Amory (Robt.)

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ITS PHYSIOLOGICAL ACTION, AND ITS USE IN TETANUS, WITH EXPERIMENTS.

Communicated for the Boston Medical and Surgical Journal

BY

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ATROPINE; ITS PHYSIOLOGICAL ACTION, AND ITS USE IN TETANUS.

Having had an opportunity of trying two well-known and violent poisons in some cases of tetanus, I thought it might be interesting to publish some account of the effects of these remedies, and must ask for a brief space in your Journal.

Two forms of tetanus are recognized, the idiopathic and traumatic; names which indicate their supposed origin, but which reveal our ignorance of the pathological conditions under which they may occur. Tetanus may follow a slight injury, or some more serious wound. Dr. Dewees, in the *Medical Gazette*, considers* "that in idiopathic tetanus a very frequent first step is sudden arrest of violent perspiration; and that certain reflective acts may be thrown upon some disordered or impressible cerebro-spinal centre, causing convulsive mus-

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*Dec., 1862.

cular manifestations ; " and goes on to show " how these repressed excreta act specifically, abrogating or over-exciting the nervous functions, thus producing all sorts of incurrent disorders." If this be so, the same effects which cause the disease, unless modified by some remedial or restraining action, tend to increase its manifestations. In accordance with these principles veterinary surgeons try by tremendous doses of aloes and other purgatives to relieve the system of excreta, and allow the animal to recover. Sometimes this treatment meets with success, especially in the form called idiopathic, but, generally, the prognosis is made (and correctly) that the animal will die.

The animals generally die from asphyxia or exhaustion, and in frightful convulsions. It would seem from what is known of the pathological condition produced by tetanus, that the sympathetic nervous system is in an abnormal state, that of continued excitability, in which there is spasmodic contraction of the capillaries as well as of the voluntary and involuntary muscular system.

The pathological investigations made after death from tetanus, throw but little

light upon our knowledge of the disease. The results are very often contradictory or doubtful, and have often been explained by a reference to the position of the body examined, in which extravasated blood was shown to gravitate towards certain points.

Chloroform has a restraining influence upon the tetanic spasms, but they recur as soon as the inhalation ceases. Before speaking of Belladonna as a remedy, I should like to notice some of its physiological effects.

Atropine seems to be poisonous to all animals, provided it is received and retained in a sufficient quantity in the blood. Herbivorous animals appear to eliminate the poison very rapidly, and both belladonna and atropine, in doses sufficient to kill several men, have been borne by goats, rabbits, guinea pigs and sparrows, with no inconvenient symptoms beyond dilatation of the pupil and diarrhœa. In carnivorous animals, however, its poisonous effects are very manifest, even in minute doses. Two milligrammes ($\frac{1}{36}$ of a grain) produce cerebral trouble and serious accidents in man. If, however, fatal poisoning by this drug occurs, it follows very soon after its admin-

istration, as the drug is very rapidly eliminated.

Slight doses accelerate the capillary circulation, reducing the calibre of the arterioles, to 1-3 or 1-2 (by micrometer) their normal size. This retraction of the blood-vessels is not uniform, but the walls of the arterioles become unevenly contracted in undulations.* The diminution of calibre coincides with the acceleration of the circulation. Hayden† has concluded that this constriction is due to reflex action. For in cutting the integument of a frog's leg this same phenomenon occurs. The sciatic nerve contains some filaments of the sympathetic system also, so that we must not be surprised to find that the constriction produced by this operation is not as marked as that caused by the atropine. Hayden also notices the coincidence of accelerated circulation *with* the constriction. These effects on the circulation continue but a short time, and the arteries soon return to their primitive condition. The veins do not diminish in volume.

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*Wharton Jones, Med. Times and Gazette, 1857, p. 27.
†Dublin Quarterly Jour. of Med. Science, Aug. 1862.

If, however, the dose be larger, the circulation slackens, and then completely stops. All the vessels are gorged with stagnant blood, a perfect hyperæmia results. This stasis commences in the venules and then ensues in the capillaries and arterioles. The blood stops in the artery only after the stasis occurs in the capillaries. These same effects occur, also, when the drug is applied to a portion of the circulation under microscopical observation.

The effect of the smaller dose is exciting, and its local application seems painful to the frog. In the denuded skin of man the pain is compared to that produced by a hot iron.

In larger doses it seems to paralyze the vaso-motor system; the flesh has a blood-red appearance, and with the microscope is seen to be in a state of hyperæmia. These peculiarities have been also observed in the mesentery of the rat, and in the ear of rabbits. Meuriot * would then consider atropine as a vasculo-cardiac agent, and to his memoir, mainly, I am indebted for much of my knowledge of its action.

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* Paris, 1868.

With regard to its qualities as an anæsthetic, Meuriot affirms that superficial neuralgia derives much benefit from atropine if applied topically. In small doses, however, exhibited by the stomach, I know of three cases of nervous headache which have been often and decidedly relieved by belladonna. In fact, homœopathists prescribe their sugar-plums of belladonna for all headaches of this kind, and their success is notorious.

The inconvenience of hypodermic applications of atropine is the severe pain caused by its contact; which, as I have already said, has been compared to that caused by a hot iron. This may persist for two or three days, and is supposed to be owing to the trouble in the capillary circulation of the skin. We see the same conditions in severe chilblains. This drug never destroys sensibility, but may induce analgesia.

Nerves in contact with atropine preserve their excitability, and the contact of the electrodes causes contractions, reflex movements, and cries.

In frogs peripheric sensibility is diminished, but this is not the case with other animals experimented upon.

Its action upon the spinal cord as compared with strychnine and bromide of potassium is peculiar.

Strychnine produces an exaltation or exaggeration of the excito-motory functions dependent upon this central organ. The bromide diminishes the activity of these functions, whilst atropine has an intermediate action, but with a tendency to their increase rather than their diminution. The effects are in proportion to the dose administered, large doses tending to a stasis, the smaller to a diminution of blood in the spinal meninges and nerve-substance.

It would seem strange (if the foregoing summary of the physiological action of belladonna be correct) that this drug should be recommended in tetanus. If in this disease there is congestion of the nervous centres or peripheries, we shall be increasing rather than diminishing the determination of blood to the capillaries and to the spinal cord, unless we should use much care in apportioning the dose ; as we have seen that it is *only* in small quantity that atropine tends to diminish the amount of blood in the spinal meninges and nerve-substance. But it would be a very difficult matter to

determine an amount which in every person should produce the same effect. It would be only by carefully watching that we could produce a modification of the tetanic spasms and keep the action of the drug within the limit. Thus, much caution would be required in the application of the drug to those cases in which we wished to produce oligæmia or hyperæmia in the tissues of the body.

Oligæmia of the brain resulting from a deficiency of blood-globules acts in the same way as a section of the spinal cord, or an exaggeration of the excito-motor power, and therefore we must beware, lest in avoiding Scylla we fall into Charybdis.

It may be said, that the physiological action of drugs upon man and animals is not subject to the same laws, and, frequently, does not produce the same effects. This cannot be exactly true with this drug, as its action, so far as at present known, is the same upon man and animals; provided that the drug has entered the venous circulation in a form sufficiently concentrated. Some animals can so rapidly eliminate it, that only a quantity insufficient to produce toxical effects, is present in the capillary cir-

culation at one time, and hence their apparent immunity to its baneful action.* That the urine of a goat fed with belladonna leaves was injected into the stomach of a dog with fatal results, and that his urine caused dilatation of the pupil in another dog, is a very curious fact; and shows that a dose which a dog cannot quickly enough eliminate may remain in a goat's bladder, unabsorbed into the capillary circulation. If the urethra of the goat had been tied up, *imbibition* of the poison and prevention of its elimination would probably have produced a different result.

†The action upon the pupil results from a destruction of the excitability of the fifth pair of nerves. Electrization, and the action of certain excitors of muscular contractility (myotiques) upon atropinized eyes seem to show that the sphincter of the iris will preserve its power of contracting. But the feeble action that is observed from the exhibition of atropine after the section of the great sympathetic, and the different results obtained from electrization of eyes under

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* N. Y. Medical Journal, 1868, p. 278.

† Meuriot, sur la Belladonne, Paris, 1868, p. 137.

the influence of atropine, depending on the destruction or integrity of the sympathetic nerve, *seem* to indicate that this drug has an exciting action upon the terminations of the sympathetic. The demonstration is also given in the effects of atropine on eyes of which the motor occularis communis is completely paralyzed, and experimentally on animals when the sphincter iris is destroyed. Belladonna is not a hypnotic but possibly a stupefying narcotic. In small doses it induces agitation and insomnia, in large doses stupor, in intermediate doses dreams and general tremblings.

The effect upon the temperature has been found by numerous observers to be an increase of from 1-2 to 8-10 of a degree centigrade.

Atropine causes dryness of the skin and of the mucous surfaces, probably from a reabsorption of the liquids on account of the increased rapidity of the circulating current. Thirst from atropinization may be thus accounted for. The local action of the drug upon the mouth produces salivation. As the peripheric sensibility is also diminished, the secretions are decreased. In this state acetic acid placed upon the tongue does not salivate.

Small doses augment the pressure of the blood in the kidneys, large doses diminish the pressure, and thus, according to Bernard,* in the former case we obtain diuresis, and in the latter suppression of urine.

M. Behier † recommends for tetanus subcutaneous injections of the valerianate of atropia along the nape of the neck, and gives the following formula:

℞. Atropiæ valerianatis, .30 = grs. v.
Aquæ, 30.00 = ℥i.

Of this 5 drops to be injected every two hours. Pescheux (Verneuil) reports a case of tetanus relieved by subcutaneous injections of atropine sol. 1-100. Three-fourths of the syringe of Pravaz (3 grammes) were injected, in doses of 10 drops at a time. Symptoms of atropic poisoning (slight) occurred, and the tetanus disappeared.

ATROPINE AS A REMEDY FOR TETANUS.

On the 2d of April, 1868, I received a request from Dr. Stickney to visit a horse suffering from an attack of lockjaw, in a stable in my vicinity. On inquiry I found

* Lecons sur les Liquides de l'Organisme, 1859, tome II. p. 155.

† Dict. de Med. et Chir. Paris, Baillière et fils, 1866, tome IV. p. 86.

that the animal had been ailing for a few days, and that sulphur in large quantity had been given by the hostler in charge. He had not eaten anything since Friday, and had had but little discharge from the bowels or bladder. The facial muscles and those of the neck were very rigid, though elsewhere they were but slightly if at all affected. The animal could not open his mouth, nor could it be forced open. Dr. S. had ordered him small doses of prussic acid by the rectum every two hours.

Three days afterward I was told that Dr. Stickney had given me the liberty of resorting to any expedient that might be suggested, and I went again to see the horse. He was respiring rapidly and was in much distress, and the spasmodic contractions were more extended and severe. The eyes were half closed.

It is unnecessary to give more details. The peculiarities of tetanus are well known and easily understood from the descriptions recorded in standard works. The disease had increased very rapidly during the twenty-four hours, and now there was no muscle which was not tense in a greater or less degree. Several methods occurred to my mind to try as alleviations of the

spasms, as a cure was now out of the question. I had in a previous case tried hydrocyanic acid unsuccessfully. Strychnine and electricity I thought of, especially the latter. However, upon reflection I considered it advisable to ask Prof. Brown-Séquard, what drug it would be advantageous to experiment with. Several drugs were discussed, but the one he preferred was atropine, and, at his advice, I publish the record of the experiment. I procured one-sixth of a grain of the sulphate of atropia, which I dissolved in two drachms of water.

At 7 P.M., on the same day, I injected subcutaneously, according to the advice of this eminent physiologist, this solution in three different doses (with ten minutes interval between each) under the fore-shoulder. The animal was under the influence of chloroform for ten minutes before the first injection was made, in order to prevent any serious agitation.

In half an hour after the last injection he discharged a moderate quantity of urine; and, as he appeared much easier, I left him for an hour. On my return I found him still more comfortable, and again three hours after the hostler told me that he had been lying down and had got up again; the

muscular spasm was a little reduced, especially in the hinder part of the body.

On the next morning, the man showed me about a hatfull of soft fæces that the horse had passed during the night, and said that the bedding was well soaked with his urine. I then obtained one grain more of the sulphate of atropia, which I dissolved in eight pints of water. I directed that one pint of this solution should be injected into the rectum every hour, and that between the first and second doses they should inject some milk and water. The first injection was made at 7 P.M. At 3 o'clock the man came down and said that they had succeeded in opening the horse's mouth, that he was in a great sweat, and that he had been trying to eat his bedding; he wished to know what he might give him to eat. I directed first that the medicine should be omitted; second, that they should boil some carrots and squeeze their juice into a pail of water, put in this a handfull of bran and a wine-glassful of alcohol; that while this was preparing they should give him some water if he could drink it. In an hour afterwards I found him bathed in a profuse sweat, the muscles surprisingly relaxed, and the animal drinking water of his

own accord from a pail. His mouth was partially open, and the eyelids so drawn up that with difficulty could I see the iris. He had drunk some of the liquid food, prepared as directed, but did not like it, probably on account of the alcohol. So I was ordering some other mixture when Dr. Stickney appeared. He was much surprised on seeing the change in the horse, and we were both sanguine (too much so as it afterwards proved) of the animal's recovery. He said that he had never seen so sudden a change in tetanus in a horse. I asked him to prescribe the diet, and soon we left. On my return, three hours after, the animal had passed a large amount of fæces, and much urine. His mouth was still open, and the muscles much relaxed, but *not* so much as on my previous examination. I therefore ordered another pint of the diluted medicine to be placed in his pail of water. He had just drunk a quantity of oatmeal gruel, and had lain down and got up again several times. Still, as the spasms were apparently stronger, I considered it important to give another dose of atropine. Two pints had been injected, making a quarter of a grain of atropine introduced into the rectum. At 9 o'clock the next

morning (Wednesday, 7th) I found on inquiry that the horse was dead. On an investigation I found that at 5 o'clock a noise of kicking was heard in his stall, and the man on going down found the animal throwing his head round while lying on his side, kicking violently with all four feet, and bathed in sweat. Evidently, from his description, the horse was in a convulsion, which lasted twenty minutes or so, after which the animal expired. He said that the muscles were not very stiff, not so much so as before the atropine had been given.

A natural question is suggested, whether this was a case of traumatic tetanus? There was no proof that it was. The horse had been lying idle all winter in a cellar stable, and had been shod four weeks before his attack. He had been exposed in a paddock to our last severe snow storm, and shortly after began to ail.

ATROPIÆ VALERIANAS.

June 27th, 1868.—Tetanus. Colt 1 year old. This disease manifested itself June 26th, P.M., two weeks ago, after castration.

This morning the long muscles of the neck are distinctly marked by tension of their fibres. The membrana nictitans is drawn

over the eye when a hand is placed near his head. As in the last case there is hyperæsthesia of the skin. The hind legs appear stiff, though the individual muscles are not particularly tense. The wound in the scrotum appears well. There is no swelling of the sheath or neighboring parts. There is a slight running of serum from the scrotum down the legs (this I understand is perfectly normal, and another *healthy* colt, castrated at the same time, shows the same phenomenon. Respiration appears easy, and the animal can chew grass slowly, and drink water, though the latter is swallowed more noisily and with more difficulty than is usual with horses. Fæces have passed recently and appear moist. The man in charge *says* that he has passed urine, but of this I have my doubts. The man is not to be relied on, as he is apt to speak as he thinks he is desired.

I administered subcutaneously a solution of atropiæ valerian., containing a little less than 1-24 gr. The puncture apparently gave a good deal of pain, though he did not seem to mind the injection of the fluid. He afterwards ate and drank as before the injection. The pupil was not dilated half an hour after the injection, nor was there any

amelioration. I left directions for 1-50 gr. to be injected per rectum two hours after, and 1-24 gr. two hours after that, and another dose at 9 or 10 P.M.

The directions were carried out and a large amount of the drug was administered per rectum.

The physiological action upon the *iris* was very marked, but the disease had gained ground and the animal died three days after I first saw him. The colt had taken 2½ grs. of the drug in all. In this last case no effect upon the tetanic symptoms was observed. The disease increased, in spite of the drug, and this even while the system was showing the physiological action of this drug.

Perhaps it may be of interest to the readers of this article to give the conclusions regarding the action of Belladonna arrived at by M. Meuriot in the *brochure* before alluded to:

I. "Atropine is the active principle of belladonna, and assumes all the properties of this solanum.*

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* In this family are also included tobacco, henbane, datura, stramonium and the dulcamara; as also the tomato, egg-plant, potato and capsicum. Prof. A. Gray, p. 456.

II. "The intensity of its action varies with the species of animals. Herbivora are less sensible to its action than the Carnivora. In man its poisonous action is the most violent; but no animal is exempt.

III. "Its action also varies with the dose employed; for small doses accelerate the heart's pulsation and augment the vascular tension; poisonous doses diminish the tension and modify the cardiac pulsations.

IV. "Belladonna is a vasculo-cardiac poison, in the classification of M. Sée. Its action produces especially the innervation of the heart and of the vessels.

V. "The varied phenomena produced by Atropine depend mostly upon its primordial and elective action, or are due to the elimination of the poison.

VI. "Atropine acts upon the heart through the pneumogastric nerve, whose peripheral extremities are paralyzed. It augments the frequency of the cardiac pulsations.

VII. "In a small dose it augments the tonicity of the vascular muscles; in a poisonous dose it diminishes, and even destroys this; whence the application of Belladonna to epilepsy, in which the access seems to be due to modifications of cerebral circulation.

VIII. "The variations of the arterial tension are subordinate to the state of excitation or paralysis of the muscular coat of the vessels.

IX. "In small doses atropine accelerates the respiration; in poisonous doses it diminishes its frequency.

"The acceleration of these movements depends upon the excitation of the respiratory centres; the consecutive retardation, upon a paralysis of the extremities of the vagi nerves; whence its application in the treatment of asthma.

X. "Atropine in a therapeutical dose, increases the activity of the excito-motory functions of the spinal cord.

"In a poisonous dose it exaggerates the reflex power till it may produce convulsions.

XI. "Atropine *always* produces agitation, insomnia, delirium, and in a poisonous dose, coma; it is not at all a narcotic.

XII. "Atropine is eliminated by the kidneys, by all the mucous surfaces, and sometimes by the skin of man. Its elimination is always rapid; so that its action is of short duration.

XIII. "The effects due to elimination are numerous, viz.: redness of the mucous surfaces and of the skin, frequent desire of

micturition; colic; anal and vesical tenesmus; profuse sweat, diarrhœa, &c.

XIV. "The redness and dryness of the mucous membrane explains aphonia, dysphagia, dysuria, &c.

XV. "Not only are all the secretions of the mucous membrane diminished, but there may be also, on account of the activity of the circulation, a rapid reabsorption of all the liquids which have exuded from mucous surfaces or from wounds; whence its advantage in exaggerated secretions, and its effect upon coughs, &c.

XVI. "Atropine, applied locally to the tissues, produces an activity of the capillary circulation, and, in a considerable dose, true hyperæmia and sanguineous stasis.

"Angina and erythema produced by belladonna are analogous to the inflammatory process.

XVII. "The modification of the urinary secretions are dependent upon the variations of the arterial tension.

XVIII. "Belladonna is not a paralyzing agent to the smooth muscular fibres; it produces no phenomena of paralysis except in a very powerful dose, and in these cases it follows exaggerated contractions; thus it is of benefit in incontinence of urine and

of the fæces, in paralysis of the bladder, in constipation, irreducible hernias, &c.

XIX. "Atropine has no elective action upon the sensitive nerves. Its local application is always followed by acute and persistent pain. Atropine acts only upon nerves in a state of hyperæsthesia and often determines analgesia, but it should be applied directly upon the seat of pain (les nerfs affectés).

XX. "Small doses of atropine augment, toxical doses diminish, the temperature.

XXI. "Atropine, especially, possesses the property of causing dilatation of the pupil, and this is its most constant and persistent effect.

"It paralyzes the terminal branches of the third pair of nerves; this is the only fact well shown by experimental physiology, in the study of the hyoscyamus also. (Gubler).

"To this paralysis of the ciliary branches of the nervous motor ocularis communis is attached the paralysis of the muscle of accommodation.

XXII. "Certain experiments and several considerations that have been made public by the author, tend to show some exciting action upon the sympathetic nerve or upon the *dilatateur*. However, a more vigorous demonstration is still essential." *

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* Meuriot, op. cit. p. 138, et seq.