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THE PHYSIOLOGICAL ACTION

OF

Belladonna and its Alkaloid, Atropia,

ON THE EYE.

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THE PHYSIOLOGICAL ACTION OF BELLADONNA AND ITS ALKALOID, ATROPIA, ON THE EYE.

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It has been known, for a very long time, that when belladonna was taken inwardly in large doses, the pupils of the eyes would become dilated and the vision affected. Charles Himly, taking advantage of this fact, made a local application of it in the eye, to prevent the adhesion of the iris to the anterior capsule of the lens, and occlusion of the pupil in cases of iritis. C. v. Graefe, the father of the great oculist A. v. Graefe, followed up the same idea, and applied it in scrofulous and rheumatic inflammations of that organ. Also Prof. M. Langenbeck used it, with success, to dilate the pupil in cataract operations, to prevent injury to and adhesions of the iris, as well as to combat any inflammation arising from the operation.

Since this first introduction of the use of belladonna, locally, in the eye, it, or its alkaloid, atropia, has become the sovereign remedy in most of the diseases of that part, just as opium

or its alkaloid, morphium, is the sovereign remedy in most cases of pain.

In former times, a decoction of the leaves was applied over the eyes; then the extract was made from the plant and the root, and it came into use by rubbing it over the eyebrow and on the temple, as well as dissolving some in water, and dropping it in the eye; but in the present time the alkaloid, or active principle, "atropia," has been extracted, and is now almost universally used.

Atropia, being almost insoluble in water, is made into a sulphate by dissolving it in ether or alcohol, and adding, very carefully, sulphuric acid until saturation only, without excess of acid. It is crystallized by evaporation, and washed from excess of acid by ether or alcohol, then re-dissolved and re-crystallized until perfectly pure.

This sulphate of atropia is easily soluble in water, and has become one of the most important remedies, not only to the ophthalmologist, but also to the general practitioner, for hypodermic injections, etc.

The use of this salt in solution, as an eye wash, has become so general, that almost everybody prescribes and recommends it for every and all troubles of the eye. Druggists prescribe it over their counters continually. It is not to be supposed that such persons know anything of its action, whether good or bad, upon the eye; but there are, no doubt, many physicians, who, following the course recommended

by some writer or friend who has found it beneficial in some cases, prescribe, daily, collyria and ointments containing either belladonna or atropia, to dilate the pupils, or to relieve inflammation, without knowing its true physiological action on the eye.

It will be my pleasure, therefore, to lay before you this afternoon, in brief, the results of some of the anatomical and physiological researches upon this subject that have been brought to light by the great workers of the day, among whom I may mention Müller, Manz, von Graefe, Donders, Bowman, Arlt, Helmholtz, Stellwag, Leber, Krause, Henle, Kölliker, Luschka, etc.

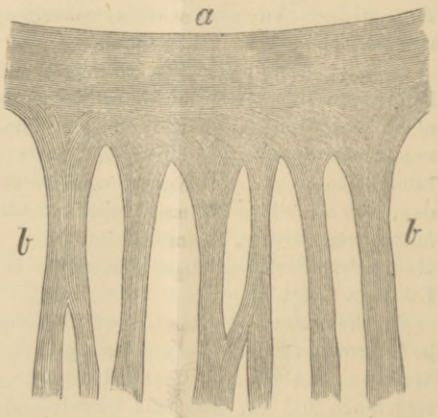
For the better understanding of the action of belladonna on the iris, I will follow, principally, Stellwag, and necessarily translate and quote very much that has been said by this eminent authority upon this subject

The iris contains circular and radiary muscular fibres. The circular fibres form a smooth, ring-like muscle, located around the pupillary part. This muscle is called the "sphincter pupillæ," and contracts the pupil. The radiary fibres do not form a continuous muscle, but extend from the ciliary border in a radiary manner, and are inserted into the circular fibres by slender fasciculi. These fibres serve to dilate the pupil, and the muscle is called the "dilatator pupillæ." See Fig. 1.

The iris is influenced by four nerves: the

third (oculomotor), the fifth (trigeminus), the sympathetic and the optic.

FIG. 1



(*From Kölliker.*)

a. Circular fibres of the Sphincter pupillæ.
b. Radiary fibres of the Dilatator pupillæ.

"The sphincter pupillæ and the ciliary muscle are supplied with branches of the third nerve, which pass through the ciliary ganglion, and form, with the other ciliary nerves, four main bundles of fibres, which reach to the ciliary body and separate in a quadrant of the ciliary muscle and sphincter pupillæ muscle. The dilator pupillæ and the vascular muscles of the iris are influenced by motoric fibres of the sympathetic. These fibres originate in the medulla oblongata, run downward in the

anterior column of the spinal cord, enter the anterior roots of the two lower neck and upper breast nerves, unite with the sympathetic, and pass with it upward through the superior cervical ganglion. The fifth nerve supplies the iris with sensible fibres.

"The optic nerve has only an indirect action on the iris, inasmuch as the iris contracts when light falls on the retina. The ciliary nerves (branches of the third, fifth and sympathetic) lie in the outer layer of the choroid, in the lamina fusca, and run through many little knots, the so-called intra-ocular ganglia" (Schweigger).

FIG. 2.

Ganglion cells and nerve fibres found in the Choroid. (Schweigger.)

"These ganglia officiate as centres, because conditions of excitation of the sensible nerves can be reflected on the motoric nerves without the brain or spinal cord partaking thereof. On these ganglia the atropia acts" (Stellwag).

The action of atropia is of a twofold nature; it dilates the pupil and paralyzes the accommodation. After the proper length of time of

action of the agent, the dilatation of the pupil is a maximum, the iris recedes until only a small seam is perceived; it remains perfectly immovable, and does not react either on reflex irritation, contrast of light or consensual action as accommodative impulse. Stellwag says that "this powerful dilatation is hardly attainable through the paralysis of the sphincter pupillæ alone; there must be some active power present, which drives the blood out of the iris back into the posterior uveal tract; and this power is developed through the contraction of the dilatator pupillæ and vascular muscles. A proof of which is, that in complete paralysis of the oculomotor nerve the pupil is only half dilated, and if atropia is put into the eye at this stage the dilatation becomes greater, showing that through the atropia a particular power is brought into action that can still dilate the pupil."

"It remains now the question, If, from the above expressed facts, it can alone be explained by the sole contraction of the dilatator pupillæ?"

"The dilator lies on the posterior border of the iris, and consists of an evenly formed, thin layer of smooth, muscular tissue; the larger vessels of the iris lie before it (*i.e.*, anteriorly). If it contracts alone the pupil is dilated, but the vessels are not compressed. The retreating iris forms a small but thick fold. This fold is not found, however, by a thoroughly dilated pupil. If we examine the iris by a contracted and a completely dilated pupil, we do not find

it thicker in the latter (dilated) state than in the former, a proof that the vascular muscles have also contracted."

Rossbach and Fröhlich, in their experiments with atropine on rabbits, noticed that very weak solutions (three to six millionths of a gramme) caused contraction instead of dilatation of the pupil, through irritation of the ends of the oculomotor nerve. In somewhat stronger solutions the ends of the oculomotor nerve became paralyzed and the pupil dilated slightly. Still stronger solutions increased the dilatation by irritating the sympathetic and the dilatator pupillæ; and on the use of very strong solutions the sympathetic and dilatator pupillæ were paralyzed, so that the pupil contracted somewhat from its extreme dilatation.

They found that atropine has the contrary action on the pupil of a frog to that of man or warm-blood animals. It contracts it instead of dilating, and physostigmin (the active principle of the calabar bean) dilates the pupils.

I have made some very careful experiments with the sulphate of atropia and sulphate of eserine (physostigmin) on the eyes of the frog; and my experience does not accord with that of Rossbach and Fröhlich. I found that the action of these salts was not different in this case from that in man and warm-blood animals, except that the dilatation from atropia was so slight, and remained such a short time, that it could hardly be observed. It required the closest attention and scrutiny. In making my

experiments, I found that simply dropping the solution of either atropine or eserine on the eye, gave not the least action. I then introduced a probe behind the lid and held it off from the ball, while my assistant, Dr. Thomas H. Fenton, let a drop of the solution I was using fall in the cul-le-sac made by the probe.

Weak solutions of either salt did not give any reaction, but from a solution of sulphate of atropia of four grains to the ounce of water, a very slight dilatation was observed. From a solution of eserine, of the same strength, marked contraction took place in a short time, with considerable irritation in the eye, causing him to wink often, then close it and rub it with his fore leg. The contraction of the pupil did not remain but for a few minutes, although it reached a very marked degree in that short time. The frog felt the toxical effects for over an hour, exhibited by great spasmodic breathing, then closing the eyes and remaining motionless for a time, then again spasmodic action of the respiratory organs.

A peculiarity which we noticed in the eyes without any drops was, that in the morning, until about 9 o'clock, the irides were somewhat contracted; then they slightly dilated until about 11 o'clock, when they began to contract, and remained in this condition until 2 P.M., when dilatation took place until about 3 or 4 o'clock; then a slight contraction occurred till toward evening, when they began to dilate again, and by night were widely expanded.

A solution of atropia, gr.iv ad. ℥j dropped in the eye of a pigeon, did not produce the least dilatation of the pupil; but, after eserine, of the same strength, there was in two minutes great spasmodic action of the lids, and contraction of the pupil, which, in four minutes, reached its maximum, the pupil being as small as a pin's point, and death occurred in half an hour. I also tried the action of both these salts on chickens, and did not see any effect, except that the eserine created a temporary irritation and congestion of the conjunctiva.

Giguel has observed, that "when a not too concentrated solution of atropine is injected under the skin, in the neighborhood of the eye, dilatation of the pupil of that side only takes place. In some cases when a concentrated solution ($\frac{1}{10}$) was used, its action was noticed in the pupil of the other side, but never by a weak solution." He coincides with Potain, that the one-sided mydriasis following a hypodermic injection of atropine in the peri-orbital region is the result of reflex action in the benumbing of the peripheric ends of the trigeminus. But when the mydriasis is double, it shows direct action from the centre. He recommends the hypodermic injection of atropine for facial neuralgia, to be made in the immediate neighborhood of the diseased nerve.

Beside the dilatation of the pupil, there takes place, on the use of atropia, loss of accommodation, and the condition of refraction is generally reduced somewhat below the standard measure,

which is found in complete rest of the apparatus of accommodation. This is particularly the case if it is put in the eye in strong solutions, or at short intervals.

It has a twofold action on the eye. It irritates the sympathetic, belonging to the motoric nerves of the dilator and vascular muscles, and paralyzes the motoric nerves of the sphincter pupillæ (contractor) and ciliary muscles.

"The paralysis of the oculomotor nerve is only relative, it consists only for certain innervations, during the reaction of the muscles from other impulses, and during which the iris is not sensitive to reflected and consensual irritation, nor impulse of the will, but contracts when the intraocular ganglia are directly irritated, or through interposition of the sensible branches of the fifth nerve, as is to be seen in the sudden contraction that takes place if paracentesis of the cornea is made, and the aqueous let out in a case where the pupil has been dilated, or if a strong chemical reaction is brought to bear on the ball in the same case.

"We have the same action by morbid irritation of the ciliary branches of the fifth nerve. It is constantly seen that atropia will not act in the least in cases of great ciliary irritation, as is often met with in iritis, many forms of keratitis, etc. It frequently occurs that, in cases where the pupil is well and largely dilated by the instillation of atropia, a severe ciliary irritation will suddenly set in, and cause the pupil to contract at once.

"Really the extent of the dilatation where there are no posterior adhesions is the best barometer for the degree of ciliary irritation" (Stellwag).

"By intense irritations of the sensible ciliary nerves, spasm of the ciliary muscles occur; this still more excites the sensible ciliary nerves, and through these the vaso-motoric nerves, which increases the inflammatory condition and appearance. This irritation and spasm often occurs in hypermetropic eyes, where there is great strain of accommodation in acts of vision.

The atropia relieves this spasm; and acts also sedatively on the fifth nerve. Its principal action consists in the contraction of the vessels in the anterior ciliary region, and thereby takes its place as a true antiphlogistic."

"As an antiphlogistic remedy, we have nothing like it in medicine; it acts to relieve inflammation on a particular circumscribed part of the body without affecting any other part."

Its absorption takes place through the conjunctiva and cornea, and soon after the instillation it can be detected in the aqueous humor. If a few drops of a solution of the strength of 2 to 4 grs. ad. ℥j is put in the eye, the pupil begins to dilate in 15 minutes, and reaches its extreme dilatation in about 30 minutes. The decrease of the accommodation is not simultaneous with the dilatation of the iris, but begins to diminish only after the pupil is somewhat dilated; and does not reach its fullest extent of

paralysis until some hours after. After 3 or 4 days the pupil will be somewhat smaller, and a slight degree of accommodation reappears; but the latter is not fully re-established until 10 and sometimes 14 days.

The use of atropia is indicated in all cases where a dilatation of the pupil is necessary. With some few exceptions it is used in all diseases so long as there is any ciliary irritation. In many cases of severe ciliary irritation and spasm of the muscle, a leech or two, or the artificial leech, on the temple, will assist the action of the atropia in dilating the pupil.

A solution of the strength of four grains to one ounce water is strong enough to paralyze the accommodation if applied often enough. Generally one or two instillations in one day are sufficient; but in cases of spasm three or four are necessary, and sometimes it must be continued for two or three days. In very severe cases I find it best to instill a drop every five or ten minutes for half an hour, then wait an hour, when the instillation should be repeated for half an hour, as before. This has always relaxed any spasm that I have seen.

I think it a great mistake to use stronger solutions, or even the pure salt, as I have seen practiced, for the reason that they are too irritating to the conjunctiva, causing, in a very short time, too great a relaxation of the vascular muscles, thus developing a chronic form of conjunctivitis, and also from the probability of the sympathetic and dilatator becoming para-

lyzed, thereby causing the pupil to contract again somewhat from its maximum dilatation.

The use of atropia is contraindicated in cases where glaucoma is suspected.

"The greater part of the arteries of the iris bend direct into the veins, and these empty their contents almost without exception, through the venæ vorticosa of the choroid, with which they are in intimate connection through the ciliary processes.

"The pressure of the circulation in the eye is regulated in the normal condition partly by the contractile walls of the vessels, and partly by the elasticity of the ball, which extends in equal proportion. If more arterial blood flows into the eye, more venous blood is forced out, thus regulating the circulation. In this way the intraocular pressure and tension remain always an equal standard. If, however, from some cause, the eyeball loses its elasticity, it will not be in a condition to regulate the circulation as formerly. The consequence thereof will be, that by a temporary arterial increase the fresh blood cannot be pressed out with rapidity enough to keep the intraocular pressure at the normal standard, and then a slight choking of the veins will take place, causing an increase of tension in the ball.

"Hard eyeballs, with little elasticity, are often found in advanced age in connection with dilated atheromatous vessels, and in some cases it is habitual from birth, being hereditary in some families. Bulbs of this kind can take but

little active action in the circulation of the eye, while the want of the proper elasticity can be the cause of much trouble.

"From the rigidity of the capsule the lamina cribrosa is extended, and gradually gives way, and presses back under the increased intra-ocular tension, thus causing the excavation in the disk as seen in glaucoma.

"By continued pressure the vessels passing obliquely through the sclera are eventually obliterated; the meshes in the lamina cribrosa become reduced and the main stems of the central veins compressed. From this the excavation will be the cause of a still greater choking of the vessels and an increase of the intra-ocular pressure; the greater part of the blood will try to relieve itself through the anterior ciliary veins which pass straight through the sclerotica, and whose calibre is not at first affected by the pressure, but become enlarged by the increased flow through them.

"We therefore see that eyes of greater than normal tension are disposed to glaucoma; and in such cases glaucoma often arises by outward influences of the slightest kind, as by any interference in the circulation of the eye, etc." (Stellwag).

As before mentioned, the action of atropia causes the blood to be driven out of the iris, back into the posterior uveal tract, and thereby an overfilling, and choking of the vessels of the choroid can take place, with the develop-

ment of glaucoma in persons whose eyes are so disposed.

From this we see that there is danger in the instillation of atropia in the eyes of persons when there is an abnormal hardness of the ball.

By long continued use of atropia in the eye, the sympathetic fibres become somewhat weakened, and the blood vessels cannot perform their proper function. They become suddenly enlarged, pain sets in, and the conjunctiva and episcleral tissue become swollen and inflamed. Naturally, in such a condition, the use of atropia must be discontinued, and a light astringent or chlorine water used for a time. I have seen some persons of extreme scrofulous diathesis who could not bear the least particle of atropia without its being combined with chlorine water, or a very weak solution of sulphate of zinc.

Care should be taken to see that the solution of atropia used is perfectly clear and neutral. Sometimes the salt is not thoroughly washed, and it contains some excess of acid, which causes irritation. Solutions of atropia become cloudy and flocky on standing, from collections of free particles of carbon that get in it during manufacture, etc., and should be filtered or renewed.

In its use, some naturally passes, with the tears, through the lachrymal duct into the nose and down the throat; and on continued use symptoms of poisoning appear, as dryness of the mouth, bitter taste, headache, excitement, fever, etc.; to remove which quickly, one or

two hypodermic injections of $\frac{1}{8}$ to $\frac{1}{2}$ gr. of morphium should be made, in the temple or arm.

Great care should be taken in its use by small children and infants. It is not advisable to allow the parents or others to apply this exceedingly dangerous remedy to such patients, for they are likely either to put in too much, or to let it run down the face into the mouth, and thus seriously, and perhaps fatally, poison the child. I have seen some cases of infants and very small children, where not the least particle of atropia could be used without toxic symptoms, while the extract of belladonna, in weak solutions, could be made to answer very well.

In examining eyes, and using atropia, it should not be forgotten that, when the pupil is dilated, the accommodation is paralyzed, and the vision reduced; it is well to inform the patient of this fact, otherwise they are apt to become alarmed, and run from physician to physician, in their anxiety and worriment, fearing they are going blind from what has been dropped in their eyes.