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EXPERIMENTAL INVESTIGATIONS ON THE ANTIDOTAL AND REVIVIFYING PROPERTIES OF NITROUS OXIDE.

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IN the Journal of May 5th, I gave a resumé of the results of some experiments on dogs, which I had instituted for the purpose of securing more efficient means of preserving life, by resuscitating and sustaining the vital energies in cases of suspended animation from the asphyxia induced by the poisonous action of narcotizing agents, privation of air, &c., reserving the details for a future period, with the intention of prosecuting the investigation to a much greater length. A combination of circumstances, however, caused its suspension, and subsequently prevented its resumption. These details, therefore, I here present, with such remarks and deductions as seem appropriate.

To render these experiments more reliable, and the evidence therefrom as conclusive as possible, I adopted the following method of investigation, viz.—firstly, making a *test* experiment, by poisoning or otherwise asphyxiating the animal, and then employing the remedy for its recovery; and, secondly, a *comparative* experiment, which consisted in placing the same animal, by the same means, in a similar condition, though for fear of a fatal result, never permitting the asphyxia to become so great as in the former instance, and then trusting exclusively to the *vis vitæ* for a spontaneous recovery. The object of this comparative experiment was to obtain more correct data for the explanation of the phenomena presented, and to qualify the evidence afforded by the preceding, and, as far as possible, to exclude all sources of error, it was never instituted until after complete recovery from the effects of the latter, always allowing sufficient time for that purpose, generally from twenty-four to forty-eight hours.

EXPT. I. Carburetted Hydrogen.—A dog was confined in a close vessel, and the common illuminating gas, taken directly from the pipes, introduced therein through a suitable orifice. After a brief period (the time was not noted) he was brought fully under its poisonous influence, and when taken out and thrown on the floor appeared to be quite dead; his body and limbs being somewhat extended, indicative of the rigor mortis; innervation, respiration and circulation having apparently been

completely and permanently suspended. The nitrous oxide water was now injected into the bowels, and notwithstanding the profound asphyxiation, returning animation was speedily manifested by respiratory efforts, which rapidly increased to very strong and prolonged ones, similar to those produced by the direct introduction into the lungs, of the gaseous protoxide of nitrogen. This exalted respiratory action, however, subsided into the more tranquil and natural effort soon after the cessation of the injection. Also during and after the injection other evidences of the aroused vital excitability were presented by vomiting and purging, followed by the ordinary and more striking signs of returning animation. Consciousness was soon apparent, and manifested by the wagging of the tail in response to our calls, and some time before voluntary power had sufficiently and generally returned to permit the elevation and support of the body in an upright position. In less than twenty minutes the animal could, by coaxing, be induced to exert himself, though the locomotive efforts, at first, were very unstable, and not under full voluntary control. This power, however, rapidly returned, and before the expiration of one hour his energies were fully restored, and he was as actively and voluntarily exercising and eating as if he had not been subjected to any experiment whatever—not appearing to suffer in the least from the poisonous effects of the carburetted hydrogen. The quantity of the nitrous-oxide water used in this experiment, and introduced into the animal's body per anum, was about one quart.

EXPT. II. Comparative—Carburetted Hydrogen.—About twenty-four hours subsequently, the same dog was again confined and subjected to the poisonous influence of this same agent. The asphyxia was not, however, suffered to become so profound as in the former instance. After, therefore, an incomplete and partial asphyxiation, he was removed and exposed to the sole revivifying power of the atmospheric air and sustaining influence of the vital energies, but without avail, as they were not sufficiently powerful to restore him at all, and death was of course the consequence.

EXPT. III. Chloroform.—In this instance the asphyxia was produced by chloroform, using for that purpose about $f\frac{3}{4}$ j., by pouring it in the vessel previously used and confining the animal therein. This plan was adopted in consequence of the difficulty of controlling him sufficiently to exhibit it properly and to avoid its effects personally. The dog was soon reduced to a similar condition to that in the first experiment. Innervation was in complete abeyance, respiration entirely suspended, and although the heart's action was still perceptible, yet it was beating very feebly and frequently. The nitrous-oxide water was now injected into the bowels in small quantities at a time, until less than one quart was thus introduced. In a few moments after the commencement of the injections, indications of re-animation were apparent, differing, however, from those of the first, in the absence of the strong and forcible respiratory efforts previously exhibited (and which were probably dependent on the stronger injecting apparatus before used, and the consequent larger quantity and more rapid introduction of the surcharged fluid), they being in this instance more gradually and naturally increased.

They differed also in the existence of irregular or spasmodic movements, especially of the facial and masticatory muscles, with retraction of the lips, clashing of the teeth, &c. Complete recovery was, however, much more rapid, as in about eight (8) minutes the animal was capable of great voluntary effort, getting up and responding, by running, readily and actively to our calls, and in twelve or fifteen minutes was seemingly as lively and as well as before the experiment.

EXPT. IV. Comparative—Chloroform.—The same dog was again, on the subsequent evening, subjected to the influence of this destructive agent. The asphyxia was not, however, so completely induced as in the preceding, the desire being not to sacrifice the life of the animal, but merely to obtain comparative results. In this instance, therefore, the respiration was not suspended, but only reduced, though considerably below the normal point, until it became quite slow and imperfect. The cardiac action was also less feeble and frequent, though there was complete insensibility and deprivation of motion. On being removed and exposed to the atmospheric air, recovery gradually supervened, accompanied with similar irregular muscular movements. The time required for a return to consciousness was, however, twice as great as that in the preceding, in which the surcharged liquid had been used. The restoration of physical power was also much more protracted, and the subsequent voluntary activity much less, with increased languor and lethargy and greater disposition to quietude and repose during the remainder of the evening.

EXPT. V. Carbonic Acid.—In this case carbonic acid was used in the form of the fumes arising from the combustion of charcoal. The asphyxia was seemingly permitted to become too profound, as the usual attempts at resuscitation proved ineffectual and death resulted. This termination, however, appeared to result from the privation of the stimulus afforded by the nitrous oxide in consequence of the impaction of fecal matter in the bowels, as the injected fluid almost wholly escaped therefrom during its attempted introduction. This impacted condition was also more strongly indicated from the impression of the fluid against a solid body.

EXPT. VI. Carbonic Acid.—Another dog was similarly exposed to the noxious fumes of carbonic acid, which for greater convenience was obtained by the action of sulphuric acid on carbonate of lime; and to prevent the spasmodic closure of the glottis usually dependent on the attempted sudden inhalation of this gas, it was generated very slowly and in small quantities at a time. About one hour was thus consumed in bringing the animal fully under its influence. When taken out of the box, in which he had been confined, he was profoundly comatose; his body and limbs relaxed to flaccidity; respiration very slow, imperfect and labored; and a large quantity of frothy mucus and saliva was issuing from and filling his mouth. The asphyxia, though not so great as in the former test experiment, was sufficiently so to place life in a very precarious and highly dangerous condition, and excite just apprehensions of a speedily fatal termination. The injection of the nitrous-oxide water, in small quantities at a time, was now commenced, and continued rapidly.

until about two pints had been thus introduced, when complete recovery somewhat suddenly resulted, and in the short space of six (6) minutes of time, though animation had been gradually increasing from the commencement of the injections. The recovery was so perfect, and the activity and vigor so great, that he was immediately capable of vaulting and did vault out of a window, the sill of which was about twice as high as himself, being directed so to do from the manifest disposition to evacuate the bowels, the desire for which, immediately after recovery, was generally active in these experiments, though the passage was usually also involuntary during the production and existence of the asphyxia. Another frequent concomitant of re-animation was emesis. In less than twelve (12) minutes he had returned into the room in the same way (the distance from the ground to the window being still greater, and sufficient to require a somewhat unusual effort of a vigorous dog to successfully accomplish), and was eating as voraciously and heartily as if he had been deprived of food for a considerable period, and had never been, and especially so recently, in such an exceedingly critical condition.

EXPT. VII. Comparative—Carbonic Acid.—The same dog was again, on the following day, for a similar period of time exposed to the poisonous vapor of this gas, and insensibility produced, with the usual accompaniments of frothy saliva from the mouth, &c. The asphyxia was not, however, so complete as in the former instance, in consequence of the exhaustion of the material for generation of the acid, and the indisposition to urge it to the same extent. On removal and exposure to the sole influence of the atmospheric air, recovery gradually ensued, but consciousness was not apparent till the expiration of eight (8) minutes, and no general voluntary effort was made till the lapse of about twelve (12) minutes, when he regained the upright position. Locomotion was, however, very languidly performed, nor even during the remainder of the evening did he exhibit any of that animation, activity and vigor immediately displayed by him on the previous evening when the nitrous-oxide water was administered. The character of the respiratory efforts during and after recovery was also strikingly dissimilar in the two experiments. In the preceding one, in which the antidotal agent had been employed, there was no perceptible increase in rapidity, but the gradually returning, gentle and natural action peculiar to a due arterialization of the blood, which had thus been already seemingly effected by the introduction of the protoxide of nitrogen. In the latter, however, the deficiency of the atmospheric stimulus and elements, and the desire and necessity for them, were energetically manifested by the active and forcible panting and rapid respiration which were continued for some time, until this deficiency was supplied and the equilibrium restored; thus proving most conclusively in the one case, that the sanguinary chemical equilibrium had been previously artificially re-induced; and, in the other, that it was so much in abeyance in consequence of the deleterious exposure, and the deprivation and absence of the atmospheric constituents, as to require a rapid acceleration of the function of respiration to restore it, by speedily supplying them. Another feature in the latter case was, that, instead of purging, recovery was attended with vomiting.

This was probably in consequence of the diversion of the vital energy on the bowels by the injections in the former, while, from the absence of such extraneous influences in the latter, and more in accordance with the usual course, the excitability was first re-established in the stomach.

EXPT. VIII. Hanging.—Asphyxia was produced by strangulation from the suspension by the neck, taking care to avoid the organic lesion usually induced by the sudden forcible succussion of the neck from the falling of the body as in the ordinary process of hanging. This state of asphyxia unfortunately proceeded to a greater extent than was compatible with the existence and re-induction of animation, and death resulted. The time of suspension was about nine minutes.

EXPT. IX. Comparative—Hanging.—The animal in this case was suspended by the neck in all eleven (11) minutes, though not continuously, the loss of the other dog causing more care to be exercised; hence when the cardiac action began to subside too rapidly, experience teaching us that it would fail very suddenly, he was relieved to ascertain the character of the respiratory effort. At the time above specified, the indications of insensibility (subsidence of the heart's action and diminished power of respiration) appearing to be sufficiently strong, he was liberated, but on the removal of the rope respiration was so immediate and perfect that I concluded not to administer the nitrous-oxide water, but to make this the comparative experiment. Consciousness returned very speedily (in about two (2) minutes), but no great or general voluntary effort was successful till the lapse of nine (9) minutes, when he succeeded in getting upon his feet and had recovered sufficient power to walk about, yet very languidly. This debility and lassitude continued during the evening, as he evinced no desire for voluntary locomotive effort, but remained quietly reposing in a recumbent position. Before the experiment, however, he was remarkably vivacious and playful. Recovery was attended with the usual rapid and forcible respiratory efforts to speedily renew the due proportion of the atmospheric elements and equalize the chemical condition of the blood; also for some time subsequently with strong sonorous respiratory sounds.

EXPT. X. Hanging.—The same dog was again, on the succeeding evening, suspended by the neck for twenty-two (22) minutes in all, relieving him occasionally as before to determine whether sufficient vital energy remained to renew respiratory action. The temporary relief thus afforded does not, however, militate against the general result, but rather strengthens it, as this process more permanently and effectually debilitated the *vis vitæ* and proportionately destroyed the subsequent chances of recovery. By comparison these intervals were not more frequent than the former, and the whole time of suspension was twice as great. When the animal was finally liberated, innervation was abolished, respiration entirely suspended, and the heart's action imperceptible. In fact, these principal functions were so completely in abeyance as to simulate if not actually constitute that condition termed death. Under these unfavorable circumstances, the injection of the nitrous-oxide water was commenced, and after a moment of great doubt and uncertainty, to my surprise and

gratification, the heart, as if from a sudden impulse, resumed its action by a somewhat decided though labored effort, the impression of which was obvious to the eye by the succussion and tremulous motion communicated to the thoracic parietes. Immediately following the cardiac action, respiration was re-established, but somewhat peculiarly, appearing to be dependent solely upon, and limited to, the movements of the diaphragm, as the thoracic parietes were fixed and quiescent while the abdominal region was in lively activity. The medulla oblongata and other nervous centres were, however, soon fully aroused and influenced as the respiratory efforts speedily became more general, vigorous and prolonged, similar to, though not so powerful as those exhibited in the test experiment with nitrous oxide and consequent recovery from carburetted hydrogen. Consciousness was not so immediately manifested as in the preceding comparative experiment, yet general voluntary power was much more rapidly, suddenly and perfectly acquired, as the animal was able to, and did recover the upright position, and made active locomotive efforts in five (5) minutes of time, while in the former he could not succeed in these efforts, and then but feebly, till the expiration of nine (9) minutes. Again, in a few minutes after recovery he ran to and actively vaulted into his box (an ordinary packing box), the sides of which were higher than himself; an effort he totally failed to accomplish after repeated languid attempts on the evening previous. Another striking difference from the former, was presented in the entire absence of that subsequent panting, rapid, forced and sonorous respiration, indicative of the necessity and instinctive desire for the atmospheric constituents; the respiration in this instance immediately subsiding into and resuming its natural character on the discontinuance of the injections. There was not immediately on recovery that vivacity and vigor which was so strongly exhibited in the previous experiment with, and artificial resuscitation from, the influence of chloroform, but a somewhat similar disposition to dulness as in the preceding. This was, however, of temporary duration, as in a brief period he was again quite active and lively, though not so much so as before the experiment.

EXPT. XI. Drowning.—The dog was immersed in water for about three minutes, which unfortunately produced too decided asphyxiation and necessarily consequent death. There are good reasons for believing, however, that extraneous influences were in some measure operative in the production of this result, as the water was exceedingly cold, thus destroying more effectually excitability, and the absence of our usual assistance prevented the immediate and rapid supply of the nitrous-oxide water, hence it could not be exhibited sufficiently early and in proper quantities to insure success.

EXPT. XII. Drowning.—As before stated, believing that the previous fatal result supervened to some extent in consequence of the deficiency and too late administration of the nitrous-oxide water, this experiment was repeated, and although the animal was immersed but about one minute, asphyxia was so complete as to render abortive the usual efforts at resuscitation. The only explanation which appears at all reasonable for the powerful depression and sudden fatality in these two

experiments, is that the coldness of the liquid, in which the animal was immersed (the experiments being performed at that season of the year in which this liquid is at a very low temperature), connected with, though somewhat independent of, the asphyxia from the privation of air, produced such a sudden prostration or exhaustion of the vital energies from the shock (analogous to that from lightning, blow on epigastrium, &c.) on the peripheral extremities of the afferent nerves and thence communicated to the nervous centres, as to destroy so immediately and effectually all the vital excitability necessary to the continuance and restoration of life action, that no means or influence, however powerful, could arouse or induce sufficient energy to preserve the existence of the organic operations. Notwithstanding this explanation, it may be supposed, from the apparent deficiency of its influence in this form and in these cases, that the nitrous oxide is not applicable to such conditions; but it is believed that further experimentation will demonstrate its utility in this as well as in the other instances, and particularly if introduced in its gaseous form through the lungs, especially as in the process of drowning the exhaustion of the vital excitability is not usually so positive or immediate, its complete destruction or death generally being more gradual.

EXPT. XIII. *Hydrocyanic Acid.*—In this case f 3 ss. of the official prussic acid was poured down the dog's throat. Evidences of its effects were speedily presented by the failure of voluntary power, convulsive action and insensibility, during the inception of which vomiting was induced, and notwithstanding the supposed relief which this act of ejection would afford, the animal continued gradually sinking, and at the expiration of five minutes, conceiving that the effects were sufficiently strong, the injections of the nitrous-oxide water were commenced and continued till about two and a half or three pints (Oijss. or iij.) were thus administered. After eleven (11) minutes from the introduction of the poison, and six (6) minutes from the commencement of the injections, consciousness was apparent, and about two or three minutes subsequently voluntary power began to return, but not fully until the expiration of about twenty-seven (27) minutes. This return was much more gradual than in the former test experiments, and accompanied with partial stupor and dulness, and inefficient or irregular muscular efforts and movements similar to those displayed under the influence of alcohol. In about three quarters of an hour, however, the cerebral and nervous centres and energies were more fully relieved and aroused, and shortly after, in less than an hour, the animal appeared to be as lively and active as before the experiment, eating freely and greedily.

EXPT. XIV. *Comparative—Hydrocyanic Acid.*—On the following day the same quantity was administered to the same dog, with the production of similar effects, though not so rapidly or strongly manifested. In three minutes he vomited freely, and much more so than in the previous experiment, having had in his stomach, from the evidence thus presented, a very large quantity of ingesta, that ejected being twice or thrice as great as before. From this time improvement began, and in twelve (12) minutes there was speedy recovery.

EXPT. XV. *Compt. Hydrocyanic Acid.*—Thinking that probably the

quantity of ingesta and the perfect ejection of the poison prevented its effects from being more strongly experienced, the same experiment, twenty-four hours subsequently, was again repeated ; but notwithstanding the vomited matter was much less in quantity, the poisonous effects were still less apparent than before, as the animal did not lose his consciousness at all, and very little of, and for a very brief period, his power of voluntary motion.

EXPT. XVI. *The Same*.—Still conceiving that there might be some source of error in the deterioration of the acid, rather than that the dog had become so speedily accustomed to its influence, though suspecting this might be the true cause, nearly forty-eight hours were permitted to elapse before another attempt was made, when having procured some fresh acid, the same quantity was again administered, but without the slightest apparent effect of any kind. This proved most conclusively that the rapid depreciation of its effects was dependent on the increased power of the system to protect itself against this virulently poisonous agent. Dogs thus appear to become rapidly accustomed to the influence of this, and probably also all similar agents. In a practical point of view this is of some importance with respect to experiments upon them. This fact also renders the evidence afforded by the rapid recoveries in the test experiments stronger than before, as all the comparatives with these agents were secondary. Hence it is presumable that the differences were not so strongly marked as they would have otherwise been, particularly as in all of the latter the prospects for recovery, and that speedily, were much more favorable in consequence of the asphyxiation being much less than in those in which the nitrous oxide was administered.

EXPT. XVII. *Aconite*.—In this case f 3 ss. of the concentrated tincture of aconite was administered to a dog, which gradually exerted its influence on the system, especially on the stomach, vomiting being induced in nine minutes, with subsequently frequent efforts at such, attended with a somewhat copious discharge of white frothy liquid like saliva. In half an hour the animal was so fully under the poisonous influence as to be insensible and incapable of any movement, lying quietly on his side. Respiration soon ceased, but the heart was still beating, though very feebly and rapidly, and he was evidently *in articulo mortis*. At this time and in this condition of things, the injections of the nitrous-oxide water were commenced, and during the introduction of about one pint and a half (Oiss), respiration became established and the heart's action more decided and regular ; and after the expiration of three (3) minutes consciousness was apparent, and was manifested by the wagging of the tail in response to our calls, not having yet recovered the power of moving any other part of his body. This state of improvement continued for a few minutes, when suddenly he extended his limbs and body, and sank back again into his former insensible and dangerous condition ; yet by the rapid injection of the nitrous-oxide water he was again brought out of this state and restored to consciousness, and so continued for a brief period, with every prospect of ultimate recovery. But he soon relapsed, and was again revived by the injections of the surcharged liquid. Such strong prospects were presented in favor of his complete and ultimate recovery, that strict attention to his condition was temporarily

withdrawn (former experience having taught us that after the re-establishment of respiration and consciousness, perfect recovery was very speedy and certain), when he sunk so deeply and permanently that all efforts at resuscitation failed, and life was destroyed.

Several other experiments, with similar agents, as opium and empyreumatic oil of tobacco, were attempted, but in consequence of their ready rejection by emesis and the want of time to continue, we failed to get the animal sufficiently under the influence for the administration of the nitrous oxide; and, as before stated, circumstances at this stage caused the suspension of the investigation, and have since prevented its resumption and the previous presentation of the foregoing details. My intention is to resume these experiments, and also to review the preceding by the direct introduction into the circulation, through the lungs, of the gaseous protoxide of nitrogen; its influence in this form, thus exhibited, as is well known, being very powerful, and very rapidly manifested.

An objection to this mode of experimentation with water charged with this gas and thus introduced into the bowels, has been made under the erroneous view that a prominent source of fallacy or deception would arise from the stimulant effects of the water alone. To this I would answer, that the stimulant influence of this liquid is but transitory, and only stimulant when it is in momentary contact with vital surfaces, its prolonged application being powerfully sedative. Besides, the phenomena exhibited in recovery in the foregoing experiments, are in direct opposition to any such supposition, the character of the reestablished respiration and the general recovery being entirely at variance with the hypothesis that they were excited or dependent upon the mere or exclusive stimulant influence of water or any other agent, the nitrous oxide acting both chemically and vitally. In fact, the difficulty in cases of poisoning from the more permanent narcotics, like aconite, opium, &c., is, that the antidotal influence must be continued for a proportional protracted period, and the use of the nitrous oxide in this form of combination with a liquid is on that account objectionable, the quantity of water being too great for prolonged administration, and not supplying a sufficiency of the active agent. The aqueous influence is, besides, directly in opposition to that of the agent desired, it being a powerful sedative when retained for any length of time in contact with the living surface, as it must be when thus introduced into the intestinal canal, the great proportion of the water introduced in these cases being retained, as the subsequent alvine evacuations are comparatively consistent and very much less in quantity than the liquid previously extracted. Again, when there is sufficient excitability still remaining in the system to be acted upon and promote recovery, it alone may destroy and prevent such by causing an undue concentration of the nervous and vital energy on the bowels, to the exclusion of the rest of the economy, to get rid of, or expel the extraneous agent therein existing; and in this way it may prove additionally injurious by robbing the great nervous centres, and destroying the general vital equilibrium sufficiently to retard, or entirely turn the scale against, and prevent the possibility of recovery.

Therefore this liquid, in this combination and in such cases, seems to

be not only objectionable but positively injurious, except as a medium, its active ingredient being obliged to overcome both the sedative and depressive effects of this and the other influences. Hence in cases of poisoning from the permanent narcotics, it will be preferable to use the gaseous nitrous oxide, and introduce it directly through the lungs; while in those cases of suspended animation from the same class of agents having but a temporary influence, and in other analogous conditions from the privation of air, &c., the surcharged liquid would be applicable; and as shown in the preceding details, generally sufficiently powerful to induce and insure recovery notwithstanding the sedation and vital diversion produced by the liquid. In all cases, however, the former would be preferable; but as the nitrous oxide in its gaseous form is not so conveniently obtained, the latter might be employed either exclusively, or till the former could be procured.

In consideration of these facts, therefore, the following conclusions seem justifiable—viz.:

Firstly, That nitrous oxide or protoxide of nitrogen is a powerful and direct arterial, nervous and cerebral stimulant.

Secondly, That it exerts a direct chemical influence on the blood, by supplying the essential elements for the arterialization of that fluid, and to a certain extent by inducing that process, thus producing in it similar changes to those effected by the atmospheric air, as proved by the effect on, and character of the reëstablished respiration.

Thirdly, That it is in these various modes antidotal to the effects of certain narcotizing agents.

Fourthly, That where vital excitability is not completely destroyed, this remedy has the power of sustaining and increasing it rapidly, and sufficiently to preserve life in numerous instances in which it would otherwise be destroyed.

Fifthly, That it will reëstablish life action even after all the usual evidences of its existence have failed, such as innervation, respiration and circulation; provided, firstly, that the muscular contractility, or vis insita of the heart and other tissues is not lost; secondly, that the blood has not coagulated or deteriorated to such an extent as to be insusceptible of arterialization and revivification; thirdly, that there is no organic lesion of any vital part sufficient of itself to prevent recovery; and fourthly, that innervation is still susceptible of reëxcitation.

In conclusion, I will state that in my last paper on the therapeutic applications of this agent in the form of surcharged liquid more especially, I inadvertently omitted to mention a peculiarity in its physiological action, which, however, might be anticipated from its influence over the contiguous renal apparatus, viz., its stimulant effect on the generative organs, thus operating as an aphrodisiac. This effect, like its diuretic, is not, however, constant or universal; yet, nevertheless, its application may prove useful in atonic states of this apparatus. With respect to its favorable therapeutic influences and applications, therein detailed, I have no reason to change my views, further experience and reflection only confirming still more strongly all former observations and impressions.

Philadelphia, Nov. 5th, 1852.