CASE 3.—This case came to my laboratory at Gallipolis from Defiance, Ohio, Nov. 14, 1898. The dog, whose carcass was sent for examination, had bitten several school children, and the city authorities took the matter in hand, sending the children to the Chicago Pasteur Institute, and the dog to me for examination. I made subdural inoculations in three rabbits with absolutely negative results. In due time the children were returned home and no trouble was experienced.

CASE 4.—A suspected dog, which had bitten several other dogs in Gallipolis last January, was brought to the laboratory within a few hours after being killed. Experimental inoculation of two rabbits proved negative, and none of the dogs developed rabies.

CASE 5.—This was submitted by Dr. J. W. Long, Bryan, Ohio, March 5, 1901. Here a dog had bitten two men and one boy, after which it was killed and the head and neck expressed to the Pathologic Laboratory of the Ohio Hospital for Epileptics, reaching here March 6, in good condition. Three rabbits were at once inoculated with an emulsion of the dog's medulla by the intracerebral method of Leclainche-Morel, and another by the intranasal method of Galli-Valerio and Solomon. The cervical spinal ganglia of the dog were at once subjected to histologic examination, and the lesions of the Van Gehuchten-Nelis reaction were recognized, so that, thirty hours after the dog's head arrived I telegraphed Dr. Long of the positive indications of the histologic test and urged him to submit his patients to the Pasteur treatment, this time in the Pasteur Department of the Baltimore City Hospital; he did this at once. Between March 20 and 21 the three rabbits of the Leclainche-Morel inoculation died of typical paralytic rabies, and on March 22 the one subjected to nasal inoculation died in the same manner. A second series of inoculations in rabbits has since been positive. The ganglia of the first series of rabbits, including the cranial, spinal and sympathetic, have been carefully studied by the Van Gehuchten-Nelis method, all with typical results. This I shall endeavor to show you by the microscopic demonstration which you will find in the pathologic exhibit. The patients returned home after the full course of preventive treatment at Baltimore and up to the present moment are entirely well.

SUMMARY.

1. Four instances in which human beings were bitten by dogs suspected of rabies were tested by laboratory methods with positive results in two. All the patients were given the preventive treatment.

2. In three cases the patients were treated at the Chicago Pasteur Institute, and here the only one positive by laboratory test died of rabies in the midst of treatment, presumably because the inauguration of treatment was somewhat delayed and because the stage of incubation was remarkably short.

3. In the fourth case, conclusively demonstrated as rabies in the laboratory, the patients were promptly treated in the Pasteur Department of the Baltimore City Hospital, and they have given no evidence of the disease six months after having been bitten.

DISCUSSION.

DR. FRANK J. HALL, Kansas City, Mo.—I had a case of hydrophobia when I was not familiar with this method of differentiation and made a search at that time for the so-called "tubercles of Babes," but failed to find them. I did, however, find a great quantity of strongly pigmented leucocytes surrounding the vessels in the chord, in the brain and in the parotid gland. I wish to ask if these leucocytes have been observed by the reader, and if he considers them of any diag-

nostic importance, or are they observed frequently in this disorder? I had a large white bull-dog that had "gone mad" and, keeping it under observation until its death, prepared an emulsion from the medulla, and inoculated this material into the anterior chamber of the eyes of rabbits. The animals never showed the symptoms of hydrophobia and, therefore, we failed with that method. The eyes of the inoculated animals became very much swollen and became translucent as if injected with water, but aside from that, there were no changes at all. The certainty that my dog was a victim of hydrophobia was proven by the fact that a horse bitten at the same time that the three human beings were bitten, died of hydrophobia 42 days later.

DR. A. P. OHLMACHER, in reply—Concerning the presence of pigmented cells, I will say that while I have had some experience in studying the histology of the hydrophobic condition, and have made an examination of the spinal cord from a number of experimental cases, I believe I have not seen these pigmented cells, or, if they have been seen, I have not thought that they had any special relation to the morbid process attending hydrophobia.

THE NEWER PATHOLOGY OF THE RETINA.

WITH SPECIAL REFERENCE TO THE CHANGES
PRODUCED IN THE GANGLION CELLS
BY CERTAIN TOXIC AGENTS.*

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In looking through the text-books of ophthalmology of fifty years ago we are struck by the extensive group of amblyopias and amauroses. Ruete describes thirty-seven varieties. The terms were convenient, for as we read in Faust

Denn eben wo Begriffe fehlen

Da stellt ein Wort zur rechten Zeit sich ein.

By the aid of ophthalmoscopy and of pathology this great category has been reduced more and more, until now there are but a few important classes of cases for which these terms are still considered useful. Prominent among them are the toxic amblyopias. These have gradually assumed greater and greater importance. The clinical symptoms produced by the various poisons and the character and degree of the visual impairment are now quite well known. Our knowledge, however, of the pathological changes upon which these depend, of the location of the lesion in the visual apparatus, is far from being established. It is our purpose to review briefly the recent studies of this subject and note the conclusions we may draw from them.

I must begin by directing your attention to the great advance made in the histology of the nerve cell through the recently discovered methods of selective staining of different portions of the cell substance, methods which are particularly associated with the name of Nissl. For, while the older methods of staining enabled us to recognize the general structure of the nerve cell with its nucleus and nucleolus and the Golgi-Cajal and Ehrlich methods exposed their numerous ramifications and connections, the intimate structure and composition of the cell is only now revealed to us by the Nissl method. This observer has shown that the cell body contains substances which react very differently to his stains. While portions of the substance remain colorless, other parts take on an intense stain. These are known as the chromatic substance and often called the Nissl bodies.

* Read at the Fifty-second Annual Meeting of the American Medical Association, in the Section on Ophthalmology, and approved for publication by the Executive Committee of the Section: Drs J. A. Lippincott, Casey A. Wood and H. V. Würdemann.

While varying greatly in different forms of cells they are sufficiently constant under the same normal conditions to lead Nissl to regard them as indices of the normal or abnormal structure of the nerve cell.

The researches made by means of this method in the ganglion cells of the retina are not as yet extensive. Those that have appeared are important not only for their reference to the organs of vision but also in their bearing on general nerve histology.

Mann,¹ Bach,² Abelsdorff³ and others have studied the retina under normal conditions, and Dr. Ward A. Holden⁴ used the method to determine the effects of quinin and methyl alcohol. The most extensive and important work upon the subject appeared recently from the pen of Birch-Hirschfeld.⁵ This observer first endeavored to determine the normal condition of the retina, the variations of the nerve cells in different species of animals, the effects of various hardening fluids and of different staining methods, and of postmortem changes. Next, he investigated the effect on the retina of protection from light or of exposure to various intensities of daylight and of the electric arc light.

It is not possible for me to enter into the details of these results, but it is necessary to state that they were definite and constant under the same conditions. His illustrations showing the normal appearance of the retina (the stain was thionin and erythrosin), as well as those of Abelsdorff are here shown.[†] You will see that the retinal ganglion cells contain the intensely blue Nissl bodies, between which there is the unstained substance. In the eyes which have been subjected to light the Nissl bodies are somewhat more diffuse than in those in which the eye has been kept in the dark. One drawing shows the effect of exposure for five minutes to a brilliant electric light; the Nissl bodies of many of the cells are almost entirely lost. In another eye treated in the same manner but allowed to recover for one hour in the dark the Nissl bodies are regenerated and show normal conditions.

QUININ.

Various theories had been expressed concerning the action of this drug on the retina. Obliteration of the caliber of the vessels through endovasculitis on the one hand, through irritative contraction on the other were assigned as causes. De Bono⁶ in 1894 thought that its action was that of a plasma poison on the terminal retinal cells. It was Dr. Holden, as I stated before, who was the first to investigate its effect on the retinal ganglion cells by means of Nissl's method. His results showed that there were no histological changes in the vessels of the retina or nerves. He found a "constriction of the retinal vessels and particularly of the arteries followed by a highly albuminous serous exudation into the nerve fiber layer and a degeneration of the ganglion cells together with their axis cylinder processes which become the centripetal fibers of the optic nerve." The degenerative changes in the ganglion cells manifested themselves by the formation of vacuoles, wandering of the nucleus toward the periphery of the cells and disintegration and disappearance of the chromatic substance.

He states that "there is no way of determining exactly how far the degeneration of the ganglion cells and their axis-cylinders may be due to the direct toxic action upon them of the cinchonized blood, and how far the degeneration may be due to the indirect toxic action of quinin

in constricting the retinal vessels, and thus reducing their nutritive supply." He inclines to the view that "the changes in the retina in quinin amblyopia are due chiefly to deficiency of nutritive supply, and, to a lesser degree, to alteration in the quality of the nutritive supply."

Birch-Hirschfeld* has repeated Holden's experiments on rabbits and on dogs. The results were uniform. The ganglionic cells showed slight decrease in size, blurring or obliteration of the outline of the cell and the formation of smaller or larger vacuoles. The most important change was in the chromatic substance. In most cases this was still to be seen as fine particles lying peripherally. The nucleus was sometimes swollen, sometimes shrunken, the nucleolus showed irregularity in form and was situated peripherally in the nucleus. The cells of the inner nuclear layer likewise showed signs of degeneration. Vascular lesions were absent.

In order to determine whether these changes were due to the direct toxic influence on the nerve cell or were the indirect results of contraction of the vessels, he determined the effect of experimental anemia on the retina by tying the common carotid. The results were marked, but sufficiently different to lead him to conclude that the ischemia produced by contraction of the retinal vessels does not suffice to explain all the changes found in quinin intoxication. He assumes that the additional factor is the direct action of the poison on the nerve cell. There was nothing to indicate that the retinal changes are secondary to nerve changes; on the contrary, the former were found before any changes could be seen in the nerve.

Druault⁷ also reported experiments on dogs. He obtained typical changes. "At the end of ten hours one can already recognize very advanced chromatolysis of the ganglion cells and in some even complete destruction of the chromatic substance."

He also describes the changes produced in the ganglion cells by cutting the optic nerve behind the entrance of the central retinal vessels. In this experiment he claims that the retinal ganglion cells disappear at the end of ten to twenty days.[‡] He maintains that if the optic nerve is cut and quinin is injected subsequently at a varying interval that the degenerative changes will be similar in both eyes when the interval is short (two days), but that when the interval is long (six days) the degeneration will be very slight after the injection of quinin.¹³ He concludes that as the cells lose their normal condition as a result of neurectomy they also lose their susceptibility to the poisonous effect of quinin. Inasmuch as vasomotor influences are unaffected he believes the poison must act directly upon the cell. It is probable that the early changes in the nerve cell, so long as they affect only the chromatic substance, are possible of repair; when the degeneration has attacked the body and the nucleus of the cell its function is probably permanently destroyed. Birch-Hirschfeld cites the view of Goldscheider and Flatau¹⁴ that the Nissl bodies have no vital importance but are significant in that they reveal the earliest pathological changes in the cell.

* He criticises Holden's results on the ground that postmortem changes were not sufficiently excluded and that the method of killing the animal (by chloroform narcosis and bleeding to death) may in itself have been productive of certain changes. He killed his animals by a blow on the neck and the eyes were immediately removed.

‡ This is not in accord with Birch-Hirschfeld, who describes marked signs of chromatolysis 55 hours after the section; in five, ten and fifteen days these changes are more distinct, but he does not suggest the entire disappearance of cells.

† The illustrations were passed around.

Thus we see that Holden's experiments are on the whole confirmed. And we may now take it as an established fact that quinin causes blindness by its action on the retina and not on the nerve.

Parinaud¹⁵ believes that the toxic action is on the entire neuron from center to periphery. This view is purely suppositional and without any experimental basis.

FELIX MAS.

DeSchweinitz⁸ was unable to produce any change either in the nerve or in the retina in his experiments on dogs. Masius and Mahain in 1899† found marked atrophy of the nerve fiber layer, dilatation of the capillary vessels, thickening of the septa, atrophy of the optic nerve, with the formation of vacuoles in the nerve. The retinal changes were slight excepting some chromatolysis of the ganglion cells in the central fossa. They concluded that the lesions were primarily in the nerves, depended on vascular changes and that the retina suffered secondarily. Birch-Hirschfeld succeeded in experiments with this poison on rabbits. He was unable to find any ophthalmoscopic changes, but his cases showed varying degrees of change in the inner nuclear layer and in the ganglion cells, i. e., aggregation of the chromatic substance in lumps, or its disappearance, shrinkage of the nucleus and disintegration of the cell; the inner nuclear layer presented a hyperchromatic and shrunken condition of the nuclei. He maintains the degeneration and atrophy of the nerve fibers is secondary to the retinal changes.

Okamoto⁹ recently reported slight swelling of the medullary sheaths, atrophy of the axis-cylinders and hyperplasia of the interstitial tissue.

Nuel¹⁰ has likewise recently published the results of his experiments with felix mas. They are summarized in the following sentence: "Filicic optic neuritis is a parenchymatous neuritis characterized by a primary lesion and destruction of nerve fibers; only later are secondary changes produced in the interstitial tissue, first in the neuroglia and afterwards in the vessels and connective tissue. In certain parts of the nerves the subsequent changes assume exactly the characters that are considered pathognomonic of the neuritis called interstitial."

These views are in direct contradiction to those generally accepted by ophthalmopathologists and must await satisfactory confirmation. At present it appears probable that the changes produced by felix mas are to be found in the inner nuclear layer and the layer of ganglion cells as shown by Birch-Hirschfeld, and that the changes in the optic nerve are secondary.

BISULPHID OF CARBON.

This produces amblyopia of the alcohol-tobacco type; it was used by Birch-Hirschfeld in experiments on rabbits. The same poison has been found by Köster¹⁶ to produce characteristic changes in the spinal ganglion cells. Birch-Hirschfeld's results were practically negative so far as the retina was concerned. This justifies the opinion that the primary changes are not produced in the retina but elsewhere, in all probability in the optic nerve.

ALCOHOL.

Holden in one case produced degenerative changes in the ganglion cells of the retina and some medullary sheaths of the optic nerve by means of methyl alcohol and he concluded that this form of amblyopia is due to

"nutritive disturbances in the ganglion cells of the retina."

This view has recently been opposed by Gifford, chiefly on the ground of McCoy and Michael's case of optic neuritis from methyl alcohol. Birch-Hirschfeld criticises these objections because the case referred to stands alone among all in which no neuritis could be detected.

Birch-Hirschfeld's experiments were made on rabbits and chickens, and his results were definite. The early changes consist in the chromatic bodies of the ganglion cells losing their sharp definition and the substance of the cell taking up the stain, while the body of the cell becomes shrunken. Then the nucleus shrinks, becomes irregular and shows signs of degeneration. Finally the outline of the cell becomes indistinct and a shrunken nucleus alone marks the former location of the cell. The inner and outer nuclear layers likewise show degeneration, especially the inner. The retinal vessels were normal. The optic nerves showed no lesion excepting in one case—the one in which the retinal changes were most marked. In this there was a section of degeneration in the nerve but even here there were normal fibers among the degenerated ones. There were no interstitial changes in the degenerated portion of the nerve. Hirschfeld, therefore, concludes that experimental methyl alcohol amaurosis depends primarily upon lesion of the retina—first of the ganglion layer, later of the inner and outer changes in the optic nerve. He emphasizes the remarkable analogy between the optic nerve changes just described and the picture which the degenerated optic nerve of ethyl alcohol amblyopia presents. Neuritic changes were absent in the rabbit's nerve; he suggests that perhaps the period of intoxication in the rabbit (14 days) had been too short, and also cites Heilbronner's¹⁷ observations as showing that the connective tissue changes in peripheral alcohol neuritis are secondary.

It is not possible to draw reliable conclusion as to the effects of ethyl alcohol on man from these results of methyl alcohol. Uhthoff¹⁸ properly warns against accepting the results on animals as necessarily identical with those on human beings and especially the effects of the long-continued chronic poisoning as usually observed in man.

AUTHOR'S EXPERIMENTS.

In order to determine the effects of chronic alcohol poisoning the writer fed rabbits with absolute ethyl alcohol, pure methyl alcohol, commercial methyl alcohol and Jamaica ginger (made of 95 per cent. methyl alcohol).

I desire here to give in brief the results on four rabbits to which they were given in small amounts (5 to 10 c.c.) for a period of almost four months. The rabbits lost weight, but otherwise remained apparently healthy, and were killed by a blow on the back of the neck. The eyes were immediately removed and one of each animal hardened in 96 per cent. alcohol, the other in saturated bichlorid of mercury solution. The sections were cut and stained under the direction of the well-known neuro-pathologist, Dr. Stewart Paton, the director of the laboratory of the Sheppard-Pratt Hospital for the Insane. The effects of all four substances were similar. As yet it is impossible to state any specific differences.

The ganglion cells show marked signs of degeneration, but the inner nuclear and outer nuclear layers are likewise affected, especially the inner. Many ganglion cells show great shrinkage and atrophy; the chromatic sub-

† Cited by Birch-Hirschfeld.

stance is broken down and granular. Other cells show no nuclei or nuclei very irregular in shape. In other cells again the chromatic substance appears fused so that it forms an almost complete ring around the nucleus, in which case the cells are more or less irregularly contracted and the parts where the processes leave the cells are also shrunken. This change is suggestive of chronic cell degeneration. Some ganglion cells in which the cell body has disappeared, leaving a faint nucleus, suggest the acute degeneration described by Nissl.

It is very significant that the ethyl and methyl alcohols produce similar changes in chronic poisoning. I shall not venture to say whether these changes in the retina are primary or secondary to optic nerve lesions, though I incline to the former view. The question can not be answered until more extensive experiments which the writer has in contemplation are concluded. But it must be admitted that in producing these retinal changes by *chronic alcohol poisoning* we have made an important advance in the solution of the same chronic poisoning in man. I shall give a detailed report of these experiments elsewhere.

In concluding this paper I desire to point out the review given by Uththoff¹¹ at the last International Ophthalmological Congress in Paris in August, 1900, on "Toxic Neuritis." He divided this into two groups: first those toxic amblyopias that present a central scotoma and normal periphery of the field; these are the partial retinobulbar forms due to alcohol, tobacco, bisulphid of carbon, arsenic, iodoform, stramonium and hashish. The second group shows changes in the blood vessels with secondary ischemic necrosis, and in addition there is direct poisonous action on the nerve cell. He notes that the constriction of the vessel alone can not explain the affection, for ergot with its powerful constrictive action is not known to produce such destructive changes.

Uththoff is one of the most formidable champions of the neuritic theory, so far as the alcohol tobacco group is concerned. His arguments are based on the pathologic findings in his eleven cases of alcohol and tobacco blindness, in which the optic nerve was subjected to microscopic examination and in all of which, evidences of neuritis beside the atrophy of the nerve fibers were found. He therefore refuses to regard the condition as a simple degeneration.

Siegrist¹² has likewise recently written a strongly argumentative article opposing the view that the optic nerve lesions in alcohol and tobacco amblyopia are due to primary retinal lesion with ascending degeneration. It is difficult to harmonize the results of experimentation on animals and the pathologic findings of partial neuritic atrophy of the optic nerve in man.

At present the only possible way is to assume that, as Heilbronner, and recently, Nuel, have endeavored to prove, the neuritic changes are secondary to a primary degeneration of the nerve fiber. But it is wiser still to await the results of more extensive experimental and pathological research.

REFERENCES.

1. Mann: Jour. of Anat. and Phys., 1835.
2. Bach: Arch. f. Ophthalm., xii, iii, p. 62, 1895.
3. Abelsdorff: Arch. f. Augenheilk., 1900, vol. xlii, p. 188.
4. Holden: Arch. of Ophthalm., 1898, vol. xxvii, p. 583; and 1899, vol. xxviii, p. 125.
5. Birch-Hirschfeld: Arch. f. Ophthalm., 1900, vol. i, p. 166; and Bericht. Ophth. Gesellschaft, Heidelberg, 28th Meeting, 1900, p. 48.
6. DeBono: Archivio di Ottalmologia, 1894, pp. 171-227; and Annal. d'Oculist., 1896, p. 73.
7. Druault: Recueil d'Ophthalm., 1900, pp. 342-555.

8. De Schweinitz: The Toxic Amblyopias, Phila., 1896.
9. Okamoto: Zeitschr. f. Augenheilk., May, 1901, p. 382.
10. Nuel: Internat. Congress of Ophth., Paris, Reported in Rec. d'Ophthalm., 1900, p. 548; and in the Ophthal. Review, May, 1901, p. 125.
11. Uththoff: Ophth. Review, Feb., 1901, p. 33; and Rec. d'Ophthalm., 1900, p. 548.
12. Siegrist: Arch. f. Augenheilk., vol. xii, p. 136.
13. Uththoff saw Druault's specimens and found the condition he described, marked. See Report 28th Meeting Ophthal. Gesellsch., Heidelberg, p. 56.
14. Anatomie d. Nervenzellen, Berlin, 1898.
15. Parinaud: Internat. Ophth. Cong., Paris, 1900.
16. Köster: Neurol. Centralbl., 1898, p. 493.
17. Rückenmarksveränderungen bei Multipler Neuritis d. Trinker. Berlin, 1898.
18. Uththoff: Discussion, Report 28th Meeting Ophth. Gesellsch., Heidelberg, p. 55.

ATROPHY OF THE RETINA.*

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It may be sometimes quite impossible to discover the cause of disease, and it is not always easy to determine whether a lesion is dependent upon some other morbid process, or of primary origin. I have hesitated to believe it possible for atrophy of the retina to come on as a primary condition, without any discoverable preceding inflammation, or even hyperplasia; but, it is certain that, whatever disturbances may have preceded the beginning of atrophic changes in the two cases herein reported, there was no manifest hyperemia before failure of sight. I am not sure that some occult inhibition of the functions of the vasomotor nerve force may not cause primary atrophy.

Miss M. B. J., aged 19, came to me July 12, 1882, with a note explaining that she had been unable to pursue her studies without headache. After suspending her accommodation, I found that, with +1/30 C. ax. 90° for each eye she saw 20/XX, Snellen. She returned home and got along satisfactorily with her studies until April, 1888, when I received a letter telling me she had suddenly experienced difficulty in reading at night, and could not distinguish the color of roses.

She returned to Louisville, when I found this difficulty had increased progressively until she was no longer able to read on cloudy days. Her fields were irregularly contracted, and she had no perception of either red or green. Her general health seemed to be perfectly good. The menstrual function was normal. Her sight was now reduced to 20/LXX, Snellen, in the right eye, and 20/C in the left. She remained with relatives in the city until June, when she was unable to see the test type, even at 10 feet with any glass. She could not differentiate colored lights. Ophthalmoscopic examination showed nothing definite. Her fields were extremely contracted, she had central scotomata in both eyes. She went with her grandmother to New England to spend the summer; and in August consulted Dr. Hasket Derby, of Boston, who found "the central vessels of the retina extremely small, with no abnormal appearances of the discs. She is unable to distinguish any test object."

The first week in September she returned to Louisville and I again mapped her field of perception. Both fields showed increased peripheral contraction, with central scotomata of irregular outline. She described everything as "smoky and blurred." In brilliant illumination, a book held before the face seemed "covered with a fine gray network." November, she was unable to distinguish any objects. On bright days everything

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