

and in a more convenient form, and dependable dialysers more easily procurable, the test will not be generally available.

In this connection it may be mentioned that attempts are being made to simplify the technic so as to make it more generally available. Gutman, in a personal communication, expresses confidence that such a simplification can be accomplished, difficulty in procuring a special dialyser being the particular obstacle with which he is contending.

4. That it places in our hands a possible means whereby we may make a remarkably accurate diagnosis of the existence or non-existence of pregnancy, should the exigencies of any case demand a prompt determination of the fact.

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THE EFFECT OF "606" ON THE EYE, WITH THE REPORT OF SEVEN CASES OF SERIOUS EYE COMPLICATIONS FOLLOWING ITS USE.*

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WHEN Ehrlich first introduced his 606 there was a great fear in the minds of the ophthalmologists that the effects of the new preparation on the eye would be similar to that produced by other arsenical compounds such as atoxyl, arsacetin, and soamin, which had preceded it. All of these arsenic compounds had been claimed by their introducers to be harmless to the eye, but further experience proved this not to be the case. Quite a large number of cases of blindness were reported to have followed their use. Of these preparations, the one most largely used was atoxyl, an empirical, synthetical arsenic compound, which came into use in the treatment of sleeping sickness and was used to a considerable extent in the treatment of syphilis. Although, claimed at first to be innocuous to the eye, from a study of the literature for 1908, 1909, and 1910,—the years during which it was chiefly used,—I have been able to find over 100 cases of complete blindness and a large number of cases of partial blindness resulting from its administration. The ocular manifestations following its use always assumed the character of a primary optic atrophy. It was essentially a degenerative process affecting either the ganglion cells of the retina or the fibres of the optic nerve, somewhat similar to the condition produced by other toxic substances, such as methyl alcohol, quinine, and other toxic substances. Both eyes are invariably affected. The blindness may come on suddenly or gradually, but once the lesion is produced, it remains stationary or slowly progresses until more or less complete blindness results. A partial recovery occasionally occurs if the drug is withdrawn early enough. The condition is not improved by any treatment, and a second injection of atoxyl never improves vision, but causes a more profoundly injurious effect. With the ophthalmoscope the picture is seen to be one of simple optic atrophy.

The attitude of the ophthalmologists towards 606 was well expressed by Henderson, of St.

* Read at the October, 1913, Clinical meeting of the Staff of the Boston Dispensary.

Louis, who, in an article on the effects of atoxyl, in the *American Journal of Ophthalmology*, for November, 1910, says in his concluding paragraph: "The subject is worthy of careful consideration in view of the approaching distribution of 606. If I am correctly informed, this, too, is a synthetic preparation of arsenic. The world-wide publicity already given to the achievements of this remedy will result in its more or less indiscriminate use by every physician who can get it. In accepting and using this potent remedy we must not forget that all of its predecessors were for a time considered harmless in their action upon the visual apparatus by authorities in whom we had every right to repose the greatest confidence."

The important questions which the ophthalmologist wished to have answered were: (1) Is arsenobenzol innocuous to the healthy eye, especially the healthy optic nerve? (2) Can it be used when the nerve is inflamed? (3) Is it a safe and efficient remedy in the treatment of syphilitic disease of the eye itself?

Serious disturbances of the visual apparatus certainly do follow the administration of arsenobenzol in a certain number of cases, but when one considers the tremendous number of patients that have received it, the number of ocular disturbances following its use are small as compared with atoxyl and its allied drugs. An examination of the literature during the past three years shows that most authorities believe that the eye lesions following 606 are to be considered as relapses of syphilitic disease, and not a consequence of the arsenobenzol. There are still a few, however, who maintain that it is a menace to the eye and should be used only in special conditions. Ehrlich himself, in view of the bad results to the eye following atoxyl, advised caution in the use of his preparation and advised a careful examination of the eye before injection. Later, however, when he had received reports of a large number of cases without untoward effect upon the nerve, except in one case, he claimed that 606 was without detrimental effect upon the eye. He also deplored the fact that ophthalmologists were not making sufficient use of his preparation in syphilitic diseases of the eye. In defending the use of 606 against the charge that it was not without danger to the eye, in the *Wien. Klin. Rundschau* of Jan. 29, 1911, he states that disturbances of the optic nerve in recent cases of syphilis are found, not only after the use of salvarsan, but also after the use of Hg. On the other hand, when sufficiently large doses of salvarsan were used, such affections were never seen. The use of atoxyl and arsacetin show that the toxic symptoms increase with the amount of the dose injected. The optic nerve affected after salvarsan improves under anti-syphilitic treatment, and sometimes it is cured by another injection of salvarsan. An affection of the nerve caused by atoxyl could never be cured by an additional injection with an arsen-

ical preparation. Numerous other authors support the contention of Ehrlich that arsenobenzol is innocuous to the healthy eye, and the ocular lesions following its administration should be considered as manifestations of syphilis. Wechselsmann and Selligshon of Berlin gave the injections in 1400 cases of their own, and collected reports from approximately 20,000. Of these cases, none showed any harmful effect upon the optic nerve. At first they excluded from the treatment any cases showing inflammation of the nerve, but later, after they had given the injection to several doubtful cases, that is, cases where it was impossible to say whether the nerve was inflamed, or not, without deleterious effect, they used it in several cases of outspoken optic nerve affection, with the result that the condition of the inflamed nerve was considerably improved, and in some cases cured. From this they conclude that 606 may be given with favorable results, even when optic neuritis exists. This opinion is confirmed by the experience of most writers. They also gave the remedy in a number of cases of primary optic atrophy, on which it had no apparent effect, either beneficial or otherwise. This, however, is quite contrary to the experience of others. Most authors agree that the effect of the 606 on the atrophic nerve is detrimental, that it causes a more rapid degeneration of the nerve, and that atrophy of the nerve should be considered a contra-indication for the administration of the drug.

A comparison of the lesion resulting after atoxyl with that following 606 will aid, I think, in determining whether the ocular lesions after 606 are due to the arsenobenzol or not. In atoxyl poisoning the lesion is essentially a degenerative one, resulting in an optic atrophy very similar to the condition produced by other toxic substances, whereas the lesion following 606 is an acute inflammatory one. Usually four to eight weeks, or even longer, after an injection of 606 the patient notices a sudden dimness of vision, which becomes rapidly worse. With the ophthalmoscope the vitreous will be found to contain a greater or less number of opacities which at times are so profuse as to prevent a clear view of the fundus. The disk, if it can be seen, is red and veiled, may be swollen, and the blood vessels, especially the veins, dilated and tortuous; scattered through the fundus will be found inflammatory exudates in the retina and choroid, often accompanied by hemorrhages. These are precisely the sort of lesions which appear in syphilitic disease of these structures and form a picture diametrically opposite to that found in atoxyl and allied poisoning. But one eye usually is affected,—although both may be. In atoxyl poisoning both eyes are invariably affected. Antisyphilitic treatment, or another injection of the 606, will usually improve and sometimes clear up the condition. After atoxyl no treatment benefits, and a further injection of atoxyl causes a

more profoundly injurious effect. Moreover, the late appearance of the lesion after the injection of the 606 seems to me to have a bearing upon the question of its causation. Usually it is a matter of weeks, or even months, after the injection before the ocular symptoms appear. As we know, the arsenic is rapidly excreted from the system,—usually after three to four days but few traces can be found,—and it seems to me that if toxic symptoms were to be produced they would be found shortly after the injection, while the organism was still under the influence of the arsenic.

Iritis, retino-chorioiditis, optic neuritis, and ocular palsies from affection of the third, fourth and sixth nerves, as well as affection of the fifth nerve, have followed the use of salvarsan in a certain number of cases. Davids reports a case which had bilateral iritis following an intramuscular injection. Two weeks later a relapse occurred in one eye, which rapidly subsided after an intravenous injection. Van Lint reports two cases of iritis treated with salvarsan. Iritis was reproduced in the same eye after the injection. DuJardin and DeNeux have observed in two cases of secondary syphilis recently injected commencing optic neuritis, paresis of the superior oblique muscle and paralysis of the oculomotor, with beginning papillitis. They think that these conditions have a bearing on the administration of 606, but do not think it is a purely toxic action. They believe there exists a relationship between the modified syphilis and the action of arsenobenzol, causing a disturbance in the evolution of the disease. Shanz reports two cases of optic neuritis following the injection of salvarsan, which were cured by a repetition of the injection. We have had one case of affection of the fifth nerve following 606 at the Dispensary. There was anesthesia of the cornea and the right side of the forehead and the face. The lesions in the eye itself may be considered as syphiliomata produced by the immigration of the spirochetes which have been freed by the softening of foci by the injections. They are analogous to the tubercular metastases observed after the injection of tuberculin. It must be remembered that the nerves pass through narrow channels of bone lined with a tough connective tissue, which, as places of predilection for nests of spirochaetes, escape the therapeutic action of the 606. Some explain these apparent relapses as an endotoxin action, the endotoxins having been set free from the dead spirochaetes.

The relapses following 606 were much more frequent in the early days of its use, when there was more or less uncertainty in regard to the size of the dose, and the hope was entertained that it was the *therapia sterilans magna*, which would cure by a single injection. As a result, the amount given was too small to kill all of the spirochaetes, and those not destroyed were later able to cause relapses of the disease in various tissues. Moreover, it is held by some

authorities that small doses have a provocative or irritative effect. According to Ehrlich, in such cases the parasites are not killed, the dose being too small, but irritated and in this condition produce greater quantities of toxins. At any rate, during the past year, during which the drug has been administered much more energetically, relapses in the eye have not been so frequent.

It has been the custom at the Dispensary to refer those cases which were to receive 606 to the eye room for examination, especially with reference to the condition of the optic nerve and the fundus. A report is returned, giving the vision of each eye and the condition of the fundus and optic disk. If the vision of either eye is below normal, the reason for the same, refractive error or otherwise, is stated. A record of the same is kept both in the skin room and in the eye room. We thus have an exact knowledge of the condition of the eye before the injection of salvarsan, and if a deterioration of vision should occur subsequently the case is referred again to the eye room for examination as to its cause.

During the past year, from July 1, 1912, to July 1, 1913, arsenobenzol has been administered, by a coincidence, 606 times. We have the records of four cases in which disturbances of vision followed the injection during this period. In addition to these four there were three other cases which received the injection just previous to July 1, 1912, but whose eye symptoms appeared or were treated after July 1, and these we have included in this group. It will thus be seen that but two-thirds of one per cent. of the cases receiving the injection show disturbances of the eye afterwards.

Of these seven cases, six showed serious lesions of the deeper structures of the eye, and in four of these practical blindness has resulted. In one case the relapse showed itself as an iritis, which readily improved after a second injection of arsenobenzol. In analyzing these cases, the important data are:—

1. The date of the injection.
2. The date of the onset of symptoms.
3. The character of the lesions in the eye; and
4. The result of treatment and prognosis; and it is with a view to these headings that I wish briefly to describe these cases:

CASE 1. Man, 41 years of age.

(1) *Date of Injection of 606.* First injection Sept. 7, 1911. Second injection, February 20, 1912. Both eyes normal.

(2) *Date of Onset of Symptoms.* April 16, 1912, over six weeks after injection. Vision of right eye = 10/200.

(3) *Character of Lesion.* Numerous opacities of vitreous, disk blurred and veiled, several hemorrhages and exudates in chorioid and retina.

(4) *Treatment and Result.* In spite of energetic antisyphilitic treatment vision rapidly failed. At last examination, Sept. 26, 1913, vision = could

count fingers in temporal field. With the ophthalmoscope, vitreous opacities still present but not nearly so numerous, hemorrhage on disk—atrophic patches through fundus.

CASE 2. Man, 27 years of age.

(1) *Date of Injection.* June 5, 1912. Eye normal.

(2) *Date of Onset of Symptoms.* Six weeks later noticed blurring of vision of left eye—vision = 20/80.

(3) *Character of Lesion.* Dust-like opacities of vitreous, disk swollen and red, veins engorged and tortuous—exudate in chorioid and retina.

(4) *Treatment and Result.* Intramuscular injections of mercury. Vision failed rapidly for a month at which time V = 4/200. Went to New York, treated there by a physician with pills and drops. Vision improved somewhat until last March when there was sudden loss of vision—no treatment since. Seen Sept. 16, 1913, when V = light perception. Received 606 again September 19,—two days later some improvement. Last seen September 30, V = hand movements at 2 m. Examination with ophthalmoscope shows massive exudates in vitreous obscuring all details of fundus.

CASE 3. Young woman. Grace G. 22 years. Referred to eye room for specific iritis of right eye on June 20, 1912.

(1) *Date of Injection.* June 26, 1912. Vision of OD = 20/40. Vision of OS = 20/20. Fundus O.K. Iritis rapidly improved.

(2) *Date of Onset of Symptoms.* Six weeks later right eye became affected. Seven weeks later left eye became affected.

(3) *Character of Lesion.* Opacities of vitreous in both eyes—disks red and blurred.

(4) *Treatment and Result.* In spite of most vigorous antisyphilitic treatment together with pilocarpine sweats and subconj. injection of Dionin 10%, her vision rapidly grew worse and at the end of four months she had to be led to the dispensary for treatment. On Jan. 13, 1913, about five months after onset of symptoms, her lids became enormously swollen, red, tender and indurated so that she was unable to open them. A tense, tender swelling could be felt along the upper edge of orbit on both sides = orbital periostitis. Vision = hand movement. Later showed syphilitic nodule on sclera. Under vigorous specific treatment with pilocarpine sweats gradually improved in course of next few months. VOU = 20/40, July 12, 1913. Last seen September 23, 1913. Vitreous quite clear; few atrophic spots in fundus. On posterior surface of cornea deposits of inflammatory exudate. V OD = 20/100, V OS = 20/70.

CASE 4. Man, 23 years of age.

(1) *Date of Injection.* July 24, 1912. Eyes normal.

(2) *Date of Symptoms.* Two weeks later pain and redness of left eye.

(3) *Character of Lesion.* Iritis with posterior synechia.

(4) *Treatment and Result.* Received a second injection of 606 on August 28. Rapid improvement.

CASE 5. Man, 42 years of age.

(1) *Date of Injection.* August 20, 1912. Eyes normal.

(2) *Date of Symptoms.* Seven weeks later vision of left eye failing. Vision = light perception only.

(3) *Character of Lesion.* Vitreous so smoky that details of fundus could not be made out. Three weeks later developed an iritis.

(4) *Treatment and Result.* Iritis improved rapidly under local treatment—atropine. Condition of vitreous remained practically the same in spite of antisyphilitic treatment. Saw him last on January 10, 1913. Vision very slightly improved. Could count fingers with OS. With ophthalmoscope condition of vitreous practically the same.

CASE 6. Man, age 27 years.

(1) *Date of Injection.* Oct. 9, 1912. Vision and fundus normal.

(2) *Date of Symptoms.* March 26, 1913, five months later, V OD = 20/50. Could not state just when symptoms began but quite recently.

(3) *Character of Lesion.* Large vitreous opacities—disk red and veiled. Fundus indistinct.

(4) *Treatment and Result.* Received injection of 606 without any apparent improvement. Specific treatment. Last examined May 31, 1913. V OD = 20/70. Fundus indistinct—numerous floating opacities of vitreous.

CASE 7. Woman, Sarah B. Age 29.

(1) *Date of Injection.* February 12, 1913. Eyes normal.

(2) *Date of Symptoms.* Six weeks later, on March 26, 1913, returned saying vision of left eye had become dim several days before. V OS = 20/120.

(3) *Character of Lesion.* Some haziness of vitreous. Disk red and blurred—retino-chorioiditis in macula.

(4) *Treatment and Result.* Three days later showed beginning iritis. Specific treatment. Condition grew worse. April 2 received second injection 606, no improvement. April 17 vision = 7/200. Improvement from this time on. July 8 vision = 20/50. Last seen September 30, 1913. Vitreous clear. Few glistening spots in macula and other parts of fundus. Disk O.K. Vision = 20/30.

In analyzing these cases, the first point that strikes one is the length of time that elapsed between the time of the injection and the onset of the eye symptoms. In every one of the cases involving the deeper structures of the eye a period of at least five to six weeks elapsed before the onset of the symptoms. Surely all the arsenic had been eliminated from the system by this time. The second most striking feature is the severity of the eye lesions. In four out of six of the cases in which the deeper structures of the eye were involved practically complete blindness resulted. None responded to the ordinary anti-specific treatment. This is not in accordance with the views expressed by others who say that lesions following 606 are usually improved by specific treatment. In both of the other cases the vision was impaired, in one quite severely, a vision of 20-70 resulting. While I believe that in all of these cases the effects were due to the disease and not to the drug, it tends to prove that the character of the disease is changed, that its virulence is increased. This would support the contention of those who believe that insufficient doses have a provocative

or irritating effect. A third point is that these relapses are not occurring as frequently now as formerly. Since the first of the present year we have had but one case, that of Sarah B., who received her injection Feb. 12, and developed her neuro-retinitis March 26. Moreover, this is the only one in which the symptoms were less severe and the only one whose vision was restored to practically normal. May this not be the result of more energetic treatment with salvarsan?

While of course the number of cases that we have had in the Dispensary is too small to permit us to make any too broad or too positive statements in regard to the effects of arsenobenzol, yet I feel this way about it. If, as most authorities claim, these ocular lesions following 606 are simply the manifestations of syphilis, and if, as it is declared, arsenobenzol has such a remarkable beneficial effect in clearing up the symptoms of syphilis, then I believe that in all of these cases of ocular relapses the injection should be repeated, and that as soon as the symptoms appear. There is no organ in which irreparable damage to the delicate tissues can result more quickly from an inflammatory process than in the eye. Treatment after the damage has been done will not restore the destroyed nerve or other tissue. If the relapsing lesion affected the mucous membrane of the throat or the skin, one would not hesitate to give 606 any number of times it was deemed necessary to eradicate the disease. Then why not if the symptoms happen to affect the eye?

As regards the therapeutic effect of 606 in syphilitic disease of the eye, there is no unanimity of opinion as to the curative effect of the new product in ocular disease. In interstitial keratitis of inherited syphilis, for which mercury is well nigh useless, salvarsan has, on the whole, given no better results. A few men have reported good results, but the majority think the malady little influenced by it. The relief of the photophobia is generally attributed to it. This has been our experience at the Dispensary. In two of the cases, both boys, aged twelve and thirteen, respectively, one of whom received two injections at intervals of two months, the other four injections at intervals of two weeks, I think the course of the disease was shortened somewhat. In both the corneae were quite clear and glancing after three months' treatment. Usually it requires anywhere from four or six months' to one or two years' treatment. Most of the men who have reported favorable results have given the injection several times.

Iritis and iridocyclitis of secondary syphilis, usually respond well to the drug and much more quickly than to mercury. Improvement can frequently be found on the day after the injection. In four cases treated at the Dispensary, improvement was rapid, with apparent cure in about ten days, whereas under ordinary circumstances it requires three to six weeks for complete cure. The eye showed improvement

within a few days after the injection. Such rapid improvement is to be expected in such a vascular tissue where the drug can come quickly into contact with the causative factor.

As far as the optic nerve is concerned when optic neuritis exists as a result of syphilitic inflammation, most authors maintain that the injection of 606 has a most rapid and beneficial effect. Shanz, Wechselman and Selligsohn have reported cases of optic neuritis in which arsenobenzol was used with most favorable results. In three cases of papillitis reported by Shanz, improvement was noticed on the same day as the injection. In two cases of optic neuritis treated by injection at the Dispensary the improvement was marked inside of a week. When simple primary atrophy of the nerve exists the consensus of opinion is that no benefit can result from 606. In fact, the atrophic process seems to be unfavorably influenced by the drug. This seems to be the sole contra-indication for 606 in specific diseases of the eye. Some writers also maintain that no benefit results from the use of 606 in ocular paralysis. This has not been our experience in one case seen at the Dispensary. The patient, a woman 49 years of age, with specific history of twenty years' duration, was referred to the eye room on June 20, 1913, with a ptosis of the right lid, which had started one week previous. Examination showed complete ptosis of right eye, paralysis of internal, superior and inferior recti muscles. She received 606 on July 16; six days later all paralyses were very much improved. Ptosis had entirely disappeared and movements of the eye were almost normal.

Summing up the effects of 606 on the eye, I should say that no case of injury to the healthy eye has been proven. The consensus of opinion is that it is innocuous to the healthy eye. A favorable result from the application of this drug is to be expected in syphilitic disease of the iris, the chorioid and retina, and the optic nerve, in paralysis of the ocular muscles, due to syphilis, and sometimes in interstitial keratitis. As far as we can judge in the short time salvarsan has been in use, it must be welcomed as an effective specific remedy in syphilis of the eye, which seems especially indicated in cases in which speedy aid is urgent. It is not a panacea for ocular syphilis which can entirely replace our usual specific preparations. It is especially indicated when a speedy action is desired, as in primary ocular affections, or in secondary or tertiary symptoms, if a rapid impairment of function is dreaded.

ASSOCIATION OF AMERICAN MEDICAL COLLEGES.—The twenty-fourth annual meeting of the Association of American Medical Colleges was held in Chicago on Feb. 25. Five topics of medical education were discussed at the morning session; and in the afternoon there was a symposium on clinical teaching, and an address by the president, Dr. E. P. Lyon, of Minnesota, on "The Principles of Curriculum Making."