DR. BERNARD SAMUELS, closing: I wish to thank those who discussed the paper, especially Dr. Friedenwald, for bringing out so clearly how it is that in some cases we may have edema of the retina and in other tissues cystic formation. The optic nerve itself becomes edematous, the nerve fibers are separated, but no actual spaces are formed, but the adjacent retina may break up into holes. The optic nerve is the stronger tissue and the retina is the weaker and more delicate, so that under the same influence the former would show edema while the latter might be torn to pieces.

MICROSCOPIC OBSERVATIONS IN A CASE OF RETINITIS PIGMENTOSA*

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Few eyes affected with retinitis pigmentosa have been examined microscopically. The present case is only the third in which the eye was removed from a living subject, and was therefore free from postmortem changes, and the second in which the eye was fixed in Zenker's fluid. The eye was removed on account of a tuberculous process in the iris, which fortunately was too recent to have produced any changes in the posterior part of the eye. The tuberculous process will be discussed in a separate communication.

Cornelius F., aged sixty-four years, was admitted to the Massachusetts Eye and Ear Infirmary April 1, 1928, complaining that about three days previously he had severe pain in the right eye.

His sight began to fail early in life and he had been blind in both eyes for over twenty years. He could still read a newspaper at the age of thirty-five. When young he could not read in a subdued light and read fine print more easily than large print. His general health had usually been good. At the age of twenty-seven he had a severe attack of pleurisy, and since then had had a number of minor attacks, an attack eleven years ago being rather severe. The pleurisy had always been on the left side.

* From the Massachusetts Eye and Ear Infirmary.

His parents were not consanguineous. His father died of stricture, and his mother of tumor. A brother and a sister died of tuberculosis. One brother became blind at the age of about seventeen years. The patient's wife was alive and well. Two daughters and four sons were alive and had good vision. One child died at birth.

General physical examination.—A fairly well-preserved old man. No glands palpable in the neck. Chest: Percussion resonance was impaired over the right apex. Breathing sounds were vesicular except at the right apical region, where they were bronchial to cavernous, with numerous crepitant râles, marked egophony and pectoriloquy. Tactile fremitus was increased. The heart was not enlarged. Second sounds were faint and of fairly good quality. There were no murmurs. The blood-pressure was 140/80. The abdomen was soft, and there was no tenderness. The knee-jerks were normal. There was no edema of the ankles. The urine showed a slight trace of albumin, but no sugar. The pulse was 81. Temperature, 98.4°.

X-ray examination of the lungs showed far-advanced tuberculosis of the right apex, with cavity formation, a healed area left apex, and ring shadow of pleura, left mid-chest.

Examination of eyes.—Right eye: There was moderate ciliary congestion. The cornea was clear; the aqueous turbid; and the pupil small, irregular, and filled with fibrin. The iris was discolored. The fundus was not visible. The tension was 26 mm. Hg (Schiötz). V. = *nil.*

Left eye: Externally, the eye was normal. The fundus showed the typical appearance of retinitis pigmentosa. The optic disc presented the waxy appearance characteristic of this disease. There was no cupping and the lamina cribrosa was not visible. Its outline was distinct. The retinal vessels were small in caliber even on the disc, and became extremely small at the periphery. No vessels with white borders, or that had been converted into white lines, were seen anywhere. Around the disc there was very little pigmentation of the retina. Branching pigmented figures were fairly numerous at the periphery; scanty elsewhere. They were not often related to the vessels. Fine and coarse pigment-granules were seen in areas. In places where there was much pigment the retina showed a deep-seated gray opacity. Except behind these areas, the choroidal vessels were clearly seen. The vitreous was perfectly clear, showing no opacities even with a + 14 sph. lens in the ophthalmoscope. The lens showed a small, sharply defined

posterior cortical cataract, but otherwise it was clear. The tension was 14 mm. Hg (Schiötz). V. = *nil.*

The patient insisted on removal of the right eye on account of pain.

April 2, 1928: Simple enucleation of right eye under local anesthesia.

April 7, 1928: Discharged.

December 30, 1929: The general condition of the patient was unchanged. *X*-ray examination of the chest showed identical conditions found on first examination. Temperature, 98°. The Wassermann test was negative. The condition of left eye was unchanged.

PATHOLOGIC EXAMINATION OF RIGHT EYE

Fixation in Zenker's fluid twenty-four hours. Celloidin embedding.

The globe, normal in size and shape, showed nothing macroscopically noteworthy except pigmentation of the retina, as in retinitis pigmentosa. The branching pigmented figures were most numerous in the equatorial region, but were not abundant. Here they occurred at distances of 0.5 to 2.5 mm. from each other, and the largest would just fit in a circle about 1 mm. in diameter. The retina was everywhere *in situ.*

Microscopic Examination.—The cornea was normal. The iris showed a recent tuberculous process (described in detail in a separate communication*). The vitreous was free from cellular infiltration and showed slight if any increase in its stellate cells. The lens showed a slight posterior cortical cataract—a cleft 0.1 mm. anterior to the posterior capsule, 0.2 by 0.03 mm. in size, in which the lens fibers were breaking up into granules and undergoing solution.

The posterior part of the eye was entirely free from inflammatory reaction. The retina was everywhere greatly altered. No rods remained anywhere, but between the disc and macula there were short stretches, some 1 mm. in width, in which recognizable remains of cones could be seen. The external limiting membrane was intact, the layer of Henle was still recognizable, and the line of synapses was distinct (fig. 1). The cones were about twice as thick as normal, and definitely hexagonal in cross-section. Some of them did not project beyond the limiting membrane, but others

* Transactions Ophthalmic Section, A. M. A., 1930.

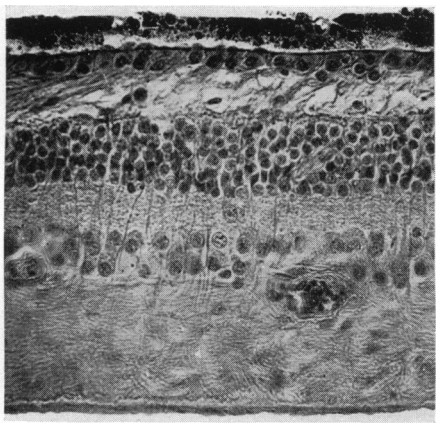

Fig. 1.—Showing remains of cones and altered pigment epithelium. The retinal ganglion cells are well preserved. Hematoxylin and eosin.

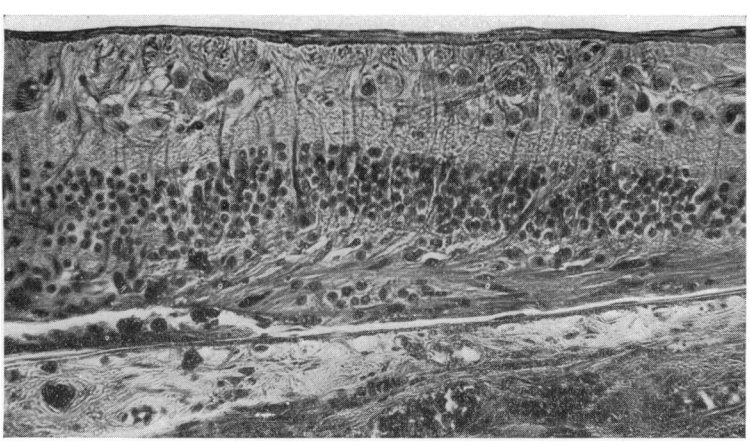

Fig. 2.—Showing gliosis of the retina. Müller's fibers extend through the retina and replace the neuro-epithelium with a layer of neuroglia fibrils running parallel with the retina. On the right, the limiting membrane has been destroyed. The normal choriocapillaris of the choroid is well shown. Phosphotungstic acid hematoxylin.

sent mound-like projections through its openings. Their nuclei were about one-third larger than normal and situated a short distance internal to the membrane. Elsewhere the external limiting membrane was still recognizable in places, but the neuro-epithelial layer had been replaced more or less completely by neuroglia. The different stages in the formation of the neuroglia were easily observed. Müller's fibers with their nuclei had grown into the layer, often curving around until they ran parallel to the plane of the retina, and finally formed a fibrillated layer between the pigment epithelium and the retina proper (figs. 2 and 3). The nuclei were large and ovoid, sometimes of giant size, and rich in chromatin. The very large nuclei each contained a large vacuole. In places the new Müller's fibers ran through the retina to the external limiting membrane, where they expanded and formed foot plates similar to those found normally at the inner surface of the retina. Where there were remains of cones, the Müller's fibers often ran between the latter up to the membrane. The new Müller's fibers stained more intensely in the neuroglia stain than normal fibers, but less so than fully differentiated neuroglia fibrils. The gliosis became progressively more marked from the posterior pole of the eye to the periphery of the retina.

The nuclei of the internal nuclear layer were well preserved, but the layer was often greatly distorted by the large number of new-formed Müller's fibers that had penetrated through it.

The ganglion cells were decreased in number, but not markedly. In places they occurred in normal numbers (figs. 1 and 4), but occasionally there were short stretches in which they were scanty (fig. 5). Most of them were normal in appearance. They were least numerous at the periphery, but some could be found as close as 4.5 mm. to the ora serrata. In the macular region they were abundant.

The nerve-fiber layer was of normal thickness. The Müller's fibers running through it were increased in number and thickness. The neuroglia fibrils running in other directions were also abnormally abundant. There was only slight increase in the neuroglia nuclei within the layer.

The hyaloid membrane was *in situ*. Upon its inner surface there was in many places a new-formed neuroglia membrane which was sometimes three or four cells thick (fig. 4). Nowhere could it be definitely seen that this membrane communicated with the neuroglia within the retina.

The pigment epithelium was everywhere altered. In stretches, some of them 1.5 mm. long, it was entirely absent, and it was entirely absent for a distance of 0.5 mm. on each side of the disc. Where it was absent, the neuro-epithelial layer, and even the external limiting membrane, had been completely replaced by neuroglia (fig. 2). Behind the areas in which there were remains of cones, the pigment layer was always present. In some places it retained a close resemblance to its normal morphology. Here it was generally almost free from pigment, although it occasionally retained its pigment, and it showed a fenestrated membrane and protoplasmic processes. As the pigment layer was followed along, a stretch might be seen entirely free from pigment, and then abruptly a short stretch of cells densely packed with pigment. In places the epithelium consisted of two layers—the outer layer was sometimes almost free from pigment, while the inner layer was densely packed with pigment. In some places the pigment epithelium was transformed into a layer of spindle-cells containing little or no pigment. No fatty granule cells could be seen in the pigment layer or elsewhere in the retina. In some places in which the pigment cells were relatively normal they were densely packed with pigment-granules, all of which had the typical spindle form. In other places the pigment consisted of small round granules only. In still other places the pigment occurred in the form of round balls of various sizes, some as large as a cell. Within these balls a greater or less number of denser pigment-granules could be seen. The larger balls seemed to have been formed by coalescence and partial solution of the original finer pigment-granules. Pigment, in addition to that around the vessels, was found in the retina proper, almost exclusively in the outer part (fig. 5). However, occasionally it was seen in the nerve-fiber layer. Here it generally consisted of large balls lying free, but sometimes was contained in large round cells about the size of normal pigment epithelial cells, each with an ovoid nucleus lying in contact with the cell membrane. The pigment around the retinal vessels was usually in the form of discrete fine granules, but occasionally it showed changes similar to those seen in the pigment layer.

The central retinal vessels and their main branches in the disc showed no thickening of their walls and were not obviously reduced in caliber. None of the retinal vessels showed endovasculitis, but as they were followed away from the disc their adventitia became increased in amount (fig. 6). Even vessels of almost capillary

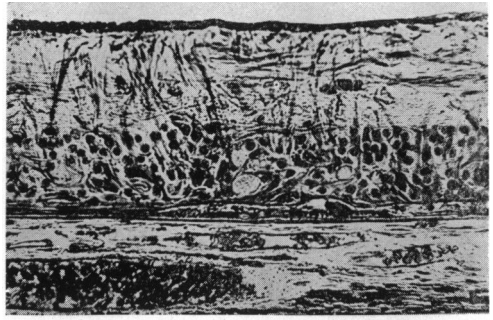

Fig. 3.—Showing gliosis of the retina. Phosphotungstic acid hematoxylin stain.

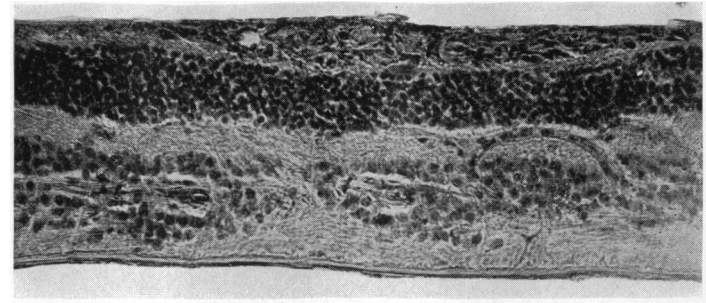

Fig. 4.—Showing neuro-epithelium replaced by neuroglia. The ganglion cells are well preserved. There is a neuroglia membrane on the inner surface of the hyaloid membrane. Hematoxylin and eosin.

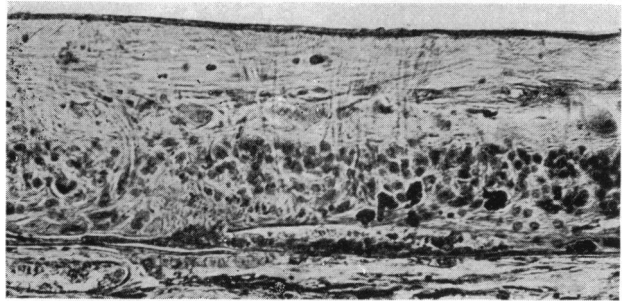

Fig. 5.—Showing altered pigment epithelium and pigment in inner nuclear layer. On the left, the pigment epithelium has become changed into a layer of spindle-cells. The limiting membrane persists, but the neuro-epithelium has been replaced by neuroglia. The retinal ganglion cells are not well shown, but are scanty here. Hematoxylin and eosin.

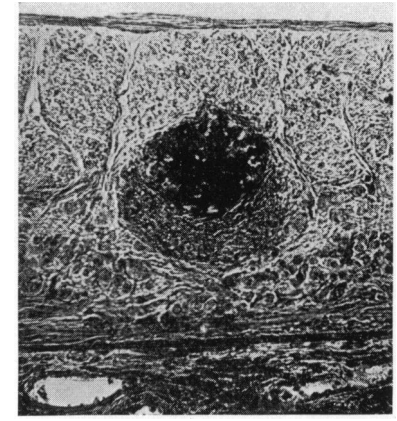

Fig. 6.—Showing marked thickening of adventitia on one side of retinal vein. Phosphotungstic acid hematoxylin.

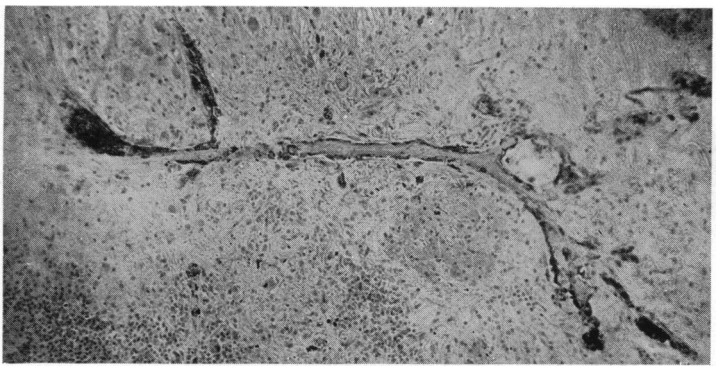

Fig. 7.—Flat section of retina showing obliterated hyaline vessel coated with pigment cells. At the curve in the vessel is an area apparently composed of pigment cells which have largely lost their pigment. Hematoxylin and eosin.

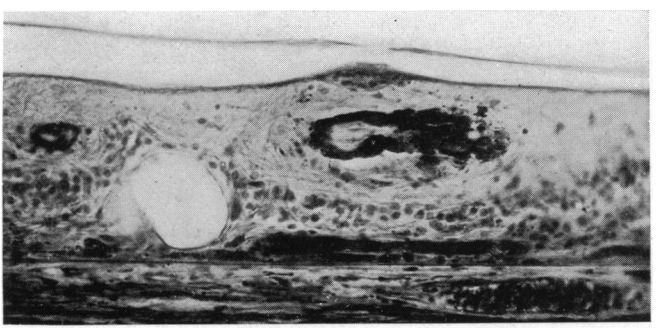

Fig. 8.—Showing altered pigment epithelium and pigment around obliterated vessels. The small cyst has been formed by infolding of the neuro-epithelium, and is lined by the original external limiting membrane. There is a small nodule of neuroglia cells beneath the hyaloid membrane. A delicate neuroglia membrane has been artificially separated from the hyaloid membrane. Hematoxylin and eosin.

size showed an abnormally thick adventitia. At and anterior to the equator in sections stained in hematoxylin-eosin very few vessels were recognizable and few vessels containing blood were seen. In sections stained in Mallory's connective-tissue stain, however, numerous vessels were seen, but almost all of them had been converted into solid strands of hyaline connective-tissue entirely free from cells (fig. 7). Rarely a minute empty lumen could be recognized in the center of a strand. Even vessels of capillary size had thus been transformed. About the vessels the neuroglia had proliferated and formed long thick neuroglia fibrils which followed along the vessels. These were best seen in flat sections of the retina. Sections stained in Verhoeff's elastic tissue stain showed no proliferation of elastic tissue in the walls of the retinal vessels. Posterior to the equator none of the larger vessels and few if any of the smaller vessels were obliterated.

The sections stained in connective-tissue stain showed here and there small vessels penetrating the external limiting membrane and extending between the pigment layer and the retina. In places delicate connective-tissue fibrils, no doubt derived from the vessels, could be seen between the pigment layer and retina, and sometimes also between the pigment layer and Bruch's membrane. These vessels and connective-tissue fibrils were not recognizable in sections stained in hematoxylin and eosin.

In the fundus few vessels surrounded by pigment were seen, but in the equatorial region and beyond, there were many such vessels (figs. 8 and 9). Almost all of these vessels had been converted into solid hyaline strands (fig. 7). The pigment cells around them sometimes consisted of discrete round cells, densely packed with pigment; sometimes the cells took the form of a continuous epithelial layer. In several instances this epithelium could be traced into continuity with the original pigment epithelium (fig. 9).

Near the ora serrata the retina showed cystoid degeneration of moderate degree, entirely similar to that observed in senile eyes. In the retina elsewhere, even in the fundus, small cysts of a different nature were occasionally seen (fig. 8). These were always in the outer part, and the largest was about half the thickness of the retina. They were lined by a membrane and contained serum. Various stages in their formation could be observed, and it was seen that they were due to infolding of the external limiting membrane and altered neuro-epithelium resulting from contraction of the new-formed neuroglia.

The optic disc showed a delicate neuroglia membrane extending over its surface, which was continuous with the similar membrane on the surface of the retina described above. Otherwise, in sections stained in hematoxylin and eosin, the disc and nerve stem appeared normal (fig. 10). They showed no obvious increase in neuroglia nuclei. The neuroglia stain, however, showed definitely an increased amount of neuroglia in the disc, especially near its surface. The neuroglia fibers were not only increased in number but were abnormally coarse. The myelin sheath stain showed no atrophy in the nerve stem.

The choroid, including the membrane of Bruch and the choriocapillaris, was perfectly normal with the exception that some of its arteries showed endarteritis. This was no greater than would be expected at the age of sixty-four years. The membrane of Bruch showed slight basophilic staining in places, but this is normal in senile eyes.

Comment.—The most complete critical analysis of the literature relating to retinitis pigmentosa is that of Leber,[1] who refers in his discussion also to many of his own observations. With the exception of the communications of Collins,[2] Takahashi,[3] and Sugita,[4] I have been unable to find anything of noteworthy importance in the subsequent literature. Leber concluded that the essential retinal lesion in the disease was degeneration of the neuro-epithelium, the rods being the first affected, and that, as a result of this degeneration, there occurred degenerative and proliferative changes in the pigment epithelium with migration of the pigment cells into the retina, growth of pigment cells around the vessels, replacement of the neuro-epithelium by neuroglia, hyaline change and obliteration of the vessels at the retinal periphery, and atrophy of the ganglion cells and optic nerve. He concluded also that the choroid including the choriocapillaris was not concerned in the process. These conclusions were based chiefly on the microscopic findings of Gonin,[6] Stock,[5] Ginsberg,[7] and Suganuma.[8]

The microscopic findings in my case confirm these conclusions except in regard to the ganglion cells and the optic

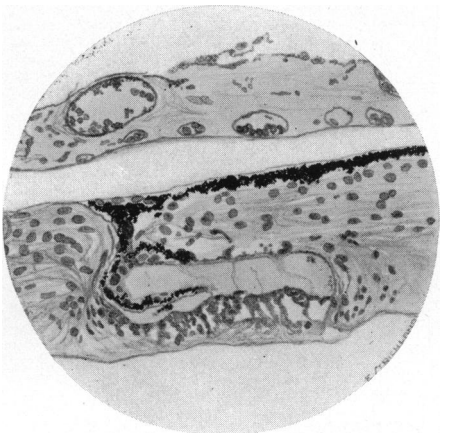

Fig. 9.—Drawing, showing pigment epithelium proliferating inward and surrounding a vessel. Hematoxylin and eosin.

Fig. 10.—The optic nerve and disc appear normal, except for a delicate neuroglia membrane extending over the surface of the disc. The membrane is artificially separate. Hematoxylin and eosin.

nerve. Since this was a typical case in a far-advanced stage, the condition of the choriocapillaris in it was of great significance. Fortunately the eye was fixed in Zenker's fluid, which caused little if any shrinkage of the choroid—in eyes fixed in formalin the shrinkage is often so great that the choriocapillaris cannot be recognized. The choriocapillaris was perfectly normal, and the remainder of the choroid was also normal, with the exception of some of the arteries, which showed senile endarteritis, in moderate degree. It is obvious, therefore, that obliteration of the choriocapillaris or choroidal circulation can be dismissed as a possible cause of retinitis pigmentosa. My findings also accord with the view that the rods are the elements first affected, since they were entirely gone, whereas there were remains of cones in places. The rods and cones are commonly thought of as the small structures lying outside the external limiting membrane. Degeneration of these alone would not seem to be sufficient to affect the rest of the retina greatly. As a matter of fact, each rod and each cone passes through an opening in the external limiting membrane and continues as a fiber, the fibers forming the layer of Henle, and their nuclei the external nuclear layer. All the elements together constitute the neuro-epithelial layer, and this makes up about one-third the thickness of the retina. Obviously, degeneration of this layer would produce profound changes in the whole retina. There can be no doubt, therefore, that the gliosis of the retina, and probably also the changes in the pigment epithelium, are due to this cause. The supposition of Collins that migration of pigment cells into the retina is due to the effect of light rays is unnecessary. In fact, there is no evidence that in man light has an effect on the pigment epithelium such as it has in the case of some of the lower animals.

Since pigmentation of the retina is the most conspicuous ophthalmoscopic feature of the disease, it has been thought that the primary change is degeneration of the pigment

epithelium. Simple degeneration of this epithelium, however, does not lead to the other changes associated with retinitis pigmentosa. I have examined an eye in which the pigment epithelium showed wide areas of complete senile degeneration and partial calcification, without having produced pigmentation of the retina or degeneration of the rods or cones. The possibility is not excluded, however, that in retinitis pigmentosa the changes in the pigment epithelium are partly or wholly due directly to the same cause that leads to the degeneration of the neuro-epithelium.

In spite of the eye having been blind for twenty years, the retinal ganglion cells were still abundant, the nerve-fiber layer of normal thickness, and the optic disc and nerve apparently normal. Even the myelin sheath stain failed to show any atrophy of the optic nerve. This is not in accord with Leber's statement, although he does qualify it by saying that in some cases the process ceases so that after many years the myelin sheaths are not quite lost. Stock,[5] in two cases of the congenital type of the disease, in which he examined the eyes postmortem, found no atrophy of the optic nerves and concluded that absence of such atrophy constituted an essential difference between this and the ordinary type. Ginsberg,[7] however, in his case of the ordinary type, found no optic atrophy, so that his case with mine shows that Stock's conclusion was incorrect. Why the optic nerve should show more or less marked atrophy in some cases and none in others is not clear. The atrophy of the nerve fibers is evidently dependent upon degeneration of the ganglion cells. Since the ganglion cells are not directly connected with the rods and cones, degeneration of the latter would not necessarily injure them. Probably whatever injury the ganglion cells sustain results from the gliosis and vascular changes, but why it should be greater in some cases than in others, I am unable to explain. In my case there was sufficient loss of ganglion cells to cause considerable total reduction in

nerve fibers, but no doubt the affected fibers were so completely degenerated and so greatly scattered throughout the nerve as not to be recognizable. The waxy appearance of the optic disc, which is such a characteristic ophthalmoscopic feature of the disease, is evidently not due to degeneration of nerve fibers, but probably, as assumed by Collins, to an increased amount of neuroglia in the disc. In my case the gliosis here was not marked and was evidently an extension of the retinal gliosis. The histologic features of my case, not noted in previous cases, and revealed by special staining, were the formation by some of the new-formed Müller's fibers of foot plates beneath the external limiting membrane similar to those at the inner surface of the retina, the occasional continuation of small vessels through the outer surface of the retina, and, in some instances, between the pigment epithelium and Bruch's membrane, and the formation of small cysts by the infolding of the external limiting membrane as the result of the retinal gliosis.

A characteristic ophthalmoscopic feature of retinitis pigmentosa is reduction in the caliber of retinal vessels. According to Collins, the vessels of both the retina and the choroid "dwindle." Just how degeneration of the neuro-epithelium could cause dwindling of these vessels, as he further states, is not clear to me. As a matter of fact, the choroidal vessels, as already pointed out, are not affected. Judging by the findings in my case, the retinal vessels do not dwindle, but their lumina become narrowed as a result of the thickening of their walls by connective tissue. This tissue evidently has about the same index of refraction as the contiguous retinal tissue, since usually it is not ophthalmoscopically visible. It is apparently not produced by the intima, but by the adventitia of the vessels.

While in my case the main branches of the central vessels showed microscopically no obvious reduction in caliber, judging ophthalmoscopically by the other eye they would

have appeared definitely smaller than normal. Probably their walls were actually abnormally resistant, so that during life they were less distended than normal vessels.

Leber suggests that the narrowing of the larger vessels is due to the marked changes in the smaller vessels and capillaries at the periphery. Obstruction to the latter vessels, however, it seems to me, would cause dilatation of the larger vessels, at least the arteries, unless their walls had become thickened. He also suggests that the hyaline transformation of the smaller vessels is due to the formation of a cuticular substance by the pigment cells that surround them. In my case the vast majority of the vessels which showed hyaline transformation were not surrounded by pigment cells. This was obvious, however, only in sections stained in Mallory's connective-tissue stain. In sections stained in hematoxylin and eosin the hyaline vessels were so inconspicuous that they could scarcely be recognized unless surrounded by pigment.

The retinal changes cannot be due to the vascular changes, because still greater obstruction of the retinal circulation, even complete obstruction of the central retinal artery, such as sometimes occurs in cases of arteriosclerosis, does not lead to degeneration of the neuro-epithelium. It is obvious, therefore, that the vascular changes are dependent upon the degeneration of the neuro-epithelium. The connective tissue in the walls of the vessels undergoes hyperplasia, just as does the retinal glia tissue. The lumina of the smaller vessels finally become so constricted that the walls perhaps suffer from lack of nutrition and as a result undergo hyaline degeneration. This change is not visible with the ophthalmoscope because of the transparency of the hyaline substance. For this reason, as pointed out by Leber, the fact that the branching pigmented figures are always related to blood-vessels is also often not recognizable.

Nettleship (cited by Leber[1]) ophthalmoscopically observed pigmentation only around retinal veins, never around

arteries. In my case the pigmented vessels were so greatly altered that I could not determine microscopically whether they were veins or arteries. In cases of intra-ocular tuberculosis, however, I have noted that macrophages entering the retina from the vitreous accumulate and form tubercles almost if not exclusively around the veins. It is evident, therefore, that ameboid cells are attracted to veins, a fact that is in accord with Nettleship's clinical observations.

Posterior cortical cataract is another characteristic feature of the disease. It occurs late, and is certainly due to the disease, but probably not to the original cause of the disease. It seems impossible that slow degeneration of the retinal epithelium could produce sufficient toxic substances in the vitreous to injure the lens. More likely the injury to the latter is due to an accumulation of deleterious substances in the vitreous as a result of the impairment of the retinal circulation. The same sort of cataract occurs in old cases of marked syphilitic chorioretinitis, separation of the retina, and other fundus conditions, in which no doubt it is due to disturbed nutrition of the lens.

Another complication that occurs in cases of retinitis pigmentosa too often to be simply coincidental is glaucoma. This also may be due to the impaired retinal circulation, as in cases of glaucoma secondary to obstruction of the central retinal artery.

Admitting now that degeneration of the retinal neuro-epithelium is the primary lesion in retinitis pigmentosa, what is the cause of this degeneration? The facts that the disease is undoubtedly hereditary, that it is often associated with deafness and with congenital anomalies, and sometimes with cerebral degeneration, have not thus far led to a solution of the problem.

Leber[1] inclines to the view that the effect of light in association with diminished resistance of the neuro-epithelium, especially of the rods, is responsible for the degeneration.

He points out that in congenital night blindness the rods are easily fatigued by light, and assumes that retinitis pigmentosa is simply a more marked condition in which the rods are actually injured by light. Collins[2] has advanced the view that the degeneration is due to "abiotrophy." The latter is a term introduced by Gowers, which, it seems to me, means nothing more than premature senility of specified tissues. Many of the cells of the body seem to be capable of proliferation indefinitely, some of them even *in vitro*, while others have in adult life lost the power completely. According to Gowers, the latter cells will die in a certain time which varies in different cases, no matter how favorable their environment may be. Collins points out that the rods and cones belong to this class, and that in certain individuals they die early in life, thus explaining retinitis pigmentosa. In connection with Collins' theory, the breeding experiments of Keeler may be of significance. He found that in certain blind white mice the retinal neuro-epithelium was absent or rudimentary and that the condition was a Mendelian recessive character. It could be recognized on the thirteenth day after birth, but not before this, because the retinal layers were not sufficiently differentiated. Since the neuro-epithelium may thus, as the result of hereditary influences, entirely fail to develop, it is reasonable to believe that in certain cases it may develop but lack normal vitality, as assumed by Collins.

Leber admits that no satisfactory explanation of the ring scotoma in early cases of retinitis pigmentosa has been advanced. He attempts to explain it, however, by the facts that the rods are more abundant at the periphery, the nourishment of the neuro-epithelium by the choriocapillaris is richer in the macula than elsewhere, and that relatively little light reaches the extreme periphery of the retina. He states that it is well known that the retina can be injured by sunlight. It is true that the macula can be injured by the con-

centrated rays of the sun, as in eclipse blindness, but this is an effect of the heat produced. Experiments by Bell and myself upon the human eye and upon the eyes of animals show conclusively that the normal retina cannot be injured by any light which can pass through the lens if the intensity is insufficient to produce a heat effect. For this reason, the theory that exposure to light is an essential cause of retinitis pigmentosa seems highly improbable, to say the least.

Collins' theory of abiotrophy as an explanation of the disease cannot at present be proved or disproved, but it seems to explain all the facts well. Collins explains the ring scotoma by assuming that "the part of the retina in which failure of function commences is that in which its neuro-epithelium first attains its full development." His theory, however, will always be open to doubt so long as the possibility remains that the degeneration of the neuro-epithelium is due to some toxic influence. Moreover, Collins' theory so completely excludes any hope of combatting the condition by therapy, that every endeavor should be made to disprove it and to discover a different cause.

As a matter of fact, the theory that the condition is due to some toxic influence acting through the blood or vitreous explains the known facts as well as Collins' theory. As Leber points out, in some cases of old syphilitic chorioretinitis, the retinal changes are almost identical with those in primary retinitis pigmentosa, and there may be no alteration in the choriocapillaris. I have found that here too the pigmentary changes are most marked at the equator and that the cones persist longer than the rods. In such cases the degeneration of the neuro-epithelium is unquestionably due to local toxic influences. In certain cases of leukoma adherens, without glaucoma, as Leber also points out, the retina shows typical retinitis pigmentosa. Here the toxic influence must be in the vitreous, probably due to relative stagnation of the intraocular fluid. Similar retinal changes may also sometimes

occur in cases in which a cataractous lens has remained dislocated in the vitreous for a long period of time. In connection with possible toxic influences, Leber calls attention to the experiments of Capauner, who obtained pigmentary degeneration in the retinas of rabbits by injecting papayotin into the vitreous, to the experiments of Schreiber and Vengler, who injected Scharlach oil into the anterior chamber, and to the experiments of Igersheimer, who injected atoxyl subcutaneously into rats and into the vitreous in rabbits, with resulting injury chiefly to the neuro-epithelium.

It is certain, therefore, that toxic influences acting either directly through the blood or indirectly through the vitreous could act electively on the retinal neuro-epithelium, and even electively on the rods. Conceivably they might also affect the inner ear and cerebrum. The reason the rods are more vulnerable than the cones may be simply because of their smaller size. It is possible that we have a clue to the existence and nature of such a toxic influence in the well-known fact that in certain cases of disease of the liver, notably hypertrophic cirrhosis, there is night blindness. The latter is not related to the jaundice which may accompany the condition, but this fact does not exclude the possibility that it is due to an excess in the blood of bile salts, or other substances derived from the liver, and that these may affect the visual purple and the rods in which this substance is supposed to reside. A hereditary disturbance of liver function, existing for a long period of time, therefore, might well cause degeneration of the retinal neuro-epithelium.

In this connection the experimental work of Sugita[4] is possibly of some importance. He found that the injection of bile or of some of its constituents into rats produced hyperemia of the choroid, "cholesteatose" in the pigment epithelium, and partial degeneration of the outer retinal layers. The pigment cells proliferated and then migrated inward as fatty granule cells. In some instances the pigment epithelium

showed "cholesteatose" without the retina being affected. Sugita also found that bile could dissolve visual purple. He believed that his experiments explained the hemeralopia of avitaminosis, but did not suggest that they were of significance in regard to congenital hemeralopia and retinitis pigmentosa. It seems to me, however, that in this regard they are of possible significance to the extent that they show that the pigment epithelium and the neuro-epithelium of the retina can be injured by certain constituents of bile acting through the blood. The effects in his experiments were too rapidly produced to be comparable to the changes found in retinitis pigmentosa. Moreover, in my case at least, the pigment cells did not contain lipoid granules.

Perhaps of greater significance in regard to retinitis pigmentosa is the investigation of Takahashi.[3] By a variety of methods he investigated the liver function in twelve cases, and found it abnormal in each. If further investigations confirm these results, they may lead to the discovery of some means of checking the progress of the disease.

Summary and Conclusions.—A man, aged sixty-four years, blind in both eyes for over twenty years, developed acute tuberculous iritis in the right eye. The left eye showed the typical ophthalmoscopic picture of retinitis pigmentosa. On account of pain, the right eye was removed five days after the onset of symptoms. The fundus of the right eye was entirely unaffected by the tuberculous process. The histologic changes found are described and the following conclusions drawn:

The essential ocular lesion in retinitis pigmentosa is progressive degeneration of the retinal neuro-epithelium, the rods being first affected.

The changes affecting the pigment epithelium probably result from the degeneration of the neuro-epithelium, but the possibility that they are due to the same cause that leads to the degeneration of the neuro-epithelium has not been excluded.

The reduction in caliber of the retinal vessels is due to increased thickness of the adventitia. The thickened adventitia is usually too transparent to be visible ophthalmoscopically.

The optic nerve may show little if any atrophy, even in an eye blind for many years from retinitis pigmentosa. The waxy appearance of the disc seen with the ophthalmoscope is due to gliosis.

The posterior cortical cataract is due to disturbed nutrition of the lens resulting from the impaired circulation of blood in the retina. Secondary glaucoma, which sometimes occurs, is probably also dependent on the impairment of this circulation.

Retinitis pigmentosa is not due to vascular or other changes in the choroid.

The theory of abiotrophy as a cause of the disease explains all the facts well, but should not be accepted until other possibilities have been excluded.

The theory that light is a factor in the causation of the disease is highly improbable.

The theory that the disease is due to disturbance of the liver function is worthy of serious consideration, but requires additional evidence to support it.

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DISCUSSION

DR. JONAS S. FRIEDENWALD, Baltimore: It may be interesting to add to Dr. Verhoeff's communication the report of a case which I

had the opportunity of examining in the past year. The patient was a colored woman, aged thirty-five years, who came to the clinic of the Wilmer Institute complaining of night blindness, and whose eyes showed the typical picture of retinitis pigmentosa. Unfortunately for the certainty of the diagnosis, the patient had a positive Wassermann. A short time after the first examination she died as the result of a cerebral hemorrhage. At autopsy the posterior segments of the globes were obtained for examination. There was no scarring or change in the choroid whatever, or any adhesions between the retina and choroid. In view of this, it seemed to me that the retinal lesion was a true retinitis pigmentosa, and could not be attributed to the syphilis. The findings in the retina in a large measure coincided with those that Dr. Verhoeff has reported. The rods and cones were almost completely destroyed—a few shrunken distorted cones were found here and there. The nuclei of the rods and cones were almost entirely absent. The inner nuclear layer was well preserved and showed practically no change, but the ganglion cells were almost entirely absent and there was a glial proliferation over the surface of the retina, as Dr. Verhoeff has described, and also over the disc. Most interesting in these sections was the pigment epithelium and the distribution of the pigment in the retina. For the most part the pigment epithelium consisted of a single layer of cells with only local small areas of increased thickness. However, the amount and the character of pigment in adjoining areas varied enormously. In some places the pigment cells were almost devoid of pigment, while adjoining epithelial cells contained large, dark, amorphous granules. Nowhere in the pigment epithelium could one find the normal bacillary form of pigment-granule which is so characteristic of these cells. In the retina the pigment was contained in cells of which it was impossible to say whether they were cells from the pigment epithelium which had migrated into the retina or whether they were phagocytic cells. These cells were so full of pigment that the nuclei were hidden. Similar deeply pigmented cells were scattered through the retina and also accumulated about the blood-vessels. In addition to these cells, there was some pigment diffusely scattered through the retina, not definitely intracellular. Still further, in addition to these deposits of pigment there were some cells in the retina which were apparently normal constituents of the retina which contained pigment.

It is, of course, difficult to identify specific cells in a scarred dis-

torted retina, but it was my impression that these cells which contained pigment were actually normal neuroglial cells of the retina, particularly Müller's fiber cells. This leads to the question whether Müller's fibers may not belong to the class of microglia of Hortega, which are phagocytic glia present in the brain and other nervous tissues. They have migratory characteristics and are thought to be not true glia but actually reticular cells which are a part of the structure of the brain and have come from the mesoblastic tissue. This speculation has been in part confirmed by some experiments which I did a number of years ago. I was interested in studying intra-ocular inflammations, and injected trypan blue into the eyes of some rabbits to study the course of the inflammatory reaction. Trypan blue is a colloid dye which has a marked attraction for the large phagocytic cells. In some of the sections showing the early stage of the reaction I found the dye present in the retina, where it seemed to be particularly taken up by Müller's fibers. In the later stages, after the inflammatory reaction had subsided, the dye was accumulated in the retina in a pattern more or less analogous to that seen in retinitis pigmentosa.

I feel, therefore, that the characteristic pattern of retinitis pigmentosa is due to the anatomy of the retina and to the distribution of the phagocytic cells in the retina, rather than to any essential characteristics of the disease.

DR. T. B. HOLLOWAY, Philadelphia: I am particularly interested in Dr. Verhoeff's paper from the standpoint of the number of cases of retinitis pigmentosa which it has been my privilege to see at the Pennsylvania Institution for the Instruction of the Blind at Overbrook. It has always been a puzzle to me why in some cases you have excellent capillarity of the nerve-head. In certain cases of retinal degeneration I have seen what might be regarded as a hyperemia of the disc.

DR. F. H. VERHOEFF, closing: In regard to Dr. Friedenwald's remarks: If Müller's fibers can take up pigment, it seems to me we should see so many of them containing pigment in a case of this kind that there would be no doubt about the matter, whereas it is difficult to make sure that any of the fibers contain pigment. I have not the slightest doubt that Müller's fibers are neuroglia cells, because they proliferate and form fibrils which stain differentially in neuroglia stains. This would seem to exclude the possibility of their being mesoblastic in origin, as Dr. Friedenwald suggests.

In regard to the optic disc, as I said, it may show little if any atrophy, and in Dr. Holloway's case apparently there was no atrophy at all. Its appearance will vary in different cases, according to the amount of atrophy, the amount of gliosis, and the condition of its blood-vessels. Owing to the obstruction of the circulation in the retina, the disc in some cases no doubt may be congested.

THE PERMEABILITY OF THE LENS CAPSULE TO WATER, DEXTROSE, AND OTHER SUGARS*

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In a previous paper[1] quantitative studies on the permeability of the lens capsule to various colloid and crystalloid aniline dyes were reported, together with qualitative studies in regard to the permeability for various other organic and inorganic substances. In view of the importance of water and dextrose in the normal metabolism of all tissues, and in view of the experimentally demonstrated glucose consumption of the lens,[2] it seemed desirable to obtain, if possible, experimental data of a quantitative nature in regard to the permeability of the lens capsule for water and dextrose. The method which was devised for these experiments was very simple. The apparatus is shown in figure 1. The experimental procedure was as follows:

Capsules removed from the lenses of freshly enucleated eyes were cleansed by prolonged shaking in frequent changes of normal salt solution, as described in the previous paper,[1] in order to free them from all traces of adherent lens protein. One such capsule was then tied onto the tube at c. The

* From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. The writer is indebted to Mr. Paul Spear for technical aid in the performance of these experiments.

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