ON BATES' RESEARCH ON ADRENALINE

Reprinted from New York Medical Journal, May 16, 1896, pp. 647-650. Read before the Section in Ophthalmology of the New York Academy of Medicine, April 20, 1896.

THE USE OF EXTRACT OF SUPRARENAL CAPSULE IN THE EYE.

A PRELIMINARY REPORT.

By W. H. BATES, M. D.

The aqueous extract of the powder of the desiccated suprarenal capsule of the sheep is a powerful astringent and hæmostatic. When it is instilled into the eye the conjunctiva of the globe and lids is whitened in a few minutes. The effect is very decided. None of the usual astringents, including cocaine, can produce such an astringent effect. In normal eyes the extract whitens the conjunctiva and sclera when used in very weak solutions—less than one per cent. The effect is increased by repeated instillations or by the use of stronger solutions. In eyes very much congested from inflammation, the extract produces its astringent effect. No case has been found in which the extract did not act.

The following is a partial list of diseases of the eye in which the extract has whitened the conjunctiva and sclera Trachoma, acute conjunctivitis (catarrhal), chronic conjunctivitis, phlyctænular conjunctivitis and keratitis, interstitial keratitis, rheumatic and syphilitic iritis, episcleritis, irido-cyclitis, sympathetic ophthalmia, atrophy of the globe, secondary glaucoma, traumatic conjunctivitis, traumatic keratitis, traumatic iritis, traumatic kerato iritis, lacrymal inflammations, and rheumatic ophthalmia.

Visible blood-vessels on the cornea from specific keratitis or from trachoma disappeared from view completely after the extract was used. An eye with a foreign body on the cornea was whitened. During operations on the ocular muscles, tenotomy and advancement, the extract whitened the eyeball.

The extract is not irritating. It generally produces a cooling sensation when dropped into the eye. It does not dilate or contract the pupil, and it has no effect on the accommodation. A tolerance was not established in two cases in which the extract was instilled into the eye several times daily for more than three months. A third patient used the extract daily for more than twelve months, and the extract whitened the eyeball and palpebral conjunctiva as well at the end of the twelve months as at the beginning.

The astringent effect of the extract on the conjunctival vessels is temporary—usually in an hour the eye looks as it did before the extract was used. There was no congestion after the astringent effect had passed off.

The extract when swallowed increases the frequency of the pulse. Considerable doses may be taken without harm. A lady, aged eighty-seven years, had a pulse of forty, which was intermittent and irregular; after the extract had been used in the eye for a few days the pulse became regular, increased to eighty, and remained so during a period of six months

that the extract was used. A woman, aged thirty years, swallowed sixty grains at one dose. She vomited immediately, but felt no other ill effects. A man, aged sixty years, after taking two grains three times a day for a week, was suddenly attacked with a peculiar eruption on his hands, which disappeared in ten days without treatment after stopping the extract. The hypodermic use of the extract requires care. In one case ten grains produced alarming symptoms. The face was livid; there was great pain in the head and chest, with a feeling of throbbing. Consciousness was not lost. The pulse was weak. In ten minutes the patient felt all right and walked home from the dispensary, a distance of more than a mile.

Preparation.—The powder of the desiccated suprarenal gland of the sheep is placed in cold water and allowed to stand a few minutes. The fluid is filtered through filter paper and evaporated to dryness at a temperature below 105° F. The residue is the aqueous extract. It requires sixteen ounces of the fresh glands or eight ounces of the powdered desiccated glands to make an ounce of the aqueous extract.

Chemical Properties.—The active principle of the suprarenal gland is very soluble in water, one part of the extract dissolving in somewhat less than three parts of water. It is insoluble in strong alcohol, but soluble in dilute alcohol on account of the presence of water. It is also insoluble in ether or chloroform. The dried extract has remained immersed in strong alcohol, in ether, and in chloroform for several months without apparent injury. The dried aqueous extract has a brown color. The color depends partly on the temperature at which it is dried; the higher the temperature, the darker the color. It does not crystallize. When moist, it is slightly sticky; when dry, it is brittle. It has a slight odor resembling that of extract of beef. The most characteristic chemical property is its reaction with tincture of iron. A drop of tincture of iron added to a neutral solution of the aqueous extract produces a green color. The green color gradually disappears. A precipitate is formed. The addition of more of the iron solution may produce the green color again, with the formation of more of the precipitate. The supernatant fluid loses its color at the same time that the precipitate is formed. Finally, it is possible to add sufficient tincture of iron to make the solution of the extract clear, and the addition of more iron does not produce the green color. The precipitate contains the extract and the iron, because the filtered fluid evaporated to dryness leaves no residue except the excess of iron. The precipitate is black and is composed in part of metallic iron, probably. Dilute hydrochloric acid dissolves the precipitate and the solution becomes reddish.

My explanation of the preceding phenomena is that the extract is a strong reducing agent. The green color is due to the fact that the red perchloride is reduced to the green sesquichloride by the extract. The green color changes to the black of metallic iron by further reduction by the extract. What becomes of the extract will require further experiments to determine. The reducing action of the extract is certainly remarkable. The reaction of tincture of iron with the extract is very delicate, and is valuable in many circumstances. A solution of less than one per cent. of the extract will produce the green color on the addition of less than a minim of tincture of iron. A solution of extract of the color of water may contain enough extract to produce the green color. After the extract solution has became infected and has lost its color, the green color, may be produced. The sterilized solution also produces the green color. If the extract is in a very strong solution, it may reduce the

chloride of iron to the metallic state so quickly that the green color may not be observed. This reaction does not occur in solutions of thyreoid, thymus, testicle, or pineal gland.

When solutions of the extract are filtered through animal charcoal, the solution which has passed through first does not contain the extract. Later the filtered solution contains the extract.

As the extract is easily infected and does not keep unless sterilized, experiments were made to determine if it could be combined with bichloride of mercury in solution without altering the properties of the extract. The extract forms a precipitate with the bichloride, and if enough bichloride is added all the extract can be precipitated. It requires a large amount of bichloride of mercury to precipitate less than a grain of the extract. It can not be used with bichloride. When a solution of nitrate of silver is added to a solution of the extract a precipitate is formed which contains the silver. The precipitate contains part of the extract. The solution of the extract becomes weaker as the nitrate of silver is added. The color disappears. The extract precipitates a very considerable quantity of silver. When a sufficient quantity of nitrate of silver has been added no further precipitation takes place. The clear fluid evaporated to dryness has very little residue, the little residue being mostly excess of nitrate of silver, from which we may conclude that the extract and nitrate of silver compose the precipitate. If the nitrate of silver is not in excess, the clear fluid filtered contains the extract with all its properties unimpaired. The only effect of the silver is to precipitate part of the extract. The precipitate is not soluble in dilute acids.

Before leaving this subject it may be well to emphasize the fact that nitrate of silver precipitates the extract itself as well as any chlorides or phosphates which may be present. It also precipitates all of the extract if sufficient nitrate of silver is added, and a great deal is necessary. And, finally, the nitrate of silver precipitates everything composing the aqueous extract which may be in solution with the active principle. Of course, with these facts established, it is evident that the extract can not be used in solutions with nitrate of silver.

There are many other substances with which the extract, because it is a strong reducing agent, or for other reasons, can not be used in solution. With solutions of sulphate of copper and other astringents, precipitates are formed containing the extract, or reactions occur which alter the chemical properties of the extract or interfere with its action in the eye.

When the extract was used in solution with cocaine, the eye was irritated and not anaesthetized. In my judgment, the extract can not be used in the same solution with cocaine without impairing both the properties of the cocaine and its own.

The chemical properties of the extract are impaired by dilute hydrochloric, sulphuric, nitric, acetic, tartaric, tannic, and oxalic acids; also by dilute solutions of ammonia and sodic hydrate. In short, the extract does not act well when combined with other substances. I have tried a great many compounds, and I am not sure that there was one which, if added in sufficient quantity, did not interfere with the chemical properties of the extract.

Boiling the aqueous solution produces a precipitate. The filtered fluid can be boiled a number of times and still retain the properties of the extract. It has been boiled fifteen minutes daily for several weeks and the properties of the extract were retained. However,

the extract loses its strength by prolonged boiling, and it is possible to destroy it altogether. The color of the extract is much darker after it has been boiled. When the filtered solution is evaporated to dryness, the color of the extract is almost black. The sterilized solution has all the properties of the fresh aqueous extract. It has kept more than a year without change. When infected, it soon spoils like the fresh solution.

My observations on the use of the extract in the eye were made during the past two years. As this use of it is entirely new, it was necessary to be very cautious. I have had no disagreeable effects from it, and my confidence in it increases constantly. It is the only remedy of which I know that is purely an astringent. It is the ideal hæmostatic. It acts by contracting the muscle of the small arteries until the lumen is occluded and a coagulum is formed inside the artery. The following cases of ocular disease were treated with the extract:

Case I.—A patient was treated for acute catarrhal conjunctivitis. The extract had a marked effect in lessening the ocular and palpebral congestion. The eye was well in a week.

It can not be stated positively that the extract is curative in any form of conjunctivitis. As it is only an astringent and not an antiseptic, theoretically it should not be curative in the infectious diseases of the eyelids. But, after one has seen the unusual and immediate benefit that follows the instillation of only a few drops of the solution, one must believe that it is a valuable remedy. The patients like the cooling effect of the drops.

Case II.—A severe phlyctænular conjunctivitis was treated at the dispensary. The eyeball was red, and showed no white sclerotic at all. At the end of five days there was no change. A few drops of the extract whitened the eyeball at once. Two days later the eye was entirely well. In this case the extract seemed to produce a prompt and decided benefit. The patient had other treatment besides.

In a number of other phlyctænular cases the extract was beneficial. It certainly is not curative in phlyctænular inflammations.

Case III. *Interstitial Keratitis*.—There was so much congestion on the lower part of the cornea that it seemed as though there was blood in the anterior chamber. Atropine and hot water, with constitutional treatment, did not relieve the condition after a week. A few drops of the extract caused all the corneal vessels to disappear from view. A month later they had not become visible again.

In other cases the extract was also beneficial in reducing congestion. Other treatment was always necessary to bring about a cure.

Case IV. *Secondary Glaucoma following Cataract Extraction*.—The eye was congested and very painful. The extract whitened the eye, and the patient was relieved of the pain for a short time. The extract was used many times during the day. An operation finally stopped the pain. In this case the astringent property of the extract was beneficial by relieving the congestion. The tension was not materially reduced.

Case V. *Obstinate Iritis following a "Needling."*—After three months' treatment with atropine and hot water the eye was still red and painful. A few drops of the extract applied at intervals of a few minutes whitened the eye and relieved, the pain. There was no relapse a year later. The astringent property of the extract was undoubtedly of benefit in this case. Cases of iritis in general are undoubtedly benefited by the extract. But as the extract is only an astringent, it can not take the place of atropine and constitutional remedies.

Case VI. *Acute Dacryocystitis benefited by the Extract*.—The lower lid was so swollen in the neighborhood of the punctum that the punctum could not be seen. A few drops of cocaine did not relieve the swelling. The extract relieved the congestion so much that a small probe was passed through the punctum into the sac and the sac syringed.

When the patient was seen two days later the swelling of the lower lid had not returned.

A great many cases of lacrymal disease have been treated with the extract. It is only beneficial by lessening the congestion. The nasal duct has opened by reason of the astringent action of the extract.

The extract has been of material assistance in curing a number of obstinate cases of lacrymal disease without operation.

The extract was valuable in operations on the eye in following cases:

1. *Nervous People*.—An operation on some nervous people is unsatisfactory, because cocaine does not produce anæsthesia. Such cases are quite common.

A woman was operated upon recently for tenotomy of the inferior rectus. The cocaine did not whiten the ocular conjunctiva, dilate the pupil, or produce anæsthesia after being instilled frequently for an hour. A few drops of the extract whitened the ocular conjunctiva, and the cocaine in five minutes dilated the pupil and produced anæsthesia. The operation caused no pain. Traction on the tendon of the muscle with the hook was not painful. There was very little hæmorrhage. A previous operation on the same muscle, using cocaine alone, was painful, and there was an unusual amount of hæmorrhage. The eye was bleeding six hours later. The eye was sore for two days. The extract in this case had a very happy effect by securing a painless operation without hæmorrhage and without soreness afterward.

In a number of other and similar cases the extract has been of material assistance. It is well to repeat that the extract is not an anæsthetic.

2. *Inflamed Eyes*.—It is difficult to produce cocaine anæsthesia in eyes which are congested, the reason being that either the cocaine is not absorbed or because the irritation of the nerves resists the cocaine. The suprarenal extract by astringing the vessels relieves the congestion, and complete anæsthesia with cocaine can then be obtained.

An eye with inflammatory glaucoma was operated upon painlessly by the use of the extract and the cocaine together. Previous to the operation the use of cocaine alone instilled every ten minutes for an hour had no effect on the congestion, pain, or the tension. It seemed magical to observe the eye whiten after the extract was instilled, and the patient was

relieved of the pain as well. The tension was slightly reduced. The operation did no good, the pain returned, and the patient's condition was rendered bearable by the use of the extract until relieved by another operation.

3. *Eyes Congested after Recent Operations*.—After a tenotomy there may be so much congestion that cocaine does not produce anæsthesia. The use of the extract in the eye secures cocaine anæsthesia. After cataract extraction there may be so much congestion that cocaine does not act well. It may be desirable to do an iridectomy for prolapse of the iris. In such cases the extract is indicated to reduce the congestion sufficiently so that cocaine will act.

4. Prolonged Operations.—An operation which requires more than a few minutes becomes painful in some cases, although cocaine may be instilled frequently. Advancement of an ocular muscle is generally so painful that many operators are compelled to use ether anæsthesia. The operation may begin painlessly. Later the anæsthesia wears off, particularly if there is hæmorrhage. The extract, when frequently instilled, prevents hæmorrhage, and the cocaine anæsthesia is prolonged indefinitely for this reason. As soon as bleeding occurs, one notices very soon the sensitiveness of the eye returning. A number of advancements have been done painlessly and almost bloodlessly by the use of the extract and cocaine together. It is a great comfort to be able to work over some of these cases carefully, without hurry; to operate and test immediately, and operate again and test many times when necessary. Cocaine is not always sufficient.

5. *Bloody Operations*.—The extract prevents hæmorrhage because of its property of contracting the small arteries. After hæmorrhage begins the extract is not very efficient. It is possible to perform an almost bloodless operation on the ocular muscles or lacrymal sac by instilling the extract frequently. The following case illustrates the value of the extract as a hæmostatic:

A man was operated upon four times during the last three months for stricture of the nasal duct. After each operation the patient lost enough blood to saturate two and sometimes more towels. The hæmorrhage was unusually copious. The operations were very painful. A fifth operation was done in which the extract was used with the cocaine. There was no pain and very little hæmorrhage. The towel used had one spot a quarter of an inch in diameter.

A number of other and similar cases have been operated upon with success. The extract is not an objectionable hæmostatic. It does not form clots like iron or irritate as does peroxide of hydrogen. It is better to use the sterilized solution, as infection has occurred from the freshly prepared aqueous extract of the gland and of the desiccated powder. The extract has failed to control hæmorrhage in some cases and the cause of failure was not apparent. In one case of failure, four previous operations had been done almost bloodlessly on the ocular muscles by the use of the extract.

Finally, the fact that the suprarenal extract is not a substance foreign to the human economy may explain why in the two years during which I have used it no disagreeable effects have been produced by instilling it into the eye. In conclusion, I wish to repeat that within the limits of its sphere of activity there is absolutely no other substance which can take its place.

64 East Fifty-eighth Street.