QUININE AMAUROSIS WITH REPORT OF A CASE.*

BY

ARTHUR J. BALLANTYNE, M.D.,

SURGEON TO THE GLASGOW EYE INFIRMARY.

OPHTHALMOLOGICAL literature contains reports of a great many cases of quinine amblyopia or amaurosis, yet the condition must be of relatively rare occurrence in this country. The writer has seen three cases in the course of fourteen years, but this is certainly an unusually large number for such a short experience. Uhthoff¹ tells us that he has met with only one case among 100,000 patients.

The history and clinical aspect of the "typical" case of quinine blindness are familiar to all. The patient, in a fit of carelessness or recklessness, swallows a quantity of quinine sulphate, usually much in excess of the pharmacopœial dose. Within a few hours there is tinnitus, deafness, and bilateral blindness. Occasionally there is collapse, delirium, convulsions, or loss of consciousness. Very soon the cerebral symptoms pass off, then the hearing returns, and the patient is left with a visual disturbance very often amounting to total blindness, and with widely dilated and unresponsive pupils. In almost all cases, when the first ophthalmoscopic examination is made, the discs are found to be pale and all the vessels contracted, the arteries often reduced to almost invisible threads. Sometimes the central part of the fundus has a pale cloudy aspect, with a cherry-red spot representing the fovea. After an interval, varying from a few hours up to several weeks, light perception and the pupil reactions begin to return. At first the light perception is only transient, and this feature characterises also the form vision, the return of which soon follows. The recovery of function is at first purely central. In course of time the field of vision expands, but although central vision in many, if not most, cases becomes normal in a few weeks, there remains a permanent concentric contraction of the field. There is also found to be a degree of night-blindness, which, added to the contraction of the field, hampers the patient in spite of the excellent visual acuity. Of the retinal changes, the retinal opacity and foveal spot disappear and the vessels may regain their calibre to some extent, but narrowness of the vessels and a pronounced pallor of the discs are permanent.

The facts of the case now to be reported differed sufficiently from this description to warrant some comment:

The patient, a girl 22 years of age, stated that she had been feeling "run down," and had been taking quinine in the form of pills and powder for some weeks, the powder being in a packet from which she helped herself to a small dose from time to time. On

*Read at a Meeting of the Oxford Ophthalmological Congress, 14th July, 1916.

25th November, 1915, on account of a bad attack of toothache, she took a large dose of the powder. She estimated this at two teaspoonfuls, but there is some doubt as to the accuracy of her statement. In a few hours she felt stupid, with noises in her ears, deafness, and blindness. Her doctor, who was called in, found her in a semi-conscious state, which he attributed to an hysterical fit. He was told the quinine story, but did not think it very reliable. She was admitted to the Glasgow Eye Infirmary, on account of the continued blindness, on 29th November; that is, four days after the onset of her symptoms. I found her mental condition quite clear and her hearing normal, and there was no complaint of tinnitus. Both pupils were widely dilated and quite inactive. Blindness was absolute. She could not see an electric light held close to the eyes, although she could feel its heat. The fundi were practically normal. There was, perhaps, a little haziness of the nasal border of each disc, and some streakiness of the retina along the course of the vessels leaving the temporal side of the discs.

Next day the conditions were unaltered. Further examination of the pupils showed that the orbicularis reflex was present, but neither light, near vision, nor sensory reflexes could be elicited. The girl was of a slightly pasty, anæmic complexion, but well-nourished and apparently placid in temperament. The pulse was 66, temperature normal, and systolic blood pressure 80 mm. Hg. There was a slight cyanosis of the hands. No sensory or motor disturbance existed anywhere, and the heart was normal. The ophthalmoscopic examination was repeated every other day, and on 4th December, nine days after the ingestion of the quinine, and five days after the first examination, the discs were found to be pale and all the vessels abnormally pale and narrow. There was still no vision, and the pupil light-reaction was very doubtful, even with strong focal illumination. Twenty-four hours later, vision began to return. During the brightest time of the day she recognized the face of a nurse and other light objects, but in the dull light of the afternoon she could see nothing. Next day she could count fingers with each eye at one metre, but the field of vision was strictly central and very small, and the function of the retina seemed to be readily exhausted. There was steady improvement in vision from day to day, and a gradual expansion of the field, but at the same time an increasing pallor of the discs and narrowing of the vessels. A week after admission the pulse was 72 and systolic blood pressure 100 mm. Hg.

She was dismissed at the end of December, and had then practically reached the condition in which she is now, seven months from the onset of her symptoms. There have been slight fluctuations the V.A., probably owing to variations in illumination at the times

of testing, her best being, with each eye, 4/9, Snellen, and No. 1, Jaeger. The right pupil is slightly smaller than the left. The reactions are now fairly active. The field of vision shows marked concentric contraction, its maximum extent being 40 degrees from the fixation point in the temporal direction. Central colour vision is normal. She experiences considerable difficulty in finding her way about in the dark. The discs are very pale, like ivory with a delicate suggestion of a pink colour. Both arteries and veins are narrower than normally, the arteries, especially where they cross the discs, being pale in colour.

Comments.

It will be noticed that this case differs from the great majority of those hitherto published, in that, although the patient was first seen four days after the administration of the quinine, a further period of five days elapsed before the characteristic ischæmia of the disc and retinal vessels made its appearance, and it is this feature of the case to which I desire to direct attention, since it seems to have some bearing on the pathogenesis of the condition. An observation of this kind is not unique, but it is very exceptional. Although the statement is occasionally met with in text-books and elsewhere that quinine amaurosis may occur with a normal condition of the fundi, the cases on which the statement is based are not easy to find. The first two cases, one of them unilateral, were reported by v. Graefe², and the conditions in these cases were so unusual that Uhthoff¹ doubts their being due to quinine. Browne³ mentions a case in which contraction of the vessels was first seen on the eighth day, although an examination had been made as early as the fourth day. Again, there is a case seen by Muntedam⁴ in which, five days after the ingestion of the poison, there was œdema of the retina, the disc was not pale, the vessels were not distinctly narrowed, but there was absolute blindness and the pupils were widely dilated. In this instance pallor of the disc was first seen on the twenty-second day, light perception began to return on the twenty-sixth day, and, as vision recovered, the discs grew paler and paler and the arteries became very narrow.

I have not been able to make an exhaustive search of the literature, but so far as it is accessible to me at present these are the only references I have found to quinine amaurosis with a normal, or almost normal, condition of the fundi. In the vast majority of published cases it is clear from the details given that, from the date of the first ophthalmoscopic examination onwards, pallor of the discs and narrowing of the arteries were regularly present.

It is possible that the infrequency with which negative findings have been reported is to some extent due to the fact that the first ophthalmoscopic examination is not made sufficiently early; indeed,

in looking through the published reports one is surprised to find how seldom an examination has been made within a few hours, or even within a few days, of the onset of the blindness. But it would not be safe to assume that in every case a period elapses between the occurrence of the amaurosis and the onset of fundus changes, for there are records of observations even earlier than in my own case, for instance, those of Grüning⁵, Parker⁶, Behse⁷, and Manolescu⁸, in all of which fundus changes were already present as early as from 12 to 48 hours after the poisoning. Another possibility suggests itself, namely, that some of the objective appearances described belong to what might be called the acute stage, others to the later or chronic stage, and that there is usually a gradual transition from one to the other, but that in some few cases the two groups of changes are separated by an interval during which conditions are apparently normal. There is something to be said for this view. For example, when a cloudy pallor and cherry-red spot have been seen to occupy the central part of the fundus, they have been early phenomena, and they have always passed off—usually within a few days. There are other cases in which the earlier conditions were suggestive of retinal hyperæmia, and the later changes were in the direction of ischæmia. Then, from the experimental side, there is the statement of Druault⁹, that we can distinguish between a primary anæmia, which comes on (in dogs) in six to seven hours, and disappears in twenty-four hours, and a secondary anæmia which appears on the fourth or fifth day, increases up to the twentieth or thirtieth day, and is permanent. It is likely that earlier and more systematic examination of the fundi would show the occurrence of a negative period to be less exceptional than it has hitherto appeared to be, but this has been so seldom observed that the current view of the pathogenesis of quinine amaurosis practically ignores it, and is based on the assumption that ischæmia of the vessels of the optic nerve and retina is the earliest result of the ingestion of quinine, that it is the cause of the amaurosis, and that it persists, the pallor of the nerve passing through time into a condition of true atrophy. This view is supposed to be confirmed on the pathological side by the experimental work of de Schweinitz^{11, 12}, Holden¹³, and others, but neither the clinical nor the histological foundations of the theory are complete.

Turning first to the clinical aspect, it will be admitted that even a single case of the kind here reported would be enough to prove that the presence of ischæmia is not essential for the amaurosis; but even if one considers only the "typical" cases, one must be struck with the want of parallelism between the ischæmic phenomena and the state of the vision. It may almost be said to be the rule for the pallor of the disc and the attenuation of the retinal vessels to

become more and more pronounced during the very period when vision is returning. The other fundus changes sometimes described, such as blurring of the disc margins, congestion of the retinal vessels, œdema of the retina, the red foveal spot, etc., even if they were always present, are transient, and it is still less easy to establish a correspondence between them and the profound loss of vision which characterises the early stages of the affection.

For our knowledge of the pathological histology of quinine amaurosis, we are almost entirely dependent on the results of animal experiments, for example, those of Druault, Ward Holden, and de Schweinitz, in which dogs were employed. All are pretty well agreed that at a comparatively early stage degenerative changes can be observed in the ganglion cells of the retina, while the later changes comprise an ascending atrophy of the nerve fibres traceable as far up as the external geniculate body, and organic changes in the retinal vessels in the form of endovascularitis, etc. Holden's¹³ view of the pathogenesis of the condition is that there is first a pronounced ischæmia of the optic nerve and retina, that this leads to degeneration of the retinal ganglion cells and nerve fibres (the immediate cause of the amaurosis), and that this, in turn, leads to ascending atrophy of the optic nerve. Druault^{9,10}, on the other hand, says that the degenerative changes are due to the direct toxic action of the quinine on the ganglion cells, and that the retinal ischæmia has little or no significance for the amaurosis. We have already seen that he distinguishes between a primary anæmia of the papilla and retina, which is transient, and a secondary, permanent, anæmia, which, in his view, is the result, and not the cause, of the cytological changes. Holden's theory, or something like it, is the one most generally accepted, but is unsatisfactory in so far as it fails to explain the few cases in which ophthalmoscopic examination has given a negative result. In such a case as the one I have described above, one may say with confidence that, if ischæmia of the retina and nerve is the first link in the pathogenic chain, it must have been such a transient ischæmia as Druault refers to. And no one can readily believe that a temporary interference with the nutrition of the retina might bring about changes in the ganglion cells which would persist, even after the circulation was restored. I am not aware that Druault's observation has been confirmed in any human case of quinine poisoning. A single case observed at the earliest possible moment, and kept under careful observation until the final state was reached, might clear up the whole question. On the other hand, if such a transient ischæmia does not occur (and there is no reference to it in the animal experiments of Holden and de Schweinitz, or in the human experiments of Barabaschew¹⁴), the only alternative, in such a case as my own, would be to accept the view of Druault, that the amaurosis is due to a direct toxic effect of quinine on the structures

of the retina. But whether quinine does or does not cause a direct action of this kind on the cells, one must not overlook the evidence that it can influence the vision through the circulation. Apart from evidence of arterial spasm derived from animal experiments, there is the observation of a case of quinine amaurosis by Stasinski¹⁵, in which vision improved in the recumbent and diminished in the sitting posture, and that of Zanotti¹⁶, of a girl under treatment for malarial choroido-retinitis, who after each dose of 0.75 cg. of quinine, had diminished vision associated with pallor of the discs and narrowness of the retinal arteries.

Whatever may be the change responsible for the amaurosis, we are safe in saying that it is not one of those visible with the ophthalmoscope, and if it is situated in the retina it must be microscopic. We can go further and say that while at first all the cells are so profoundly affected as to cause entire loss of vision, yet in at least a proportion of them there is complete recovery; in other words, that there may be inhibition of the function of the cells without their complete destruction.

At the best, our knowledge of the pathology of the condition is incomplete, for the researches of Holden, de Schweinitz, and Druault have not differentiated this initial, transient, change, from the permanent signs of degeneration in the retinal ganglion cells, nor have they explained the difference in behaviour of the central and peripheral parts of the retina. Again, they do not help us to understand the cloudy retinal opacity and red foveal spot which are sometimes seen. From the strong resemblance that the latter bear to the appearances resulting from embolism of the central retinal artery, it is natural to conclude that in this case also the condition of the fundus represents a coagulation-necrosis due to ischæmia. There is, however, a striking contrast in the further progress of the two conditions, for in embolism of the central artery the picture lasts for some time, and a profound loss of vision, both central and peripheral, is the rule; while in quinine amaurosis the appearance disappears in a few hours or days, and there may be complete restoration of central vision. Perhaps the difference is entirely one of degree, the arterial obstruction in the one case being due to spasm which passes off, while in the other the blockage of the central artery causes a much more complete and prolonged interference with the nutrition of the retinal elements concerned. It is evident that the retinal cloud is not, in either of the cases, the *cause* of the visual defect, since the latter can exist in the absence of retinal opacity, or persist in spite of its disappearance.

As regards the permanent fundus changes, Ward Holden, in his experiments on dogs, found atrophy of the optic nerve fibres, which he believed to be an ascending atrophy due to retinal degeneration. Nerve atrophy has also been found by others, and it appears to be

generally assumed that the persisting disc pallor in the human cases represents a true atrophy of the optic nerve. We have to remember, however, that these researches were performed on dogs, which are particularly susceptible to the effects of quinine, and that the doses given were never far short of the lethal dose. We cannot be sure that similar conditions hold good for the human eye, for opportunities for histological examination in the human subject are very rare. I have found only one such observation on record, namely, by Fortunati¹⁷, where the patient died on the eighth day; and in this case chromatolysis of the retinal ganglion cells was found, but nothing abnormal in the optic nerves. In the case which I have reported above, the blanching of the disc and the constriction of the retinal arteries came on rapidly and simultaneously, as if there were a simultaneous constriction of all the ocular vessels. This occurred on the eighth or ninth day after the onset of blindness, and it was not accompanied by a reduction in the amount of vision or in the extent of the field; on the contrary, vision began to return twenty-four hours later, and improved for some time, while the fundus changes became only the more distinct. In view of this sequence of events it seems to me that the pallor of the disc is to be explained as the result of contraction of its blood-vessels simultaneously with contraction of those of the retina. The discs are still pale, seven months after the onset of the amaurosis, but I should hesitate to describe them as atrophic.

Several explanations might be offered to account for the better recovery of central than of peripheral vision. In the first place, it might be supposed that the initial ischæmia, assuming that to be the cause of the amaurosis, led to a more profound and permanent loss of function in the ganglion cells of the less vascular periphery of the retina. Here we are met with the difficulty which confronts all vascular explanations of the affection, namely, that there is no parallelism between the degree of vascular contraction and the amount of visual loss, for in the presence of a stationary, or even increasing, ischæmia, the vision may be steadily improving. Nor does the analogy of embolism of the central artery assist us at all, since, in a few cases of the latter which regain some vision, it is sometimes peripheral, sometimes central, sometimes in sectors, apparently according to peculiarities of the vascular supply. Again, it has been suggested that quinine exercises a selective action on the ganglionic elements in the periphery of the retina, just as tobacco selects those of the macular region. On the other hand, if we are to accept the theory that quinine acts by a direct toxic effect on the retina, through the blood stream, we must assume that the rods and cones, deriving their nutrition from the rich vascular supply of the choroid, are at least equally exposed to the poison. The different distribution, and the structural and functional differences of the rods

and cones, makes it at least possible that we have an explanation of the peripheral defect in a selective action of quinine on the rods. The night-blindness, so often complained of in these cases, supports this view; but although I suggest this as an alternative explanation, I am not aware that any histological changes have been found either to confirm or to contradict it.*

To summarise what has been said, I think that a consideration of the subject in the light of the case here reported entitles us to conclude:

1. That in quinine poisoning complete loss of vision may be found in association with a normal condition of the fundus oculi, and that there may be a striking recovery of vision in spite of the presence of well-marked fundus changes.

2. That in all, or nearly all, cases of quinine amaurosis, ophthalmoscopic changes, such as congestion of optic nerve and retina, pallor of the disc, narrowness of the retinal vessels, and cloudy opacity of the retina, make their appearance sooner or later, but that there is no correspondence between the character or severity of these changes and the intensity of the visual defect.

3. That the visual defect cannot, therefore, be due to such changes, but rather to a condition of the retinal elements invisible with the ophthalmoscope.

4. That this change may be induced, or aggravated, in the first place, by ischæmia due to contraction of the vessels of the optic nerve and retina, but that it is, in the main, the result of a direct toxic action of quinine upon the retina itself, and that the ultimate recovery of central vision, with loss of peripheral vision, and failure of vision in twilight, suggests a selective action of the poison upon the rods.

REFERENCES.

1. **Uththoff**.—Graefe-Saemisch *Handbuch*, Vol. XI, Section 2A, 1911.
2. **v. Graefe**.—*Archiv f. Ophthalmologie*, Vol. III, Part 2, p. 396, 1857.
3. **Browne, Edgar**.—*Transactions Ophthalmological Society U.K.*, 9th December, 1886.
4. **Muntedam**.—Reference in *Centralblatt f. prakt. Augenheilkunde*, Vol. XXIV, 1900.
5. **Grüning**.—*Archiv für Augenheilkunde*, Vol. XI, p. 145, 1882.
6. **Parker, T. J.**—*Archiv für Augenheilkunde*, Vol. LVI, 1906.
7. **Behse, T.**—Reference in *THE OPHTHALMOSCOPE*, 1900.
8. **Manolescu**.—*Klin. Monatsbl. für Augenheilkunde*, Vol. XLIX, p. 369, 1911.
9. **Druault**.—*Archives d'Ophthalmologie*, 1902.
10. **Druault**.—*Transactions Heidelberg Congress*, 1900.
11. **de Schweinitz, G. E.**—*Ophthalmic Review*, Vol. X, p. 49, 1891.
12. **de Schweinitz, G. E.**—Norris and Oliver's "System of Diseases of the Eye," Vol. IV, 1900.

* Dr. F. W. Edridge-Green, with whom I have had an opportunity of discussing this case, supports the suggestion here offered, and points out that if quinine inhibits, and to some extent permanently destroys, the function of the rods in the production of the visual purple, his theory of vision would lead us to expect just such a visual result in quinine poisoning as that described.

A. J. B.

13. **Holden, Ward.**—*Transactions American Ophthalmological Society*, 1898, Reference in *Ophthalmic Review*, 1899.
14. **Barabaszew.**—*Vestnik Ophtal.*, Reference in *Ophthalmic Review*, Vol. X, 1891.
15. **Stasinski, J.**—*Klin. Monatsbl. für Augenheilkunde*, Vol. XLVII, 1910.
16. **Zanotti, M.**—Reference in *Ophthalmic Review*, Vol. XVIII, 1899.
17. **Fortunati.**—Reference in *Centralblatt f. prakt. Augenheilkunde*, Vol. XXIX, 1905.

THE INFLUENCE OF VASCULAR DISEASE IN THE RETINA ON THE PROGNOSIS AS REGARDS LIFE.*

BY

P. H. ADAMS, F.R.C.S., D.O.,

MARGARET OGILVIE READER IN OPHTHALMOLOGY, UNIVERSITY OF OXFORD.

THE most numerous cases of general medical interest that we, as ophthalmic surgeons, see are those that have some form or other of disease of the vascular system. It is by no means unusual for the failure of vision to be the first symptom that obtrudes itself on the notice of the patient, and sends him to seek advice of the eye specialist. These cases one examines and finds various pathological manifestations in the retina, returns them to their general medical adviser for treatment, and not infrequently loses sight of them henceforth, or else they attend the hospital, are put on to potassium iodide, and attend for a variable length of time, and then are no more seen.

With the idea of finding out what happens to these patients and when, I have undertaken an enquiry and endeavoured to trace the end of such cases. When I began, I imagined the majority of them would be dead, and accordingly first applied to the various registrars for details, but meeting with somewhat poor results, I next sent reply-paid postcards to the patients themselves, enquiring after their health, and was very agreeably surprised to find the number who were still living.

The types of retinal lesions I selected were flame-shaped hæmorrhages and signs of vascular disease in the retina, venous thrombosis and hæmorrhagic retinitis, "embolism" of the central artery, retinitis circinata; in fact, all those conditions usually associated with the condition of arterio-sclerosis. I purposely omitted true albuminuric retinitis, as the fate of such patients is well-known. A few cases of diabetic retinitis have crept in accidentally and a few traumatic hæmorrhages, but these latter have not been included in the statistics.

In one way or another I have collected 159 cases from the

* Read at the Oxford Ophthalmological Congress, July, 1916.