Injected into thigh of a moderate-sized frog one drop of nitrite. 5.52. As before injection; put two minims into belly. 5.54. Hardly able to get from back on to belly. 5.55. Lies quiet on back. 5.56. Has frequent convulsive movements of legs. Opened thorax. Heart beating actively. 6.5. Heart still beating. Very infrequent respiratory motion. 6.11. Galvanization of crural nerve causes active motion of muscles supplied. 6.17. Heart

beating regularly and strongly. 6.20. Galvanic and mechanical stimulation of spinal cord excite repeated and marked general muscular contractions.

Expt. 10.—4.51. Injected four minims of nitrite into belly of a small frog. 4.52 General, apparently perfect, paralysis. 4.57. Heart beating very slowly. No other signs of life. 5.2. Has made several spasmodic efforts to jump. Shows no signs of feeling. Galvanization of crural nerve causes active contractions of muscles supplied. 5.12. Galvanization of spinal cord, both high up and low down, induces active motion of legs.

Expt. 11.—A moderate-sized frog, quite lively, having been some hours in a warm room. 3.15. Injected about three minims. 3.18. Signs of weakness, breathing laboured. 3.20. Lies on back quietly when placed there, although still able to jump when aroused. 3.25 Unable to jump his own length; has just had an apparent convulsion, which did not, however, exhibit any power. 3.28 Muscular motion, except respiratory, abolished. 3.30. Exposed heart, which is beating freely; frog showed no signs of life during operation. 3.37. Apparently reviving; pulls away his leg when it is pricked with a knife. Respiration more frequent. 3.42. Pulsations of heart have ceased, although respiration still persists. At times strong convulsive movements of feet. 3.45. Pricking heart causes a single attempt at motion. The auricles distended; the ventricles whitish, bloodless. 3.53. No respiration for some minutes, although there are still occasional active motions resembling those of jumping, but not decidedly voluntary; powerless to raise body from ground. 3.55. Galvanization of crural nerve causes free motion of muscles supplied.

From these experiments it is evident that neither the conductility of the nerves, nor the power of the muscles of responding to impulses, is destroyed by nitrite of amyl. My experience affords no evidence whatever that there is produced, as asserted by Dr. Richardson, a paralysis of the extreme filaments of the nerve. The crural nerves were isolated in such a manner that I think it impossible there should be any transmission of the galvanic current itself to the muscles, and yet the latter never failed to respond to the application of the current. Moreover, mechanical stimulation of the nerve, such as pinching, would cause muscular contractions in the part supplied. While, however, there can be no doubt that the paralysis was not due, in these experiments, to destruction either of the conducting power of the nerves or of the contractile power of the muscles, yet it appeared to me that the contractions were less forcible than if both of these were normal, and that there might be a lessening of either one or the other.

The following experiments were undertaken to determine whether the conducting power of the nerves was affected at all or not:—

Expt. 12.—Two frogs of moderate size, alike in all respects. 2.58. Injected two and a half minims of the nitrite into flank of one of the frogs. 3.25. Frog universally paralyzed; apparently dead; exposed crural nerve and placed it on a silver grooved director, then touched it with iron forceps moistened with strong solution of salt, then put the solution freely on the nerve; no motion was elicited, although, where the solution touched the muscle, it excited strong quivering motions. Pure salt was then put on nerve, without result for nearly half a minute, when active twitchings of muscles of leg were aroused, producing feeble motions of toes, but no general movement of foot or leg. The above-described procedure was now gone through with on the other leg, with similar results, save that the twitchings followed more closely upon the application of the salt to the nerve. The spinal cord of the other frog was now cut high up, the crural nerve of one thigh exposed, and the moistened forceps applied as above;

active motion was immediately induced. The salt solution, when applied to the nerve, induced very active tonic and clonic contractions of muscles, the leg becoming firmly flexed, and the toes widely extended, and in a short time active movements were manifested all over the body. The spinal cord of each frog was now exposed; on applying salt to that of No. 1 (amyl frog), a few feeble movements supervened, whilst in doing the same to spinal cord of No. 2, exceedingly active and universal movements resulted.

Expt. 13.—Similar to the preceding in method and results.

These experiments show that the nitrite of amyl in lethal doses does affect the conducting power of the nerves. For whilst powerful stimulation of the nerve-trunk is immediately followed by muscular contractions, yet stimulation of a mild type, but sufficient to act very decidedly in the normal state, fails to produce motion. In Experiment 13, even the very decided application of salt to the nerve failed to cause any effect; and in Experiment 12 motion was only manifested, on similar provocation, after the lapse of a very appreciable period of time. I think these various experiments are sufficient to show, then, that the nitrite of amyl very greatly impairs, but does not entirely destroy, the conducting power of the nerve-trunks.

It is a point of some interest to determine whether the vital functions of the muscles themselves have also suffered detriment or not.

With this view the following experiment was performed:—

Expt. 14.—Two small frogs as nearly alike as possible.

No. 1. 8 P. M. Two and a half minims of the nitrite were injected low down into the right flank, so that the nitrite probably went to some extent into thigh. 8.10. All movement whatever suspended; frog apparently dead. Skinned the thighs and legs, and dissected out and removed the nerves. One of the muscles of the thigh was very much discoloured, evidently from local action of the nitrite. Salt was now sprinkled very freely over both thighs and legs. Very little motion was excited in the right thigh, not enough to move the leg; the discoloured muscle scarcely quivered. In the left leg there was very active quivering of all the muscles, so that the leg was moved slightly, and the toes considerably.

No. 2. The spinal cord was severed high up, the legs skinned, and the nerves removed as in No. 1. Salt was now applied freely to thigh and leg muscles, producing violent twitchings and contractions, and movements of the leg and toes very much more forcible and active than in the previous instance.

To establish exactly to how great an extent lethal doses of the drug under consideration impair muscular contractility, would require much more elaborate and repeated experimentation. This is not, however, necessary in order to establish the bare existence of such impairment. I think the above-detailed experiment is sufficient, especially when taken in conjunction with the fact indicated above, but which will hereafter be established, namely, that the local application of the nitrite to a muscle totally destroys its contractile power.

Having completed the investigation of the effect of the amyl salt upon the nerves and muscles, the following experiments were instituted to determine how far the motor centres of the cord are affected. It has already been shown that after death from the internal administration of nitrite of amyl,

it is possible by mechanical and chemical stimulation of the cord to produce slight convulsive movements in the limbs. This would seem to show that there is a little power of propagation of impulse remaining. The best measure of the capability of the ganglia of originating a motor impulse, that I am aware of, is the activity of the reflex actions, it being of course allowed that the conductility of the spinal nerves is not seriously impaired. The following experiment was instituted to test the effect of the nitrite upon reflex action. It was not repeated, because sufficient corroborative evidence was obtained in certain experiments bearing upon another point, which will be detailed later in the memoir.

Expt. 15.—Two frogs.

No. 1. Moderate-sized frog. 5.12. Cut the spinal cord near the head. 5.14. Dropped on foot strong acetic acid; instantly most violent and rapidly repeated extensions and flexions of both legs occurred, ending after a time in their being strongly flexed on the abdomen. 5.25. Some difficulty in getting frog to lie with legs extended. When this is done, minutest portion of the acid causes leg to contract forcibly on body.

No. 2. A frog decidedly larger than No. 1. 5. Injected about three minims of the nitrite into right thigh. 5.5. When laid on back, unable to get off; can croak feebly and kick. Right leg rigidly extended, powerless. 5.7. Acetic acid dropped on right foot causes no motion. 5.10. Injured leg seems stiff; joints not bending fully with weight of body. 5.14. Acetic acid on uninjured foot causes very quickly violent movements, frog jumping violently with the right leg extended, motionless. 5.18. Acetic acid dropped on uninjured foot does not cause motion for several seconds, then a good deal of it. 5.20. Acid on left leg causes no motion for several minutes, and then the leg slowly and partially flexes on the abdomen. 5.25. Respirations very infrequent. Exposed heart; it is beating vigorously. Frog apparently conscious, tried to get away during the operation. 5.28. Frequent, sudden, general convulsive starts, as though produced by an electric shock. Right leg never partakes in these. 5.40. Frog motionless. Cut into right thigh; muscles all seem rigid, mechanical stimulation of nerve produces no motion. 5.42. Mechanical stimulation of spinal cord causes slight movements of muscles generally, save only of right leg, which remains stiff and quiet.

From this experiment it is obvious that there is a great lessening in the activity of the motor centres. The only objection that can be urged against trusting to it as evidence is, that it has already been shown that the conducting power of the nerves is much impaired by the poison, so that the apparent want of vitality in the motor ganglia may really be due to the affection of the nerve-trunks. The original impulse must, of necessity, be weakened by the time it reaches the centres, and the reflex impulse still further reduced by the time it arrives at the muscles. I do not think this double diminution is at all sufficient to account for the results obtained in my experiments upon the reflex excitability. Yet, in order to test still further the condition of the spinal centres, the following experiment was instituted:—

Expt. 16.—Two frogs of about the same size.

No. 1. Ligature passed through the body so as to include nerves and artery, and tightened, interrupting the circulation in hind legs. Three minims of the nitrite were now injected into the upper body. After death, acetic acid applied to foot caused no motion. Crural nerves exposed, and to one salt applied; motion

of muscles and foot occurred in corresponding leg. Very slight movements of other leg. Salt was applied to exposed spinal cord; very few movements whatever were caused.

No. 2. Ligature was applied as above, and ten minutes afterwards spine cut high up. Nerves of legs were now exposed, and to one salt applied; moderately active movements of the opposite leg occurred, decidedly greater than in No. 1. Motions of the leg to which the salt was applied also more active than in No. 1. Salt was now applied to the cord, causing very violent general movements.

These experiments are rather ruder than I like; it would have been better to have exposed the bloodvessels and compressed or tied them alone, but the small size of the frogs made this impracticable. That the circulation was very much interrupted, if not altogether checked, I have no doubt. That the nitrite did not freely penetrate into the hind legs of No. 1, is shown by the marked contractions of the muscles when salt was applied to the crural nerve. The nerve-trunks were therefore but very slightly impaired. Yet reflex actions were almost totally abolished; whilst in a similar frog, whose nerves and arteries had been exposed to at least as much pressure, they were quite active.

There is one very strong proof of the deficient power of the motor ganglia to which I have scarcely yet called attention, namely, the very slight effect that strong stimulation of the spinal cord itself has in inducing muscular contractions in frogs just killed by the nitrite. This was very manifest in Experiments 13 and 16. In the frogs whose spinal cord had been severed high up, the application of salt to the wound, and therefore to the cord, produced the most frightful spasms and contortions imaginable—intense opisthotonos, mouth stretched widely open, toes all spread out and stiffened, muscles everywhere jerking or rigid—whilst in the frogs killed by the poison, the sprinkling of salt on the spinal cord caused only feeble muscular twitchings.

The following experiment is interesting as having been made upon warm-blooded animals, and I think corroborates the opinions expressed in regard to the action of nitrite of amyl on the nervous and muscular systems:—

Expt. 17.—Two kittens of the same litter, between two and three months old.

No. 1. Rapidly killed by inhalation of nitrite of amyl. Autopsy: muscles everywhere contracting actively on galvanization. Crural nerve now being insulated, a weak induced current caused vigorous movements of the muscles supplied; no reflex actions whatever excited. A weak current was now passed through the insulated exposed cord, and elicited no movements.

No. 2. Stabbed to death. Galvanization of cord as before, with a similar current, produced active movements of the dorsal and lateral muscles, but no general convulsions.

The above experiment adds its mite to the store of evidence, and I think that it has been sufficiently shown that the nitrite of amyl is a powerful depressant of the motor system, affecting to some extent muscular contractility, to a greater extent the conducting powers of the nerve-trunks, and still more profoundly the central motor ganglia.

In regard to the action of the nitrite on the sensory ganglia, my experiments have convinced me, as has been before stated, that sensation is not abolished until very near death. I have little doubt that there is a diminution of activity in the sensory ganglia, but it does not appear to be so rapid as that of the motor centres.

The cephalic part of the cerebro-spinal axis is also very slowly affected. Consciousness is retained until the whole system is most profoundly influenced, nor have I ever been able to detect any perturbations of the special senses. Nitrite of amyl is, therefore, distinctly not an *anæsthetic*, the term being properly confined to those drugs which affect the centres of consciousness and feeling more rapidly and profoundly than those of motion.

The next point to be investigated, according to the plan of this inquiry, is the effect of the nitrite upon the circulation. From the passages already quoted, it is very plain that the conclusions of Drs. Richardson and Brunton do not entirely agree. Those of Dr. Brunton appear to have been worked out the most carefully and thoroughly, and his experiments are detailed. Dr. Richardson's results have been published in a number of places, but I have never seen any report of the experiments themselves, and therefore shall pursue the plan of examining the truth of Dr. Brunton's opinions first, and, if I find them correct, say no more about those of Dr. Richardson.

Dr. Brunton has published several papers upon this subject, the most important of which is one in the *Journal of Anatomy and Physiology*, vol. v., and another in *Der Bericht der Mathem.-Phys. Classe der Königl. Sächs. Gesellschaft der Wissenschaften*, 1869. The former of these is the later and fuller, but the latter contains the accounts of the experiments.

Like other similar papers, those of Dr. Brunton contain both assertions of facts, and conclusions drawn from these facts.

I shall first examine the truth of the former, and then endeavour to determine how far the latter are justifiable.

His facts are as follows:—

1st. Inhalation of the nitrite causes diminished blood-pressure, as tested by a cardiometer, with or without quickening of the heart's action, increase in the number of the cardiac beats per minute being especially seen in dogs.

2d. After section of par vagi, inhalations of the amyl salt still cause diminution of the blood-pressure.

3d. After division of the spinal cord in the neck, the nitrite still is able to produce lowering of the mercury in the cardiometer tube.

4th. That if the cord be divided in the neck, and the aorta be compressed in the abdomen, so as to check the flow of blood to the lower extremities, "a rise took place in the inhalation; but generally a sinking, much less, however, than in the normal condition."

The experiments proving the above are given in the German paper before spoken of. It is somewhat unfortunate that more details are not published, but I copy a few of the experiments as they are given, because to most medical men the *Bericht*, &c. is an inaccessible book. Instead of transcribing all, I limit myself to a few typical ones. When the animal was poisoned with curare, it was done with the idea of avoiding the disturbance of circulation which the altered breathing and the frequent occurrence of convulsions gave rise to, a regular, steady, artificial breathing being substituted for the natural unequal one.

No. of experiment.	Time in seconds.	Inhalation of nitrite.	Blood pressure in mm. of mercury.	Pulse in a unit of time.	Remarks.
1	0	Commenced	104.5	9	
	10		57	9	Convulsions.
	22	Ceased	65		
	59				
	87				
2	0	Commenced	83	9	
	19	Ceased	52	9	Convulsions.
	33		102		
	36		98		
3	3		141	11.5	Poisoned with curare, and
	6		157	11.5	artificial respiration kept
	12	Commenced	139	11.5	up.
	19		99		
	30		112		
	41		100		
	59		108		
	72		88		
4	0	Commenced	43		Spinal cord cut near occi-
	6		43		put.
	25		32		
	33		30		
	64		42		
5	0	Commenced	97		Convulsions.
	5	Ceased	76		
	47		126		
	110		119		
6	1		20	8	Spinal cord cut.
	25	Commenced	92	7	Aorta compressed.
	31		95	8	
	33		80	6.5	
	38		75	8	
	61		78	7.5	
	72		20		Aorta loosened.
7	1		24	7	
	14		107	7	Aorta compressed.
	21		113	7	
	22	Ceased	105	6.5	

In order to test the facts of Dr. Brunton, I instituted the following experiments:—

Expt. 18.—A very strong terrier, moderately large. 3.40. Inserted tube of cardiometer into femoral artery; pulse 100; blood-pressure 130–175. Mercury constantly rising and falling, but most of the time between 140–160. 3.45. Blood-pressure and pulse as before. Two drops of the nitrite inhaled. No effect visible on cardiometer. 4.4. Injected a drop. 4.7. Blood-pressure nearly as before, but very rarely going above 160. 4.18. Injected between three and four minims. 4.22. Blood-pressure as before; pulse 96. 4.33. No change in blood-pressure. Injected fully ten minims into peritoneal cavity. 4.37. Blood-pressure 140–160; pulse 108; breathing very much affected. 4.47. Blood-pressure mostly 130–140—going down to 120—never above 150. Arterial and venous blood alike. 4.51. Blood-pressure 120–130. 5.10. Individual beats hardly perceptible in cardiometer tube; mercury now standing at 95. Dog was now let off, and was able to walk; next day was all right except as to his leg.

Expt. 19.—A stout young spaniel-cur. 4 P.M. Inserted cardiometer tube in left femoral artery; pulse 150; blood-pressure 125–140; mostly above 130; whilst dog is howling, range from 105 to 165. 4.10. Ten drops nitrite inhaled. 4.12. Blood-pressure 105–130. 4.13. Pulse 164; blood-pressure mostly from 105–120—generally below 120. 4.14. Blood-pressure same. No general symptoms. 4.25. Pulse 168; blood-pressure 120–145; 30 drops inhaled. 4.25½. Blood-pressure 110–120; dog quiet. 4.26½. Blood-pressure 95–130, mostly below 115; pulse 170; dog howling. 4.28. Blood-pressure 95–115. 4.28. Breathing very deep and laboured. Heart's motion hardly perceptible in mercury. No marked general symptom from the amyl, save the change in colour of blood. The thorax seems very full, distended, tympanitic. Pupils natural. 4.49. No marked improvement in colour of the blood. Dog let up, can walk very well.

Expt. 20.—Moderate-sized cur dog. 3.30. Cut the pneumogastrics. 3.45. Inserted cardiometer in carotid. Pulse 180; heart-stroke 3; blood-pressure 130–150. 3.50. Injected five minims into peritoneal cavity. 4.4. Blood-pressure 105–115, going to 120 on violent breathing. Pulse 204; heart-stroke 3. 4.11. Pulse 195. 4.14. Breathing laboured. Blood-pressure mostly 110–120. 4.17. Dog still quiet. Blood-pressure 115–125. Five drops inhaled; the mercury fell almost instantly, but violent efforts at breathing coming on, mercury vibrated between 90–140 during each breathing effort. After a few seconds of quiet, mercury stood at 100. 4.30. 5 gtt. nitrite injected; cardiometer immediately afterwards indicated a blood-pressure 90. Violent, forced breathing now coming on, mercury vibrated between 75 and 130. Heart-stroke 2. 4.44. Quiet; blood-pressure 90–95. 4.45. Very laboured breathing—mercury vibrating between 80–130; 10 gtt. of nitrite were now inhaled, and mercury fell at once to 75–85; violent breathing coming on, mercury followed each effort from 70–120, then stood for a few seconds 110–120, then rapidly fell. 4.50. Dog able to walk.

Expt. 21.—The cord of a large Scotch terrier was cut low down in the neck at 3.30 P.M. A great deal of blood was lost. 3.40. Blood-pressure in carotid near 20. 3.50. Fifteen drops were given by inhalation. The mercury almost immediately fell to zero, beating feebly. On very forcible respirations coming on, it rose, and then remained a little while pretty steadily from 8–12, then fell again to near zero. 3.60. Dog dead.

Experiments 18 and 19 certainly corroborate the assertion of Dr. Brunton that the nitrite of amyl diminishes the blood-pressure, although sometimes increasing the rapidity of the heart's beat. He states that this quickening of the pulse does not take place in rabbits, but that in dogs it is very marked. It was, perhaps, not so pronounced in my experiments as his language would seem to indicate, yet it was very evident. In the first

trial, it was not very apparent until the circulation was profoundly affected, but the increase in rapidity was finally nearly 50 per cent. In the second essay, the gain in rapidity was only about 15 per cent. Experiments 20 and 21 are also in agreement with those of Dr. Brunton, confirming his second and third facts (of my enumeration). Circumstances have prevented my repeating the final experiments of Dr. Brunton, but having found his other facts correct, I think it little to allow that his fourth is also.

Dr. Brunton's facts being correct, is his deduction also? His reasoning leads him to the belief that the chief factor in the reduction of the blood-pressure is expansion of the capillaries. I must content myself with a reference to his paper (*loc. cit.*), for a *résumé* of his arguments. Some of them will be incorporated in this paper, but so intermingled with my own, that it would absorb too much time and space to acknowledge each separately.

The researches of Cyon and Ludwig, Stilling, Roever, and other German physiologists, have demonstrated that there are four ways in which the heart can be influenced.

1. Through the vagi. 2. Through the accelerator nerves, which pass downwards from the brain through the cervical spinal cord, to form one of the roots of the last cervical sympathetic ganglion. 3. By acting on the muscular structure of the heart. 4. Action on the bloodvessels.

That the nitrite does not act in either the first or second ways, is directly proved by experiments already given (Expt. 19 and 20), since division of the nerves did not affect the result.

That the nitrite does not act in the beginning upon the heart itself, is, I think, fairly deducible from the experiment of Dr. B., in which the aorta was compressed. If it did act in such a way, how could compression of the artery affect the result? Moreover, Expt. 19 corroborates this, because the individual heart-beats retained their pristine force long after the general blood-pressure had fallen. For these reasons, I think it must be allowed that nitrite of amyl does not act upon the heart until a considerable point of saturation of the blood and system is reached.

If the nitrite does not reduce the blood-pressure in any other way, it must do it by acting on the capillaries, either directly or through the vaso-motor nerves. It would seem, therefore, a fair conclusion that it does so act. Moreover, only in this way can the results of the aortic compression be explained. It is evident that compression of the aorta shuts off a very large portion of the capillary system, and therefore ought to have the effect, if the nitrite acts on the capillaries, that experiments have shown it really does have. There is also some corroborative evidence of this view. Thus the marked flushing of the face that follows the inhalation of the drug in man, and the same thing in the ear of the rabbit, show at least that a portion or portions of the capillary system are affected. It is also

asserted that the local application of the amyl salt to the web of the frog's foot produces a very sensible dilatation of the capillaries, as seen under the microscope. I have not repeated this experiment, partly because I have never had satisfactory results in similar trials with other drugs, and partly because I have not thought the experiment of pre-eminent value. From the nature of the local action of the nitrite, which will be discussed hereafter, dilatation of the capillaries must occur when the undiluted drug comes in contact with the vessels. The question at issue is, does it also do this when the small portion dissolved in the blood penetrates a capillary?

The effect of the almost pure drug on a capillary is at most only a presumptive evidence. I think, however, these minor arguments—*i. e.*, its local action, and the visible enlargement of the capillaries in the face and ear, before alluded to—so strengthen the major, that it must be allowed that one of the first effects of the nitrite taken into the blood is dilatation of the capillaries, and that this dilatation is chiefly owing to a direct action on the vessels. It will be shown directly that the nitrite applied locally is a paralyzer of muscular fibre, and it has been already shown that it exerts a similar, although less powerful, influence when taken internally. When the drug enters the blood, it comes into such immediate and intimate contact with the thin walls of the capillaries, of very necessity passing through them to reach other tissue, that I do not see how it is possible for it to fail to paralyze more or less completely their muscular fibres.

When, however, a considerable amount of the salt has been absorbed, and all the muscular structures are being weakened, I think it very plain that the heart itself must partake in the depression. There comes in then a second element of weakness in the circulation, namely, loss of muscular power in the heart. A reference to Experiment 19 will show that early in the trial, although there was a marked decrease of arterial pressure, yet the individual heart-stroke raised the mercury just as high as before the inhalation; whereas later the propulsive power of the individual stroke was plainly reduced one-third.

In conclusion, then, I think it must be allowed—1. Nitrite of amyl reduces the blood-pressure when taken into the system by any route. 2. This reduction is owing in the first place to a paralysis of the capillaries, and finally also to a direct action on the muscular structure of the heart, and is practically independent of the central nervous system.

In accordance with the plan of this essay, a study of the local action of the nitrite of amyl is next in order. In this there is a field as yet untouched, no writer, to my knowledge at least, having said aught on the subject.

Early in my experimentation I perceived that the nitrite does not act at all as an irritant. I have now given it by inhalation, and injected it into almost every portion of the body of the animal, without ever seeing

the slightest indications of its producing pain or irritation. From this the inference is obvious, that it exerts but little local influence. Experiment 15 was the first, I think, that showed me the falsity of this inference. To my surprise, the leg of the frog in a very short time was stricken with complete paralysis after the injection into it of the nitrite. Starting from this, the following experiments were undertaken to determine, if possible, the exact nature of the local action of the drug. It may be further premised, before detailing the trials, that very evidently the nitrite is not an escharotic in the ordinary sense of the term, that the past series of experiments show that it does not, like sulphuric acid, destroy tissues by taking from them certain ingredients, nor yet, like arsenic, does it so act on their vitality as to produce rapidly a distinct mass of dead tissue surrounded by a living inflamed border.

The experiments are as follows :—

Expt. 22.—12.20. Injected into left thigh of a moderate-sized frog a small amount of the nitrite. 12.30. Frog quiet on his back; acetic acid on left foot caused immediate active movements. 12.34. Still moves left leg. 12.40. No power of motion of left leg; acetic acid on foot elicits no response; on right foot gives rise to immediate general active movements; left leg extended, not rigid. 12.45. Muscles of left thigh responding to galvanism actively. 12.50. No response to galvanization of left crural nerve, except to a strong current; under stimulus of galvanism, frog struggled very much; injected more nitrite of amyl into left thigh. 1. Muscles of left thigh still respond to galvanism. 1.10. Strong galvanism of left crural nerve high up causes no motion in muscles supplied, although giving rise to active general movements, as though frog were trying to get away.

Expt. 23.—2.35. Cut cord of a small frog, high up; exposed crural nerves; then dropped on the left nitrite of amyl, which did not remain in contact more than ten seconds. 2.30. A weak galvanic current applied to left crural nerve, above point where nitrite of amyl rested, causes very slight movements of leg; a stronger current, quite active ones. The weak current to right crural nerve causes almost as much action as the stronger did to the left. 2.35. Put nitrite on left crural nerve for about half a minute. 2.37. Galvanic current applied to spine produces very powerful contractions of all the muscles of the body, except those of left leg; these do act, but not sufficiently to move the foot.

Expt. 24.—A small frog; tied very tightly around left thigh a ligature close to the body. 2.40. Injected some two and a half minims into left thigh and leg. 2.50. No power over left leg; no general symptoms of poisoning by the nitrite; a galvanic current, weak but strong enough to make itself felt in other parts of body, applied in the length of leg, produces no movements; a strong current induces decided muscular contractions. 3.7. Strong current only causes very slight movement in left leg. 3.15. Exposed individual muscles in left leg; strong currents produce feeble movements of muscles; weak currents show no action. The same is true of the crural nerve. Replaced nerve, and dropped on it nitrite. 3.25. None but the most powerful currents cause any response when applied to crural nerve or thigh muscles, and by these not enough force is excited to move even the toes, nothing but the faintest twitchings of the muscles; no constitutional symptoms manifest.

The object of the experiments just detailed was the testing of the local effect of the amyl salt upon the functional activity of the nerves and voluntary muscles. In the first of the series the nitrite destroyed the ordinary conducting power of the nerve with which it was in contact, before the

general system was very much affected, although the circulation was not interfered with. There was such a total destruction of the power of transmission, that powerful galvanic stimulation failed to awaken any response in the muscles supplied by the nerve. The other experiments were somewhat more specific. In Expt. 23 the nerve was isolated, and the amyl dropped on it. The result was a rapid loss of functional power, which was finally almost completely destroyed, the strongest galvanic stimulation of the nerve only exciting feeble twitchings of the muscles. The final experiment tested the effect of the nitrite both on the nerves and voluntary muscles, and I think shows that they are similarly affected, each suffering a gradual loss of functional power, which at last becomes almost extinct. It is an interesting point to determine whether the nitrite exerts a similar influence on the muscles of organic life, and in order to test this the following experiments were instituted :—

Expt. 25.—Opened the sternum of a small frog so as to show the heart; in doing this, I inadvertently opened abdomen so that the liver protruded; there was also a great deal of hemorrhage. 3.3. Dropped some of the nitrite out of hypodermic syringe on the heart. 3.5. Dropped some more of the amyl salt as above. 3.6. Heart beating very slowly. 3.10. Heart-beat practically stopped, a "white spot" of considerable size persistent at the apex. The systole very feeble, almost entirely auricular; frog seems pretty lively; gets over on his belly very quickly when laid on back. 3.13. Heart apparently acting a little, but never anything like emptying itself. Frog still able to get off his belly readily. Let fall two or three more drops on heart. 3.15. Respiration stopped rather suddenly. 3.20. Frog has just got off his back. Heart's action confined to the auricles. Ventricles white. 3.40. Has been making efforts at jumping.

Expt. 26.—Moderate-sized frog. 9.50. Dropped upon apex of heart, from a Wood's syringe, a little of the nitrite. Action of the heart immediately slowed. 9.59. Heart no longer beating. Pricking it awakens no response. 10.5. Frog still breathing occasionally, every now and then seized with a sudden, general, electric-like motion driving him forward. The movements are those of jumping, and sometimes the frog progresses half his length.

Expt. 27.—11.20. A frog's heart treated as before. Respiration active. Heart stopped. Acetic acid on leg caused active movements. Frog turned over from his back to belly; held his head up and looked quite bright. 11.25. Transfixion of ventricles causes a number of active auricular beats; the ventricles remaining passive. Respiration active. 12. Acetic acid on eye still causes reflex movements of head. Ventricles of heart white, bloodless; auricles distended with black blood.

These experiments prove that the nitrite of amyl applied locally to the heart, a muscle of organic life, acts in the same manner as upon the nerves and voluntary muscles.

In conclusion, then, I think the two series of trials show, in regard to the local action of the amyl salt: First, its action is somewhat gradual in its character, growing more and more profound as the time of contact lengthens. Second, at no period are there the slightest indications of exaltation of function, but at all times a steadily progressive lowering of the vital actions. Third, at no time are there any signs of irritation, such as pain or red-

ness. Fourth, all tissues, at least all of the more highly vitalized, are similarly affected.

Still another proposition, although not actually proven by any experiments yet detailed, may be added to the above. Fifth. If contact be not too transient, absolute death of the part is induced. Much that has been already given almost necessitates this as a corollary, but the following experiments may be looked upon as the actual proof:—

Expt 28.—Jan. 6. Pigeon received 2½ minims of the nitrite in breast, from whose action it apparently entirely recovers. Jan. 9. Killed with the nitrite; at point of previous injection is a largish spot or mass, in which the muscular structure is much softened, tearing readily with handle of scalpel into fibrous bundles which easily break. The colour of this mass is a dark grayish, instead of deep red, the whole looking somewhat like stringy boiled corn-beef. On Jan. 7 no soreness could be detected in breast.

Expt. 29.—Dec. 28. Adult pigeon. 8.24. Injected in left thigh 2 gtt. of nitrite of amyl. 8.35. Is unable to walk; left leg appears to be useless. 8.37. Now standing on right leg; left leg with its claws folded together and foot bent upwards so that the top of the foot rests on the floor. 8.56. Seems all right, except in regard to the left leg, which is entirely powerless. Dec. 29. Left thigh enormously swollen. The foot is drawn up, fully flexed, the toes all folded upward together, but not forcibly; when straightened, they return to their former state. Dec. 30. Pigeon found dead in the box this morning. Autopsy: Thigh tissues exceedingly softened, infiltrated with a dark grumous fluid, evidently altered exuded blood.

The ultimate method of action of drugs, the why and the how they influence the living cells, is in most instances utterly beyond our ken, and perhaps always will be. In the present case, however, there are some reasons for suspecting that it may be possible to make one step in this direction, to acquire a knowledge how one medicine acts. It has been stated by authorities that the nitrite of amyl has the power of checking oxidation in the air at ordinary temperatures, and one of the most obvious effects of it inside the body is the prevention of the change of colour of the blood in the lungs.

These two facts, if facts they be, suggest at once that the amyl salt acts upon the various tissues by checking oxidation, or, in other words, the chemical changes necessary to functional activity. In studying this, the first thing to be done is of course to determine whether the above assertions are facts indeed. For this purpose the following experiments were instituted:—

Expt. 30.—A piece of stick phosphorus of considerable size was taken and its surfaces freshened by the knife. It was then suspended in a small bottle, and in the room (65° F.) glowed very distinctly in the dark, and soon filled the phial with white fumes. The latter were now washed out, the phosphorus having been first removed, and five drops of the nitrite were then put in together with the phosphorus. The bottle was shaken so as to become filled with the amyl vapour, and it was found that the phosphorus no longer glowed or emitted white fumes. After standing some time, the bottle was placed in water 112° F., and in a little while the white fumes made their appearance. The process of washing, as above, was repeated, but before replacing the phosphorus, ten drops of the nitrite were put into the bottle. The latter still stood in the hot water, but the phosphorus did not glow or give off phosphoric acid vapour. When the

phosphorus was raised out of the bottle into the air, it instantly began to give off dense white fumes; but on its being put back, the development of these immediately ceased. It put one in mind of plunging a lighted taper into a carbonic acid bottle. The phial was now opened, and washed out so as to get rid of the amylic vapour. The phosphorus being replaced, the phial was stood in the hot water a few minutes, and then the combustible was found to glow in the dark like a live coal. Five drops of the nitrite shaken in the bottle instantly extinguished it.

Expt. 32—Venous blood was taken from the jugular vein of a cat nearly dead from suffocation. To this intensely dark blood a little carbonate of soda was added to preserve its fluidity, and then it was violently shaken in a large bottle. It immediately became light red, but not so scarlet as pure arterial blood; on the addition of a solution of the permanganate of potash, it became very bright red. Another portion of the same blood was now taken and treated as before with an alkali, after the addition of a little of the nitrite. On shaking, the blood changed its colour to the familiar brownish tint, but no amount of agitation would cause it to approach in the least towards the arterial hue, neither had the solution of permanganate of potash any more power. The cat was now hanged until dead. The body was opened immediately, and the black blood drawn from the large veins. With this the experiments just detailed were several times repeated, with similar results. After the addition of the nitrite of amyl, the blood altogether refused to become of a brighter colour.

Expt. 32.—A dog was killed with the nitrite. Blood was now drawn from the jugular vein, and some from the aorta; on being placed side by side, a slight difference in hue was detectable, the venous blood being somewhat darker. An alkali was now added to the dark blood, and the hue brightened slightly, but so little as to be scarcely perceptible. No amount of shaking in the air would affect its colour.

The first of these experiments seems to settle the point towards which it was directed, so that it is safe to consider the premise established that the nitrite of amyl checks oxidation outside of the body.

How far change of colour is a test of oxidation of the blood, is, unfortunately, not a settled question. That the change of hue from venous to arterial blood is owing to oxidation, is of course long since proven, but then it is well known that the addition of an alkali to freshly drawn dark blood will brighten its colour very materially, although not to the arterial point. This change is scarcely due to chemical alterations, but probably to a mechanical change of form of the blood-corpuscles, consequent upon the increased density of the serum, and it is therefore conceivable that a substance may prevent the change of colour of blood in the lungs without prevention of oxidation. It is, however, merely conceivable, and, I think, such influence on the blood coloration is an *a priori* reason for supposing alteration of oxidizing process, and throws the burden of proof upon those who would deny the latter.

The last two experiments show that the influence of the nitrite upon the blood-colour is not a secondary one, but is primary and independent of any action upon the nervous or other tissues.

The second premise, then, namely, that the inhalation of the nitrite checks oxidation of the blood, is a probable, but not a positive truth.

The blood being a living tissue, subject to the various laws of life, it

would seem only a logical deduction from the above premises that the nitrite of amyl, by virtue of its peculiar chemical power, checks oxidation everywhere when taken into the system, or, in other words, arrests tissue metamorphosis. As, however, the second premise is only a very probable, but not actually demonstrated fact, the conclusion must lie under the same shade of doubt.

Is there any way of removing this doubt and proving beyond all peradventure that the drug has the action spoken of, when inhaled? I think so. There are two measures of tissue changes, which separately might possibly not be convincing to all, but which together are capable of deciding positively the question, namely: Temperature, and the elimination of carbonic acid by the lungs.

These points I shall now discuss minutely, taking them in order, and commencing each consideration by details of experiment.

Expt. 33.—A large female cat. 3.40. Thermometer introduced through abdominal walls indicated 103¾° F. 3.43. 12 gtt. of the nitrite were put on inhaler, and it placed over cat's face. 3.48. Temp. 101½°.

Expt. 34.—Jan. 6. Adult pigeon. 4.25. Temp. 107½°. 4.26. Injected into breast 2½ minims of the nitrite. 4.36. Not as yet materially affected; temp. 106°. 5. Temp. 104°; no symptoms, save quietness. 5.40. Temp. 102°; no symptoms manifested. 6.15. Temp. 103½°. Jan. 7. Seems perfectly well; no soreness of breast manifested.

Expt. 35.—Jan. 9. Same pigeon as in last experiment. 12 P.M. Temp. when brought out of yard, 109½°. 12.20. Injected about 5 minims. 12.28. Walks very staggeringly, with head down; temp. 108°. 12.40. Perfectly conscious, but unable fairly to walk. 12.49. Conscious, quiet, breathing very deeply; temp. 103°. 1.5. Temp. 101°. 1.25. Seems more lively, but not able to walk; temp. 97°. 2.10. Temp. 95°; just had a sudden, very short, violent convulsion, in which he died.

Expt. 36.—Adult pigeon. Temp. in rectum 108¼°. 4 drops of nitrite given by inhalation. 1 min. Temp. 108¼°. 5 min. Temp. 106½°; perfectly conscious, but respiration very much disturbed. 6 min. Temp. 106°. 7 min. Temp. 107. 9 min. 5 drops inhaled. 10 min. Temp. 107½°. 14 min. Temp. 106½°; pigeon in violent convulsions. 15 min. Dead.

Expt. 37.—A young rabbit. Temp. 104°. 4.45. Injected into cellular tissue 5 minims of the nitrite. 4.50. Temp. 102°. 5.15. Temp. 99¾°. 5.35. Temp. 98°; seems more lively, struggling and fighting when temperature is taken. 5.45. Temp. 97¾°. 5.55. Injected 2½ minims into cellular tissue. 6.5. Temp. 97½°. 6.25. Temp. 98°; untied rabbit, he seems all right. 7.20. Temp. 99°. 7.45. Temp. 100.

Expt. 38.—Adult pigeon. Jan. 5, 3 P.M. Temp. 107¾°; injected 2½ minims. 3.27. Injected about 5 minims. 3.30. Making violent but fruitless efforts at vomiting. 3.35. Again retching; seems decidedly weak. 3.37. Perfectly conscious; unable to stand; temp. 105°. 3.43. Quiet; temp. 104¼°. 3.48. When laid on back, remains there quietly; temp. 104°. 3.49. Apparently reviving some; holds head up more. 3.53. Temp. 103½°. 4.3. Temp. 102½°. 4.10. Temp. 101¾°. 4.18. Temp. 101½°. 4.26. Temp. 101°; has been lying perfectly quiet on back for half an hour; eyes closed; muscular motion abolished, save that of the deep, laboured, frequent breathing. 4.35. Temp. 100½°; reviving; struggled against use of thermometer. 4.37. Quiet on back; put him out in the yard. 4.42. The cold appears to have revived pigeon; he is now walking in the yard; still unable, however, to raise his body from the ground. 4.43. Temp. 100°; returned to warm room. 5.5. Temp. 99¾°; able to walk staggeringly. 7 P.M. Seems all

right; temp. 102¾°. Jan. 6, 10 A.M. Seems lively, eating. 7 P.M. Found pigeon dead in box.

Remarks.—Death not owing directly to nitrite. Pigeon had been used before thermometrically, and the rectum was small, while thermometer was rather large, and had to be slightly forced in. When present experiment was commenced it was noticed that the vent was swollen, and for a space an inch and a half in diameter feathers had fallen out. Moreover, the nitrite was injected into the peritoneal cavity. At autopsy, abdominal cavity was partly filled with a fetid, dark, purulent liquid, and some blood. How much was due to local action of nitrite I do not know.

Expt. 39.—A young rabbit. 4.30. Temp. in rectum 102°. 4.34. Injected eight drops. 4.40. Temp. 100¾°. 4.45. Temp. 101½°; injected twelve drops. 4.48. Breathing hurried, panting; temp. 99¾°. 4.54. Temp. 99°. 5. Temp. 97¾°. 5.4. Temp. 97½°. 5.9. Temp. 97°. 5.10. Dead.

Expt. 40.—A small adult dog. 10 A.M. Cut the cervical pneumogastrics. 4.20 P.M. Temp. 99½° F.; bulb of the thermometer introduced into peritoneal cavity. 4.22. Injected 12 gtt. nitrite of amyl. 4.28. Temp. 99°; injected 12 gtt. additional. 4.34. Injected 20 gtt. 4.36. Temp. 99½°; very violent respiratory struggles. 4.42. Temp. 99°; put 12 gtt. on inhaler and gave to dog. 4.44. Temp. 98½°. 4.45. 12 gtt. put on inhaler, and inhalation continued. 4.46. Temp. 98°; inhaler taken away from dog, which was quiet and scarcely breathing. 4.47. Temp. 98°; dog revived. 4.48. 5 gtt. on inhaler. 4.50. Lying perfectly quiet, with slow, regular breathing; inhaler taken off his nose. 4.52. Temp. 97½°; inhaler replaced. 4.53. Temp. 97°; quiet, some tendency to opisthotonos. 4.54. Temp. 97°; gtt. 5 on inhaler. 4.55. Temp. 96½°; very quiet; took off inhaler. 4.57. Temp. 96¼°. 4.58. Temp. 96°. 4.60. Gtt. 5 on inhaler. 5.1. Temp. 95½°; apparently dying; inhaler removed. 5.3. Temp. 95°. 5.8. Dead.

These experiments appear to be sufficient to prove that the nitrite of amyl has a very extraordinary power of lowering the temperature of warm-blooded animals. Where the nitrite is administered rapidly, as by inhalation, this effect is not so pronounced as when it is taken more slowly into the system. Thus, in Experiment 36, although the pigeon was killed by the drug, yet the reduction of temperature scarcely amounted to two degrees. If, as will be shown in the course of the argument, the nitrite acts simply by checking the generation of heat, the reason of this is obvious. The body of the pigeon is protected by its thick coating of feathers, so that although there may be a partial arrest of the heat-making processes, yet there can be in a few minutes no very great change of temperature, because cooling takes place slowly. In the cat, whose outer coat is not quite so thick, the cooling takes place at a somewhat faster rate. Thus, in Experiment 33, over two degrees were lost in five minutes, although the inhalation was not pushed so as to endanger life.

The more interesting and satisfactory experiments, however, are those in which the nitrite was administered hypodermically. This class embraces Experiments 34, 35, 37, 38, 39, 40. These again may be divided into two sets, those in which a lethal dose or doses was given, and those in which the animal recovered, the first set embracing Experiments 35, 39, 40; the second, 34, 37, 38. In Experiment 35 death was delayed for nearly two hours after the injection of the poison, and there was a little before the last an abatement in the general symptoms, so that I thought the pigeon

would recover. With a temperature reduced some thirteen degrees below the standard, the bird was yet thoroughly conscious. In Experiment 39 the temperature was reduced in a rabbit five degrees.

Although the fact has not been actually demonstrated yet, I think it may be accepted as a corollary to the arguments and experiments of my paper "On the Influence of Section of the Pneumogastrics upon the Action of Purgatives and Emetics,"[1] that after division of the vagi nerves there is a lowering of the animal temperature. Yet in Experiment 36 the exhibition of the nitrite reduced some 5½° the temperature of a dog whose vagi had been cut six hours previously.

In Experiment 34 the temperature of the pigeon was reduced some 5½° without the production of general symptoms of any import. In this case the lowest point appears to have been reached seventy-five minutes after the exhibition of the drug, the temperature rising, however, only 1½° in the next half hour.

Experiments 37 and 38 are very interesting, as showing that the temperature continues to fall after the general symptoms commence to abate, or at least that the rise in temperature does not occur until some time after the general symptoms begin to subside. In each case the first sign of returning life was struggling against the use of the thermometer. In the first instance the mercury in the thermometer fell ½° after this, and it was not until an hour had elapsed that it recovered this fall, and at that time the rabbit ran about freely, although its temperature was 6° below normal. In the other case the heat of the bird fell ¾° after the first manifestation of recovery, and forty minutes afterwards had not regained this, although the pigeon was able to walk. Two hours after this the temperature had only mounted to 102¾°, 5° below normal. This experiment is also very interesting from the fact that the bird survived a reduction in temperature of 8° Fahr.

As the result of this series of experiments, the following conclusions are, I think, warranted: First. Nitrite of amyl, exhibited so as not to kill too quickly, lowers animal temperature very remarkably. Second. In non-fatal cases, not only is the subsequent rise of temperature very slow, but the lowest point reached is generally not until some time after the general symptoms commence to subside.

It is very difficult to perceive how such a fall of temperature could be produced save by the checking of oxidation of the tissues, especially in connection with the last noted fact. Moreover, direct proof of the strongest kind that it is so caused is forthcoming.

Since the earlier days of Sir Benjamin Brodie it has been known that under certain circumstances a great rise of animal temperature follows section of the cervical spinal cord. Now what is the cause of these symptoms?

[1] American Journal of the Medical Sciences, July, 1870, page 75.

The division of the cervical cord, as every one knows, produces universal relaxation of the small vessels below the point of division, from paralysis of the vaso-motor nerves. Is this relaxation of the vessels, and consequent general congestion, in itself enough to account for the subsequent symptoms? I think not. It is very evident that no more blood passes under such circumstances through any one part than before the section ; for the action of the heart is very greatly reduced, and the general blood-pressure immensely so. The blood-current really flows everywhere more slowly, and less blood is of course offered in any given time to any one part than before the division. I think, then, we must look elsewhere for a cause of the rise of temperature. The elaborate discussion of such a point would be outside of the scope of the present paper, but many physiologists at present believe that there is somewhere at the base of the brain a nervous centre which exerts an influence upon the nutritive acts, independent of the vaso-motor nerves. Supposing such a centre to exist, what would be the probable results of division of the cervical cord? Evidently a check to the normal nutritive processes, and a general loss of vitality in the tissues, or, in other words, loss of power to resist ordinary chemical laws.

What are the facts in regard to the alteration of the animal temperature after division of the cord? They may be summed up as follows:—

1. Section of the cervical cord is followed by an immediate lowering of the temperature.

2. If the animal be kept in a temperature of not over 65° or 70°, and be not wrapped up, no rise of temperature occurs.

3. If the animal be laid in a hot place, or be so protected that no heat can escape, and consequently an accumulation occurs, a rise of temperature soon becomes manifest, the rapidity of its manifestation bearing a direct relation to the heat of the place.

4. This rise in temperature is soon followed and accompanied by a most offensive putrefactive odour.

5. Chemical changes go on so rapidly after death, that the high temperature is in a remarkable degree maintained, and decomposition will be found to be far advanced in the course of two or three hours.

Granting for the moment the truth of these assertions, what are the natural deductions therefrom ? Evidently that at first there is a lessened activity in tissue change, and that if the animal be left to itself, this diminution of normal action continues generally until death ; but that if the temperature be in any way elevated a few degrees, the ordinary chemical laws becoming more active as the temperature rises, finally assert themselves, and before the brain and respiratory centres are overwhelmed, chemical changes are set up in the body, which partake of the nature of putrefaction. It is evident that the widely-dilated capillaries and the moving blood, carrying everywhere its load of active oxygen, favour extraordinarily such changes, and that the reason the temperature falls at all

after death is, that the circulation not continuing, the inner tissues are to a great extent cut off from a supply of the needful gas.

To sum up, then, the rise of temperature after division of the cervical cord depends upon rapid chemical changes provoked by a high heat and maintained by the free supply of oxygen. I think no possible fallacy can be found in the above argument, except it be in the premises, the facts upon which the argument rests. The proofs of these are to be found in the following experiments:—

Expt. 41.—A stout cat. Nov. 11. Temperature, taken whilst in open air, and cat was under influence of ether, 98½°. 10 A.M. Cord cut between 7th and 8th vertebræ. 10.10. Temp. 96½°; now taken to a warm room. 11. Temp. 97¼°; temp. of room 78°. 11.3. Temp. 99°; temp. of room 80°. 12. Temp. 99⅞°; temp. of room 80°. 12.30. Temp. 100⅛°; temp. of room 84°. 1.30. Temp. 100⅛°; temp. of room 82°. 2. Temp. 100°; temp. of room 80. 3. Temp. 99¾°; temp. of room 78°. 4. Temp. 99°; temp. of room 70°. 5. Temp. 98°; temp. of room 62°. 8. Temp. 99°; temp. of room about 60° 10 P.M. Temp. 100°; temp. of room about 70°. Nov. 12. 10 A.M. During night was exposed to a cool temperature. Temp. 88¼°; temp. of room 56°. 10.45. Temp. 89°; temp. of room 58°. 1.15. Temp. 90¼°; temp. of room 64°. 3. Temp. 90°; temp. of room 58°. Cat dead.

Expt. 42.—A stout female cat. Cord cut 12.48. Temp. before section 101°. 1.30. Temp. 99½°; temp. of room 74°. 2.30. Temp. 99½°; temp. of room 76°. 3.15. Temp. 100°; temp. of room 70°. 4.30. Temp. 99°; temp. of room 60°. 5.30. Temp. 97°. 8.30. Temp. 97°; temp. of room 54°. Cat died during the night.

Expt. 43.—A young dog. Nov. 21. Temperature 102°. 10.47 A.M. Cut the cord, and immediately removed dog to warm room, and very carefully wrapped him up in cotton. 11.10. Temp. 94½°; temp. of room 56°. Pupils pin-points. 12.10. Temp. 90½°; temp. of room 58°. 1. Temp. 90°; temp. of room 59°. 3. Temp. 89½°; temp. of room 56°. Pupils no longer pin-points, although much contracted. 4.30. Temp. 88°; temp. of room 56°. 5. Temp. 88½°; temp. of room 58°. 7. Temp. 90°; temp. of room 78°. 9.30. Temp. 94½°; temp. of room 70°. 10.30. Temp. 95½°. 12 P.M. Temp. 97¼°. Nov. 22. 7.30 A.M. Temp. 105½°. Room over 70°. Dog breathing regularly. 11.40. Temp. 106°. Twelve drops of nitrite of amyl were now placed in inhaler, and placed over dog's nose; he died almost instantly. 12.10. Temp. 105°; room about 75°. 1. Temp. 103°. 3.25. Temp. 94°. He now became so very offensive, he was thrown out into the cold.

Expt. 44.—9.30. Cut the spinal cord of an adult cat between 6th and 7th vertebræ. 9.32. Temp. 97½; cat taken and laid over grating of flue in hot-house. 10.15. Temp. 95°. 11. Temp. 97°. 12. Temp. 100°. 2 P.M. Temp. 108°. 3. Temp. 110°; the temperature of the air from the flue is now 102°, and doubtless has been so for last two hours, and at no time below 90°. 3.4. Cat dead; temperature immediately after death, in abdominal cavity, 111°. Before death the body exhaled a very strong putrefactive odour, drawing the blue bottle flies out of their winter hiding-places, and when opened, directly after death, the smell was scarcely supportable.

Expt. 45.—An adult cat. Dec. 29, 3.10. Cut cord low down in the neck. 3.30. Temp. 98°; cat was laid over the flue of green-house. 4.30. Temp. 100°; only a moderate fire. 5. Temp. 103°. 10 P.M. Still alive; odorous. Dec. 30, 9 A.M. Cat died in the night; whole house filled with the stench; body very far advanced in putrefaction. The smell in hot-house was entirely unbearable, only dissipated by a free and prolonged airing.

Expt. 46.—Adult pigeon. 10.30. Cut cord two-thirds through, between last cervical and first dorsal vertebræ, a very few moments since. Temp. now 96½°.

(Temperature unfortunately not taken before operation, but in another similar pigeon, kept in same cage, it is 108°.) 10.30. Temp. 106½°. 12. Temp. 105°. 3. Temp. 107°. 4. Temp. 109°. 4.30. Temp. 110°. 5. Temp. 111°. 5.30. Pigeon dead; was wrapped up in cotton in a room somewhere about 70° temperature. 6.20. Temp. 102°. 7.10. Temp. 96.

The above series of experiments, I think, prove the truth of my assertions. Without going into a more detailed discussion of what I think is self-evident, I would simply point out that assertion No. 1 is proven by nearly all the experiments; that assertion No. 2 is demonstrated by Experiment 41, and probably 42, although in the latter the animal was not watched to the very time of death, and therefore the evidence is not absolute; that assertion No. 3 is established by Experiments 43, 44, 45; that assertion No. 4 rests upon Experiments 44 and 45; and, finally, that assertion No. 5 is proven by Experiments 43, 45, and 46.

I think, therefore, that the conclusion previously arrived at must be considered as proven, and it follows, of necessity, that any substance which prevents this rise in temperature does so by checking oxidation, especially if it also prevents rapid decomposition after death. To test whether the nitrite does this, the following experiments were instituted:—

Expt. 47.—A female cat. Dec. 20. The spinal cord was cut, between 5th and 6th vertebræ, at 9.45 A.M. 10. Temp. 101½°; removed to hot-house and put over flue. 10.15. Temp. 102°. 10.45. Temp. 102°; six minims of the nitrite were now thrown into the cellular tissue. 11.15. Temp. 102°. 11.25. Injected five minims additional. 11.30. Temp. 102°. 11.45. Temp. 101½°. 12. Cat dead; temperature of the air from the flue now 105°; there can be little doubt but what it has been much the same for the last two hours. 6 P.M. Cat has been lying on grating ever since; no smell as yet comes from the body; allowed it to remain where it has been. 10 P.M. There is as yet no odour from the body. Dec. 21, 9 A.M There is now a considerable odour, but not enough to cause the house generally to be offensive.

Expt. 48.—A large male cat. 10.15. Divided the cord, between 6th and 7th vertebræ. 10.30. Temp. 103°; cat immediately removed to a hot-house, and placed over the flue. 11.30. Temp. 104°. 12. Temp. 101°. 12.50. Temp. 98°; was now placed in contact with a pipe containing water at a temperature of 125° F.; violent priapism. 2.30. Temp. 99°. 3. Temp. 100°. 4. Temp. 103½°. 4.10. Injected three minims of the nitrite of amyl hypodermically. 4.30. Temp. 102°. 4.45. Temp. 102½°. 4.50. Injected four minims of the nitrite into cellular tissue; a stream of air at about 90° was now rushing through grating, and the cat was replaced. 4.57. Temp. 101°. 5.10. Temp. 102°; air of flue 98°. 5.14. Injected five minims of amyl salt. 5.38. Temp. 102½°; temperature of air-current under and around him 106°. 5.50. Temp. 102°; priapism continues. The cat was now taken and placed where the temperature was 60°. 6.10. Temp. 101°. Injected five minims. 6.20. Temp. 100°. 6.30. Temp. 99°. 6.40. Cat dead. The cat was let lie until 10 P.M.; there was then no offensive odour.

These experiments must be compared with Experiments 44 and 45, with which they are exactly parallel, save only in the use of the nitrite. They certainly show that the nitrite of amyl has the power of checking both the rise in temperature and the rapid putrefaction after death, and consequently of checking the oxidation of the tissues, whence it follows, from what has gone before, that in the healthy body it does check, to a very great degree, tissue metamorphosis.

I think, therefore, without going further, I have actually demonstrated the latter fact; but if it be so, there ought to be a lessened excretion of carbonic acid from the lungs after the use of the drug. If there be such lessened excretion, it shows that my chain of experimentation and deduction has brought a true result. To test this, then, the following experiment was instituted:—

Expt. 49.—A large adult dog. Dec. 23, 1870. 3.30. Inserted in the trachea a tube containing a valve which forced the air to pass straight onwards when expired, but allowed inspired air to come through a lateral opening. Three Wolfe's bottles had been previously connected in the usual way for washing gases, and had been filled to a certain height with freshly prepared lime-water. The first bottle was now connected with the tube through which all the air the dog breathed was necessarily passing. In this way the expired air was forced to pass through the three bottles, and, bubbling up freely from the liquid in the last, passed out through a tube. In 2½ *minutes* there was a slight appearance of haziness in the third bottle. In 3½ *minutes*, very decided change in the lime-water in the last bottle. The air as it now passed out through the exit-tube of the latter was allowed to bubble throuh three drachms of fresh lime-water; in 10 *seconds* this was quite milky. 3.47. Injected ten minims of the nitrite into the abdomen. 4. Connected breathing-tube again with Wolfe's bottles, which contained a fresh charge, the same size as before. At the end of 3½ *minutes* the exit-tube of the third bottle was placed at the bottom of three drachms of lime-water, as before. It took 50 *seconds* to induce very slight opalescence. 4.20. The bottles having been thoroughly cleansed and recharged, were again connected with breathing-tube. The animal was breathing very deeply and rather slowly, but had not the power to force the gas freely through the bottles; a little judicious aid by external pressure during latter part of expiration remedied this, and as much air passed through as in either the other experiments. It required 5½ *minutes* for the lime-water in third jar to become milky. At the end of that time the air passing out of exit-tube was forced to bubble through three drachms of lime-water; it required some 40 minutes to produce opalescence.

The object of this experiment, which was repeated with similar result on a rabbit, was, of course, not to measure absolute but relative quantities, and it shows very plainly a marked diminution in the amount of carbonic acid exhaled after the administration of the nitrite.

The result previously arrived at required that the nitrite of amyl should lessen the excretion of carbonic acid, and as it does so, it seems to be fully demonstrated that the nitrite in the system arrests tissue metamorphoses, and that its action in doing this is a purely chemical one.

This being so, does it follow that it is simply in this method that the nitrite acts; that all the peculiar symptoms are the results of its chemical action? I think not; it is very possible that it may exert at the same time a chemical and a vital influence. What experiment or experiments are capable of settling this question, I cannot conceive. There appear to be some reasons for believing that much of its action may be due to its chemical power. Such an arrest of tissue metamorphosis would, I think, necessarily involve a lessening of functional activity throughout the system, and this is just what takes place when the drug is exhibited. Moreover, the peculiar local effects of the nitrite singularly agree with this

view. When applied absolutely unadulterated, it does not act as a quick, destructive poison. There is a gradual loss of functional activity, the rapidity of the loss depending upon the strength of the application. If the time of contact be not too long, perfect recovery may take place; but if it be protracted beyond a certain period, permanent death results. No signs of irritation are produced. It is very evident how this is just what would be expected of a poison exerting no influence but a catalytic prevention of tissue metamorphoses. As these changes lessened, functional activity would die away; and yet, if the dormancy of chemical action continued not too long, the part would awake again to life.

The organization and function of the muscle is so much less complicated and more robust than that of the nerve, that it is very conceivable, indeed a seeming necessity, that any drug acting by checking oxidation must, when taken into the system, affect more profoundly the latter than the former. But is it conceivable that the motor cells of the cord are so much more sensitive and readily affected than the sensory? Is it possible that, supposing the nitrite to act solely in the way spoken of, the motor system would be so much sooner and more profoundly affected than the sensorium?

I think it is conceivable, and it would appear to be in agreement with the well-known fact that in paralysis motion is generally much more affected than sensation.

Such speculation or reasoning as this, however, proves nothing, it simply brings the matter into the sphere of probabilities; and the only conclusion that I can arrive at is that the nitrite of amyl, by virtue of a peculiar chemical power, does check tissue metamorphoses, and it is possible that its physiological properties depend upon this.

PHILADELPHIA, Jan. 28, 1871.