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# CALOMEL CONJUNCTIVITIS.

Contribution from the Eye and Ear Department of the Baltimore City Hospital Dispensary.

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It has long been known that severe inflammation of the conjunctiva results from the local application of calomel when the iodide of potassium is being administered internally. This fact is interesting not only on account of its importance in ophthalmic therapeutics, but also from the light which it throws upon the manner in which calomel is absorbed into the system, a question still under discussion. Three cases illustrating this unwelcome result have occurred during the last three years in the Eye and Ear Department of the City Hospital Dispensary. It need scarcely be mentioned that in all of these cases the potassium iodide had been prescribed without our knowledge by other physicians.

The abridged clinical records of these patients are as follows:

CASE I.—F. H., æt. 45, came Dec. 28, 1890, with a corneal ulcer of the right eye, the result of an oyster-shell injury received one week previously. The galvano-cautery was used, a paracentesis was made to relieve the accompanying hypopyon and iodoform was subsequently applied. By January 19, 1891, the inflammatory symptoms had almost entirely disappeared leaving an extensive corneal opacity. Calomel insufflations were substituted for the iodoform. On March 19, the patient, who had been using the calomel himself, complained of having had "a cold in his right eye for a week." The ocular conjunctiva was found to be very much reddened and swollen, especially on the nasal side, only slightly on the temporal, and likewise in the lower conjunctival fold with the usual subjective symptoms of

acute conjunctivitis. On inquiry we learned that he had been taking potassium iodide for one week. Two days after discontinuing the insufflations the inflammatory symptoms entirely disappeared.

CASE II.—W. M., æt. 29, came to the clinic January 29, 1892. His left eye was phthisical from injury. He had corneal ulcers on the right eye, which had been cauterized elsewhere. When seen by us the right cornea was covered with numerous maculæ. Calomel insufflations were ordered. On February 2, he returned with severe conjunctivitis of the right eye. The inflammation was especially marked at the outer side and in the inferior fold. The patient stated that he had been taking potassium iodide four or five days. The calomel was discontinued and the inflammation rapidly subsided.

CASE III.—P. L., æt. 50; November 28, 1892. He complained that the right eye was somewhat painful but no cause could be discovered; he was therefore kept under observation. Calomel insufflations were used as a placebo November 30 and December 1. On December 2, he had severe conjunctivitis of this eye. The inferior ocular conjunctiva and that of the inferior fold and lower lid were considerably swollen. There were two grayish white spots of false membrane (necrotic) on the lower palpebral conjunctiva, each about 1–2 mm. broad and 4–5 mm. long. This patient, we learned, was also taking potassium iodide. The calomel was no longer used, and on the following day the inflammation had greatly decreased and the membranes had disappeared.

The picture produced experimentally in rabbits by others as well as by ourselves is identical with that met with clinically, consisting of œdema of lids and conjunctiva, injection of the vessels, profuse lachrymation and mucous or even purulent discharge with the frequent formation of a diphtheritic membrane. Sometimes, if the inflammation is kept up, the cornea will become cloudy and there may be loss of corneal substance.

Some authors mention a discoloration of the calomel flakes lying in the conjunctival sac. This was not noticed in the above cases as they were out-patients, and as the calomel

was discontinued as soon as the inflammation was observed. Although other cases resulted in prompt recovery on discontinuing the calomel, all cases on record were not so fortunate. Fricke reports a case[1] in which even after vigorous antiphlogistic treatment, recovery was not complete in eleven days; and in Hennequin's case[2] partial symblepharon resulted.[3]

In the case of Fricke the symptoms came on about half an hour after the insufflation, increasing in intensity until not mere ly the lids, but also the cheeks and nose became reddened and swollen. There was marked blepharospasm. Experimentally in rabbits the symptoms come on in about the same time; once in fifty-seven minutes.[4]

In order to produce the conjunctivitis the potassium iodide need not be given by mouth. This is shown by the case of Meurer[5] which resulted from the external use of potassium iodide to an inflamed testicle while a mild mercurial ointment was being used upon the cornea, and by the case of Fleischer in which he experimentally produced it by using the potassium iodide hypodermatically.[6] It can be shown that neither calomel nor potassium iodide, used alone, produces the above results. That the action of calomel is not purely physical is evidenced by the fact that other physically similar powders have not the same clinical effects.

This question has recently been studied by Schlæfke[7] and by Fleischer,[8] who substantially agree as to the interpretation of this phenomenon. Calomel in the presence of animal fluids containing sodium chloride and under the influence of the body temperature is slowly converted into bichloride and free mercury. As the transformation into bichloride is slow and small in quantity, it is believed that its clinical action on phlyctenulæ, etc., is due to its action in the *nascent* state. This view is supported by the following facts:

1. Fleischer found on adding pure calomel to distilled water and allowing this mixture to stand at the body temperature that none was converted into bichloride, but on adding sodium chloride to the same mixture even at the room temperature, the fluid gave the reaction for bichloride at the end of twenty-four hours.

2. When a moderately concentrated aqueous preparation of calomel and sodium chloride is evaporated at 40° C. to dryness and the residue extracted with ether, crystals resembling those of corrosive sublimate crystallize from this ethereal extract. Calomel alone treated thus, does not give this result.

3. On placing the aqueous preparation of calomel and sodium chloride in a sealed vessel and suspending by a thread a gold plate just above the surface of the liquid, the whole being placed in an incubator, the gold on the following day will be found amalgamated in places.

4. On placing some of the same mixture in a tube heated to redness and passing the vapors of iodine through, the red iodide will be obtained; if the experiment is performed without the sodium chloride no red iodide is formed.

5. Kammerer[9] showed that after the insufflation of calomel upon the conjunctiva, mercury could be found in the urine. Alsberg and Vulpius[10] corroborate this statement.

6. Cheminade,[11] after hypodermic injections of an aqueous preparation of calomel, sodium chloride and gum Arabic, found free mercury at the seat of inoculation.

7. Fuerbringer[12] showed that on treating broad condylomata with a sodium chloride preparation of calomel, and washing off after a few minutes with water, that the washings yielded free mercury. He also obtained the same result when there was no sodium chloride in the mixture, the NaCl of the tissues acting instead. This is corroborated by Fleischer. These facts taken in connection with Voit's experiments (which proved that by long continued contact of calomel with solutions of albuminous substances, metallic mercury was precipitated), suggest the following reaction, $2\ HgCl = HgCl_2 + Hg$ as opposed to the other possibility $HgCl + NaCl + H_2O = HgCl_2 + NaOH + H$. That the first reaction is correct is furthermore supported by the fact that Fleischer's test-material (composed of calomel, sodium chloride and water) always gave a neutral reaction, even when kept at the body temperature. This would not be the ease if the second reaction had occurred.

8. The action of calomel, slow and mild, is itself suggestive;

the amount of sodium chloride in the secretions is small (at most not more than 0.8% in the tears) and little bichloride is formed at a time; therefore its mild action when used alone. In the retort the transformation of calomel is likewise slow and the resulting bichloride small in amount. Vulpius was able to secure a demonstrable amount of mercury from the collected urine of ten days, during which about 1 mgr. of calomel was insufflated once daily.[13]

Hirschberg is also of the opinion that calomel is transformed into bichloride; he states[14] that the astringent action exercised by calomel upon phlyctenulæ is due to the resulting bichloride in *statu nascendi.*

Potassium iodide taken internally rapidly appears in the secretions and excretions, (tears, urine and saliva). Schlæfke using a dose of 1 part potassium iodide to 6,000 of body weight, detected it in the aqueous humor of a rabbit by means of palladium chloride in 8 min., and in the tears in 10 min., after its ingestion. In another rabbit, after a dose of 1-10,000, the tears reacted for potassium iodide nine hours after its ingestion. Potassium iodide is not as readily eliminated by the tears as by the urine or saliva. Schlæfke, after a dose of 2 grams, failed to find it in his conjunctival sac, while his urine and saliva reacted markedly for it, even on the following day. Since one can only detect 1 part potassium iodide in 15,000 of water by means of palladium chloride and as the body weight of the adult is about 60 kilos, at least 4 grams must be administered *per diem* in order to produce the reaction. After using 5 grams twice a day, potassium iodide is continuously present in demonstrable quantity in the tears.

If a solution of any mercurous salt is treated in a test-tube with potassium iodide, mercurous iodide (Hgl) is thrown down as a golden salt, which being very unstable, readily decomposes into mercuric iodide ($HgI_2$) and free mercury. When mercurous iodide is thus treated with potassium iodide it undergoes the same transformation but the resulting iodide combines with the excess of potassium iodide, forming a double salt and liberating metallic mercury, probably as follows: $2\,HgI + 2KI = K_2HgI_4 + Hg$.

By treating any mercuric salt, as the bichloride, with potassium iodide, mercuric iodide is formed which readily dissolves in a solution of potassium iodide forming a double iodide or iodo-mercurate.[15]

As has been shown, the combined use of potassium iodide internally and calomel externally, produces the same compounds in the conjunctival sac, *i. e.*, potassium iodide being eliminated by the tears, and bichloride of mercury resulting from the decomposition of the calomel, together with the excess of calomel; we should therefore expect them to react in the above manner and experiments carry out this expectation. Experimentally and in some of the cases which were under continuous observation as one of Fricke's, the first change noted was a golden greenish discoloration of the calomel, coming on in rabbits, in from 20 to 30 minutes, suggesting by its color the formation of mercurous iodide. This change of color initiates the onset of the inflammatory symptoms. Thus Schlæfke added to 1% solution of potassium iodide a little calomel, and shaking this, a dirty green precipitate formed, the calomel finally dissolving. On placing 2 to 3 drops of the golden green filtrate in the conjunctival sac of a rabbit, the conjunctiva was found after a few minutes, reddened, chemotic, the cornea cloudy, with slight conjunctival eschars.

From the filtrate Fleischer obtained the double iodide of potassium with both mercurous and mercuric iodides. In order to show that it is non-essential whether mercurous or mercuric iodides were present Schlæfke prepared two solutions, one of mercurous iodide in potassium iodide, the other of the corresponding mercuric salt in potassium iodide. In the conjunctival sac of one eye he placed a few drops of the first solution, carefully protecting the cornea, the other eye was similar treated with the second solution; in half an hour both eyes showed marked chemosis, finally leading to the formation of pus, and eschars at the junction of the ocular and the lower palpebral conjunctiva.

We may conclude, 1, that part of the calomel is transformed into bichloride; 2, that the potassium iodide in the

tears combines with this bichloride forming the mercuric iodide and meeting the rest of the calomel forms mercurous iodide, part of which in turn gives rise to mercuric iodide and metallic mercury, while the remainder combines with the excess of potassium iodide forming a double salt with liberation of free mercury; 3, that mercuric iodide arising from the combination of the bichloride and potassium iodide, and also from the decomposition of mercurous iodide, combines with the potassium iodide forming a double iodide; and, 4, that both the above double iodides dissolving in solutions of potassium iodide or of sodium chloride act as caustics.

Returning to the clinical side of this question a few words may be added concerning the recognition of the disease. The inflammation differs from the ordinary acute conjunctivitis in being sharply limited to one part of the conjunctival membrane, usually the lower part of the ocular conjunctiva and that lining the lower lid. When very intense it may involve the conjunctiva of the upper fold, but this is rare. The cornea is not involved excepting when the inflammation is very intense as in experimental cases. In all cases which have come under our observation the disease was monocular but it is frequently binocular. Small or large patches of diphtheritic membrane are frequently seen in the lower conjunctival folds, where the little flakes of calomel collect.

Hirschberg (*loc. cit.*) believes that it is only when the potassium iodide is immediately followed by the calomel insufflation that the above inflammation ensues. This cannot be accepted, for Schlæfke, using doses of 0.5 gram, found that the insufflation of calomel twenty hours after the last dose, resulted in irritation. In our cases the doses of the iodide were moderate and had not been taken just before the calomel was insufflated.

It is scarcely necessary to mention that other preparations of mercury beside calomel may be followed by the same results. The most common perhaps are the oxides and the ammoniated mercury.

On the other hand, the iodide may be taken in other forms, as in the syrup of the iodide of iron.

Judging from the chemical action we would conclude that the bromides would have similar effects and this is borne out by Bellini.[16]

In conclusion another form of calomel conjunctivitis may be mentioned. This is due to the use of impure calomel, containing the bichloride or free hydrochloric acid. A serious case caused by the latter contamination was published by Hotz.[17] But this form of calomel conjunctivitis is very rare.

[1]Hamb. Zeits., Vol. 5, 1837, p. 3.

[2]Gaz. hebdom., 15 fev., 1867.

[3]Hennequin, from the results of the observation of his case, in which a severe pannus cleared up entirely from the resulting inflammation, proposed the combined internal use of potassium iodide with the external use of calomel for the cure of obstinate pannus!

[4]Schlæfke, see below.

[5]Hirschberg's Centralb. f. prakt. Augenheilk. Suppl., 1890, p. 441.

[6]See below.

[7]Schlæfke, Von Graefe's Archiv. f. Ophthal., Vol. 25, 1879.

[8]Deutsch. med. Woch., 1885, p. 459.

[9]Virchow's Archiv., Vol. 59, p. 459.

[10]Knapp's Archives of Ophthalmol., Vol. 9, 1890, p. 399.

[11]Union medicale, 3 s.. Vol. 48, p. 219.

[12]Zeits. f. klin. Medicin., Vol. 8, 1884.

[13]Loc. cit.

[14]Einführung in die Augenheilkunde, p. 19.

[15]Remsen, Inorg. Chem., p. 623.

[16]See Schlæfke, loc. cit.

[17]Knapp's Archives of Oph., 1882.