Additional experiments to determine the lesion in quinine blindness / by G. E. de Schweinitz.

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ADDITIONAL EXPERIMENTS TO DETERMINE THE LESION IN QUININE BLINDNESS.

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With Photo-micrographic studies by William M. Gray, M.D.

A communication presented to the College of Physicians of Philadelphia, November, 1890,* contained the results of some experiments which I had made in the endeavor to determine the lesion in quinine blindness. A brief summary of this research is the following: Quinine given hypodermically to dogs in quantities varying from one grain to four grains to the pound, produces blindness in from three to fourteen hours, the earliest appearance of the amaurosis after the injection being three hours. The blindness remained practically complete in one animal for twenty-nine days after a single injection of $3\frac{3}{4}$ grains to the pound; in one there was a slight return of vision after thirty-six hours of blindness. The effects of the drug were obtained more quickly and more surely with quin. bimur. carbamidat. than when the bisulphate was used. A dose exceeding $3\frac{3}{4}$ grains to the pound produced death; one animal perished from a dose of three grains to the pound; and one dog resisted $1\frac{7}{8}$ grains of quinine to the pound given on two successive days, but succumbed when a third similarly proportioned dose was administered. With two exceptions the animals suffered from other symptoms in addition to the blindness, viz: vomiting,

* Transactions of College of Physicians of Phila., 1890; also Ophthalmic Review, February, 1891.

or staggering gait, or paraplegia, or convulsions. The two exceptions became blind without any general symptoms, and in one of these the most noted microscopical changes were found.

The ophthalmoscopic picture in these animals was in all instances similar to that which has been noted in human beings, suffering from quinine amaurosis. In one there was complete obliteration of the vessels in the disc; in another, blurring of the edges of the papilla. In all the pupils were immovably dilated. The microscope did not discover any very *coarse* lesions except in one dog, in which the central vein was plugged with a clot, and in the transverse cuts of the smaller veins white thrombi were visible. In other nerve entrances there was some dilatation of the vessels. In the transverse cuts of the optic nerve there was some increase of the connective tissue, and a curious appearance was the spreading apart of the individual nerve-fibrils as if the tissue was œdematous. There was no true atrophy demonstrable by Weigert's method, even in the nerve of a dog blind for twenty-nine days. Chiasms, retinas, and choroids were normal. In sections from the cuneus there was remarkable dilatation of the pericellular lymph spaces, with degeneration of the protoplasm of the cells. From these results it became evident that toxic doses of quinine could produce thrombosis in the central vein, and that, as negative evidence, neither neuritis, nor atrophy in the true sense of the word, was present in an animal blind for nearly a month (although the disc was quite white and the vessels threads), but that there appeared to be a species of œdema between the optic nerve and chiasm.

Certain additional evidence is desirable, viz.:

(1) Can the same results be produced with salts of quinine other than with those composed of the bimuriate of quinine combined with the carbamide of urea, and will all of these results be apparent in animals so poisoned that blindness, unaccompanied by general symptoms, is the sole effect?

(2) Will the prolongation of the quinine blindness produce true atrophy?

(3) Is the production of thrombosis or embolism to be expected in severe cases?

(4) Is the apparent degeneration of the brain cells the result of the hardening process, or due to a lesion from the drug?

I. In the first research, the effect of the quin. bimur. carbamidat. was found to be more pronounced than the ordinary bisulphate of quinine, although it was shown that the latter was active. Since then in a number of instances I have produced blindness by using quinine dissolved with the aid of tartaric acid or dilute hydrochloric acid, and have used quinine from several different sources. It is needless to detail these experiments. The results were the same as those already published. In regard to the second portion of the first query, an affirmative answer may be given, as the detailed research presently to be given will show, as it will also answer the other questions. One experiment is detailed.

Experiment. Black dog, weight 15 pounds, was given 30 grains of bisulphate of quinine at 4.15 P. M., October 28, 1890, previous examination having shown normal fundus oculi, pupil reactions, and cornea.

October 29. Partially blind. Runs with nose stretched out and apparently finding his way by the sense of smell; frequently butts his head against objects, as one whose field of vision is deficient. *Ophthalmoscope.* Pupils widely dilated. Cornea not anaesthetic. No evident change in the color of the disc or caliber of the veins; arteries smaller than on previous day. Thirty additional grains of quinine injected.

October 30. Dog entirely blind, but not deaf. Slight vertical nystagmus. Pupil dilated. No anaesthesia of cornea. *Ophthalmoscope.* No change in veins; arteries small.

November 17. Daily record of animal's condition omitted, which may be summarized as gradual shrinking of the arteries, loss in color of disc, and contraction of veins. No general symptoms occurred, and on this date (November 17, 1890) discs entirely white; arteries not distinguishable. Only faint traces of the lower veins in each eye.

December 25. There has been practically no change in the animal. During the last day or two, however, there appears to be some return of sight, as he now avoids certain objects in the room and fails to promptly respond to the ordinary tests. The *ophthalmoscope* shows no new changes in the fundus.

December 26. Fifteen additional grains of quinine administered.

December 29. Dog apparently completely blind. *Ophthalmoscope.* In each eye the discs entirely white, only the lower temporal veins being visible. The position of the arteries is marked by faint white threads. The animal was killed, and the eyeballs, optic nerves, chiasms, and entire brain were placed in Mueller's fluid and prepared with the utmost care for section. Some days later a normal dog was similarly killed and the same organs removed and placed in Mueller's fluid for comparison.

The specimens, which were removed for microscopic examination, were sectioned for the microscope by Dr. William M. Gray, and from the sections thus obtained the accompanying photo-micrographs prepared. The following are the results of the microscopic examination: (Fig. 1, Pl. I, is the normal optic entrance.)

At the point of entrance of the central vessels — the vessel infundibulum — a cup has been formed somewhat similar to the excavation seen in glaucoma. This cup is partly filled by a fine granular substance, a portion of which is arranged in threads holding in its meshes a few blood corpuscles. A little below the cupped entrance is a dense plug of this granular substance. Below this plug the central vessel is seen, the walls of which are somewhat thickened, and its lumen almost entirely filled by a connective tissue growth composed of fine reticular fibrous connective tissue, small spindle cells with long processes, and small round cells. (Fig. 2, Pl. I). Scattered through this structure and in relation to the cells is a small quantity of pigment. Running through the center of this mass of tissue which fills the vessel there is a small capillary arteriole, narrow at its upper extremity, but at its lower fourth suddenly expanding to at least double the size of the upper portion (Fig. 3, Pl. II, high power). To one side of the upper extremity of this capillary vessel is an irregularly-shaped space, formed in the connective tissue filling the large vessels. This space contains a few blood corpuscles and seemingly is lined by endothelium, a few nuclei being seen around the edge (Fig. 3, Pl. II). At its upper extremity this space leads off into a series of branching capillary vessels, which run into and are lost in the surrounding nerve tissue. At the lower portion of the large occluded central vessel there is a blood sinus which also leads

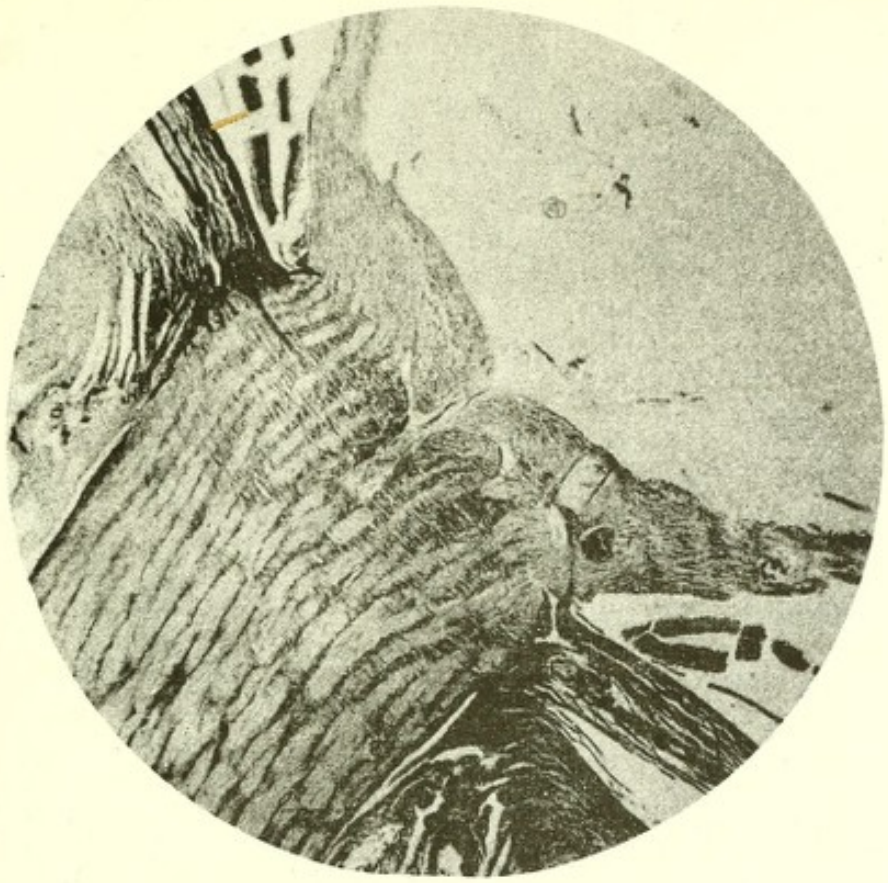

FIGURE 1. Optic nerve entrance of the normal dog. [× 75.]

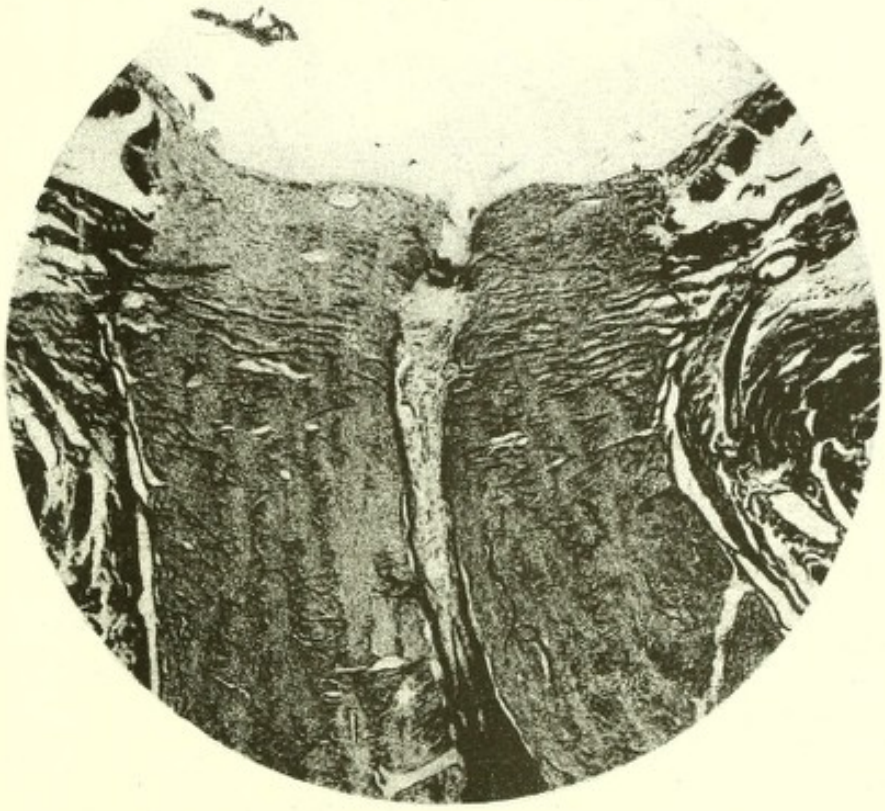

FIGURE 2. Quinine-dog nerve entrance, showing cupping and occluded vessel. [× 100.]

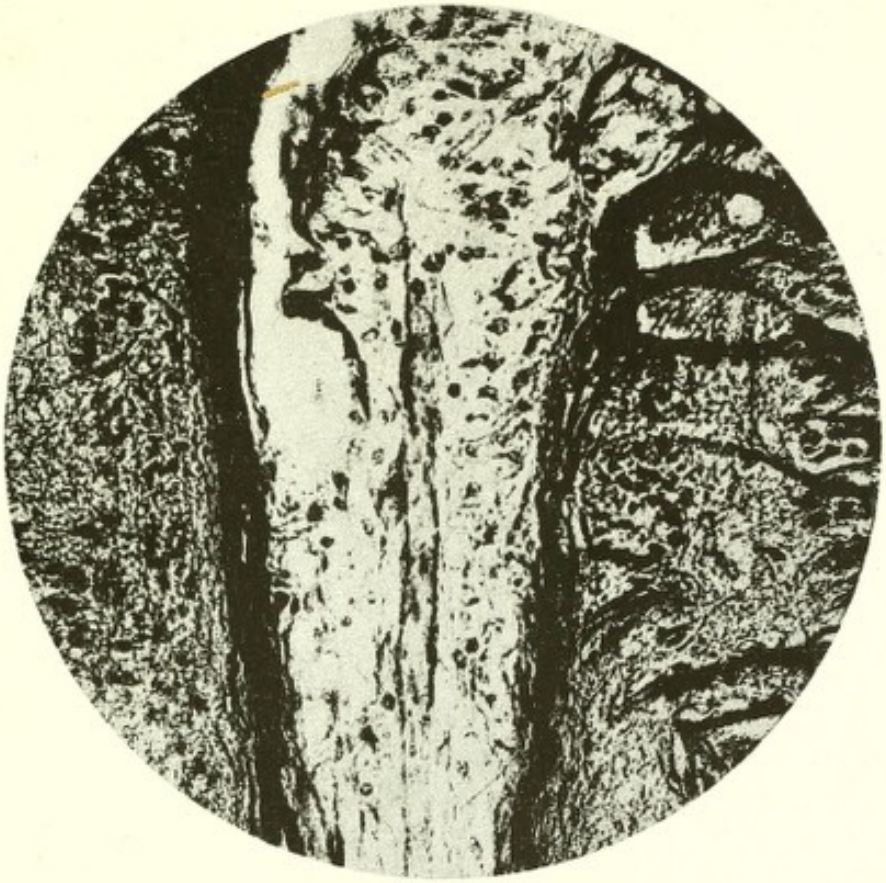

FIGURE 3. Same section as figure 1, showing the tissue filling the vessel, capillary arteriole running through the centre of the tissue, and the large cavity formed in it. [× 250.]

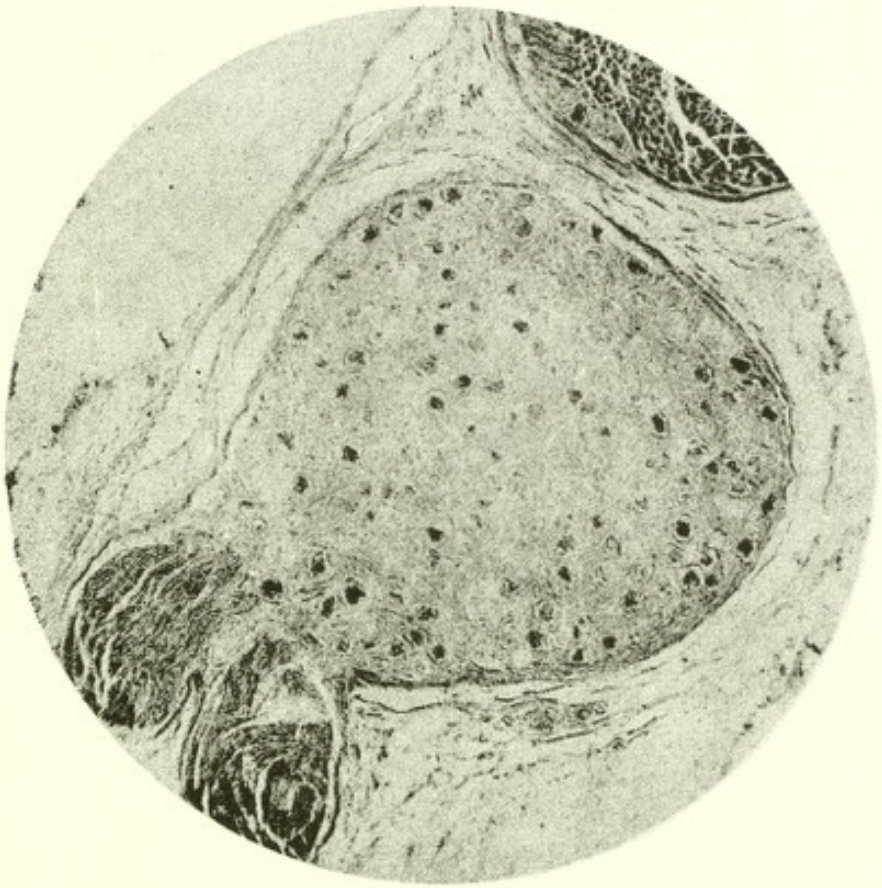

FIGURE 4. Ciliary ganglion from quinine-dog, showing above part of the oculo-motor nerve, and springing from the ganglion short ciliary nerves. [Weigert's stain.]

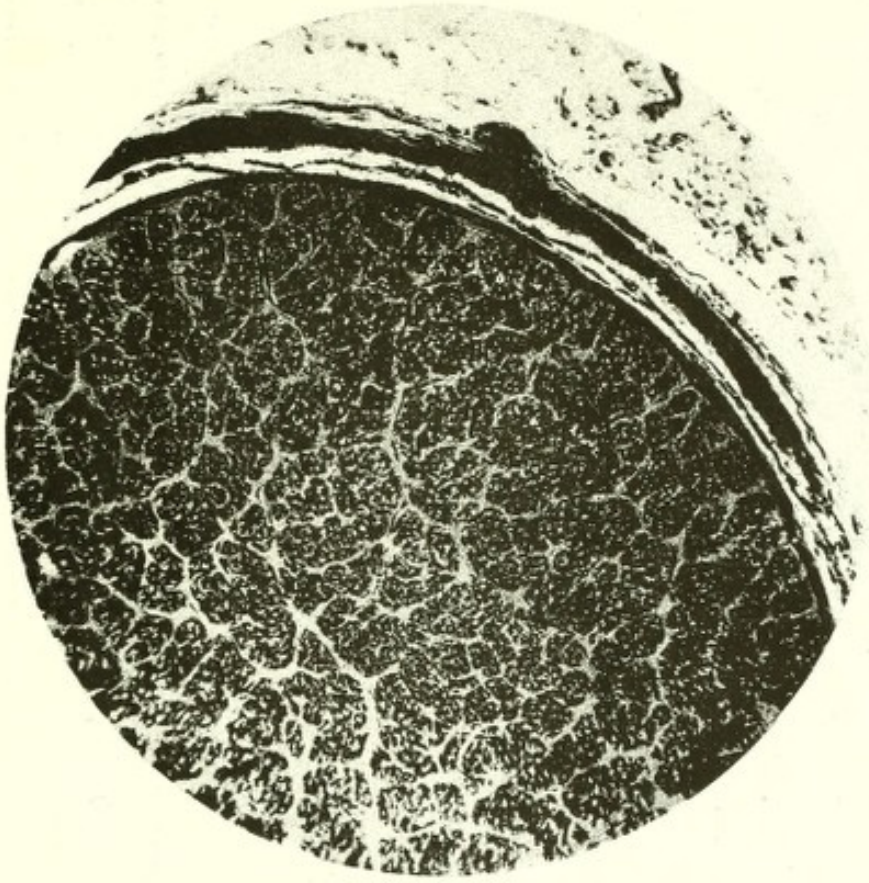

FIGURE 5. Normal optic nerve of a dog. [× 125, Weigert's stain.]

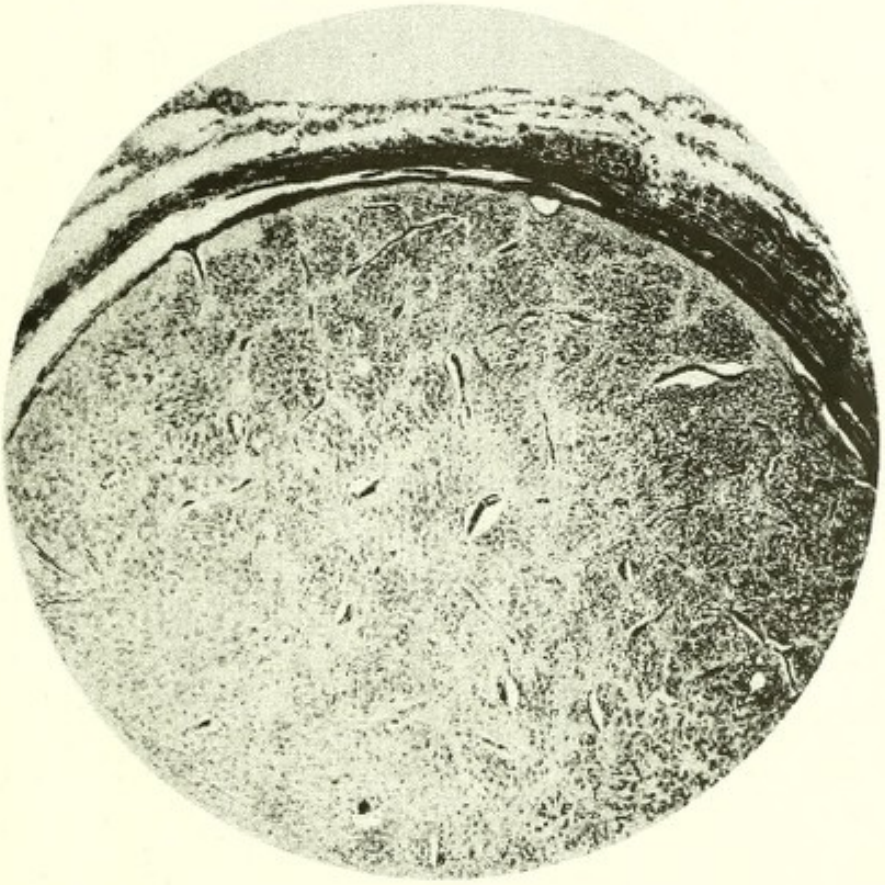

FIGURE 6. Optic nerve of a dog, blind from the effects of quinine for two months, showing atrophy and degeneration.
[× 125, Weigert's stain.]

off into the surrounding nerve tissue (Fig. 2, Pl. I). There are other, but smaller, sinuses or vessels passing from the main vessel along its entire course. In a number of the sections, both in the first series of quinine dogs and from the one which is under consideration in the present paper, the cup at the central vessel entrance is seen, and, protruding from the cup, masses of material, partly homogeneous and partly granular, containing a few nuclei. In one section the lower portion of this cupped entrance is constricted, and below the point of constriction the vessel rapidly expands, its lumen being filled by a finely-reticular fibrous connective tissue, holding in its meshes a mass of small round cells. Here and there in this mass of tissue there are blood sinuses which contain a few blood cells. To one side of the central cup, where Mueller's fibres enter the nerve from the retina, there is an expanded blood vessel filled with a blood clot. In one dog, of the original series of quinine experiments, the cupping is well marked, and protruding from the cupped entrance is a mass of the granular and homogeneous material such as has been described. The entrance to the vessel is greatly constricted immediately after passing into the upper opening, and it is partly filled by the granular material. In one section is shown a small vessel formed of this granular homogeneous material which extends through the constricted entrance to the central vessel. Below the entrance and constriction the central vessel is lost in a mass of dense fibrous tissue. This tissue contains numerous small blood vessels or channels, some of which lead off into the surrounding nerve tissue

Transverse sections of the optic nerve and chiasm of the dog blind for two months, stained by Weigert's process, show marked degenerative changes. Fig. 5, Pl. III, represents a transverse cut of a normal dog's optic nerve stained by this process, while Fig. 6, Pl. III, has been prepared from a similar cut taken from the dog blind from the effects of quinine for two months. The contrast in these two sections is well shown. In the quinine dog there is complete destruction of the nerve fibres, some increase of connective tissue, and a small amount of fatty infiltration. In one specimen the section has passed through the lenticular

ganglion, showing the development of the ciliary nerves and some slight degenerative changes in the ganglion itself (Fig. 4, Pl. II). A section of a normal ganglion stained by Weigert's process compared with the ganglion from the quinine specimen, prepared by exactly the same process, illustrates the degeneration in the fibres. The transverse sections of the chiasm may be compared with similar sections taken from the normal dog, from whence it is evident that the degenerative process and complete atrophy exist in all of the fibres up to the chiasm, in the chiasm itself, as far backward as it has been possible to trace the optic tracts. The dilatation of the pericellular lymph-spaces through the brain in the first series, especially in the cuneus, have been shown by a number of experiments to be unconnected with any action of quinine, being easily produced by any slight fault in the technique.

From what has been said, it will be seen that the answer to the second question is that the prolongation of quinine blindness produces true atrophy. The answer to the third question is also affirmative, namely, that thrombosis of the central vessels may be expected in severe cases of the toxic action of this drug; while the answer to the fourth question, as has just been stated, is negative, as the degeneration of the brain cells is the result of the hardening process, and not due to a lesion from the drug.

In *résumé* we may say in regard to the microscopical points, that we have thickening and changes in the walls of the central vessel (endo-vasculitis); organization of a clot, the result of thrombosis, an organization which has been carried on even to the extent of its being channeled by new vessels; widening of the infundibulum of the vessels as the result of the constriction of the surrounding nerve fibres, presenting appearances not unlike a glaucomatous excavation; and finally, practically complete atrophy of the visual path, including the optic nerves, optic chiasm, and optic tracts, as far as they could be traced. It seems, then, very likely that the original effect of quinine is upon the vaso-motor centers, producing constriction of the vessels; that finally changes in the vessels themselves are set up, owing, perhaps, to an endo-vasculitis; that thrombosis may

occur, and that the result of all of these is an extensive atrophy of the visual tract. Not the least remarkable is the selective influence of quinine on the optic nerves and the optic tract. In the sections and the micro-photographs herewith presented, it will be seen that the ciliary and oculo-motor nerves, side by side with the optic nerve, are perfectly normal, and that even in the lenticular ganglion many of the fibres are perfectly intact, although others appear to have undergone a slight degeneration. The same, no doubt, is true of the other cranial nerves. The selective action of drugs is, of course, well known, the characteristic action of digitalis upon the heart being, perhaps, the most typical example. This, however, in addition to the well-known physiological action of drugs, appears to be a histological demonstration of such affinities. Why quinine should produce these lesions upon the nerves of special sense which supply the eye and the ear, it is difficult to understand; that it has such action is unquestioned, and here meets with a positive microscopic demonstration. While, no doubt, the original effect is in some sense due to the influence of this drug upon the vaso-motor centers, this cannot be the entire explanation, or we should have similar actions under the action of well-known vaso-motor stimulants, like ergot.