THE CYTOID BODY REACTION OF THE HUMAN RETINA*

BY *J. Reimer Wolter*, M.D.

THE VIEW THAT cytoid bodies of the retina may be a product of degenerating neurites in the nerve fiber layer has found the support of some of the most outstanding eye pathologists of the present day.[1,2] However, a good histologic demonstration of cytoid bodies with proper staining methods is still rare and the histologic details and phases of this nerve fiber reaction are virtually unknown. In the present paper the nerve fiber changes in three most instructive eyes are used to demonstrate details of what may be called the cytoid body reaction. In a fourth case the nerve fiber reactions in the spinal cord after cordotomy are presented for comparison in order to show that the cytoid body reaction of the retina actually is a non-specific reaction that commonly occurs in many parts of the nervous system.

CASE HISTORIES AND HISTOPATHOLOGIC FINDINGS

CASE 1

This 73-year-old white male suffered painless loss of vision in his right eye early in 1954. Occlusion of the central retinal vein was diagnosed. Secondary hemorrhagic glaucoma developed two months later. Conservative treatment failed to control the intraocular pressure and the pain. The eye was enucleated on April 28, 1954.

Gross examination revealed a normal-sized right eye. The anterior chamber was shallow. The lens was clear. Hemorrhages were seen all over the retina. The vitreous was mostly liquefied and brownish in color. Microscopic examination of routine sections revealed bullous epithelial changes and diffuse loss of endothelial nuclei in the cornea. The chamber angle showed partial occlusion by anterior peripheral synechiae. A layer of fibrous tissue containing new-formed blood vessels was found to cover the anterior iris surface. Diffuse lymphocytic infiltration was seen in the iris and ciliary

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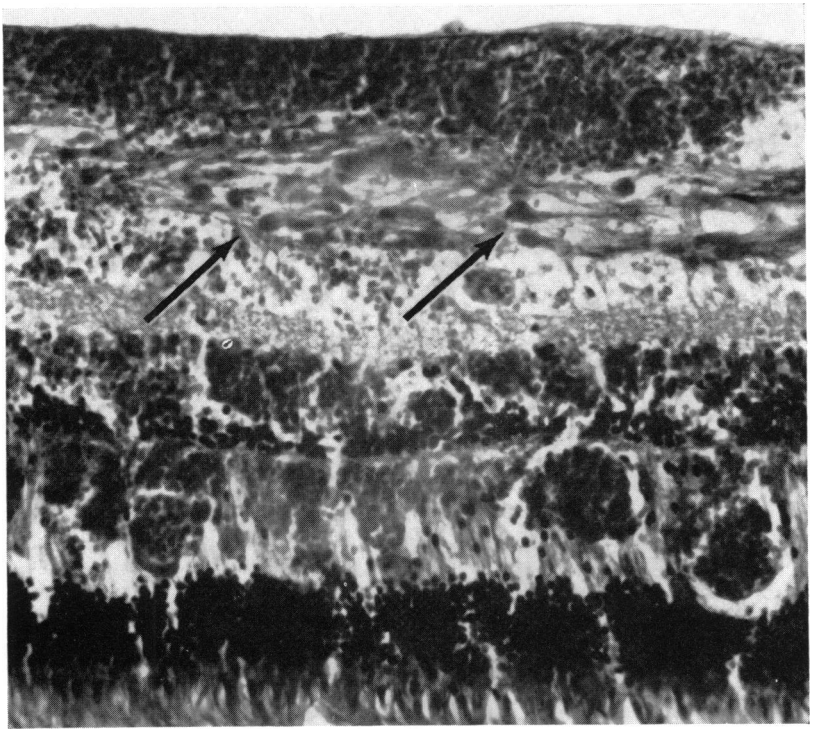


FIGURE 1

Cross-section of posterior retina (Case 1) showing retinal hemorrhages everywhere, swelling of the nerve fiber layer with many cytoid bodies (arrows) and diffuse degeneration. Paraffin section, H and E stain, photomicrograph × 250.

body. Extensive hemorrhages as well as microcystic degeneration were seen throughout the retina. In addition, swelling of the nerve fiber layer with many cytoid bodies and swollen neurites was observed in the central retina (Figure 1). The retinal blood vessels showed extensive fibrosis as well as endothelial proliferation. Occlusion of the central retinal vein with partial recanalization was found in the optic nerve head directly behind the lamina cribrosa. The histopathological diagnosis of secondary (hemorrhagic) glaucoma following occlusion of the central retinal vein confirmed the clinical diagnosis.

Flat frozen sections of the retina were stained with the silver carbonate nerve fiber method of del Rio Hortega[3] for a demonstration of the cytoid body reaction in the nerve fiber layer that was very well developed in this case. These flat sections showed numerous typical cytoid bodies in all phases of their development everywhere in the nerve fiber layer (Figure 2).

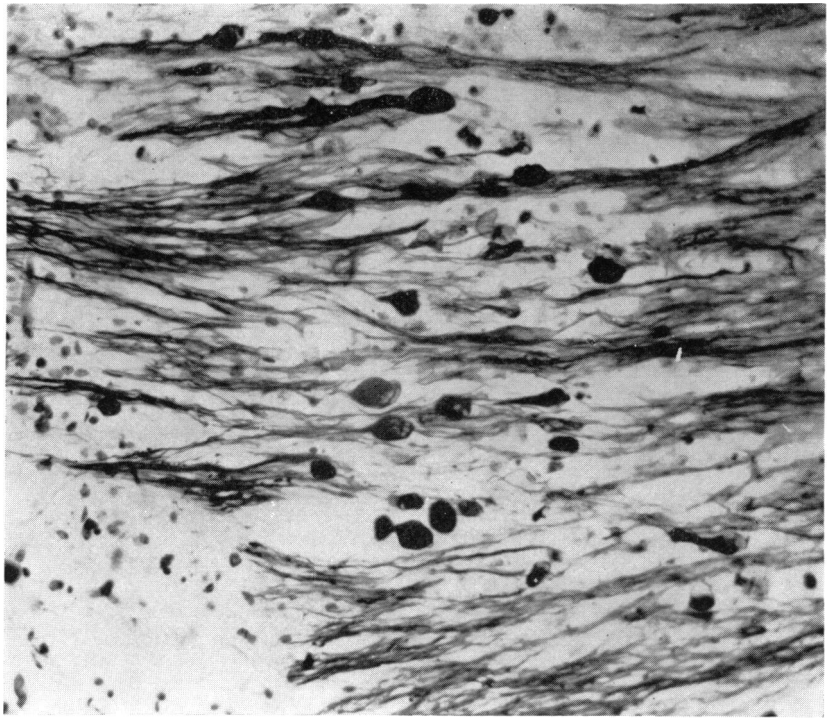


FIGURE 2

Flat section of the retina (Case 1) showing the arrangement of the cytoid bodies at low power. The optic disk would be at right side of picture. Frozen section, Hortega stain, photomicrograph × 250.

With the nerve fiber stain the majority of the cytoid bodies were seen to represent the terminal swellings of interrupted neurites (Figure 3). All the larger cytoid bodies had developed on neurite stumps which pointed towards the disk (Figure 3). However, there also were less numerous small terminal swellings on nerve stumps which pointed away from the disk (Figure 6).

Free cytoid bodies without connections to any neurites were also seen in great numbers (Figure 4). In addition to these there were many cytoid bodies on the ends of nerve fiber stumps with distinct degenerative changes (Figures 3 and 4). It thus became obvious to the observer that the free cytoid bodies were later stages of the same basic process. These free cytoid bodies had been terminal nerve swellings, but their nerve stumps had later degenerated and disappeared.

Continuous nerves with local swellings in the area of accumulations of cytoid bodies were seen in many areas of the nerve fiber layer. These local

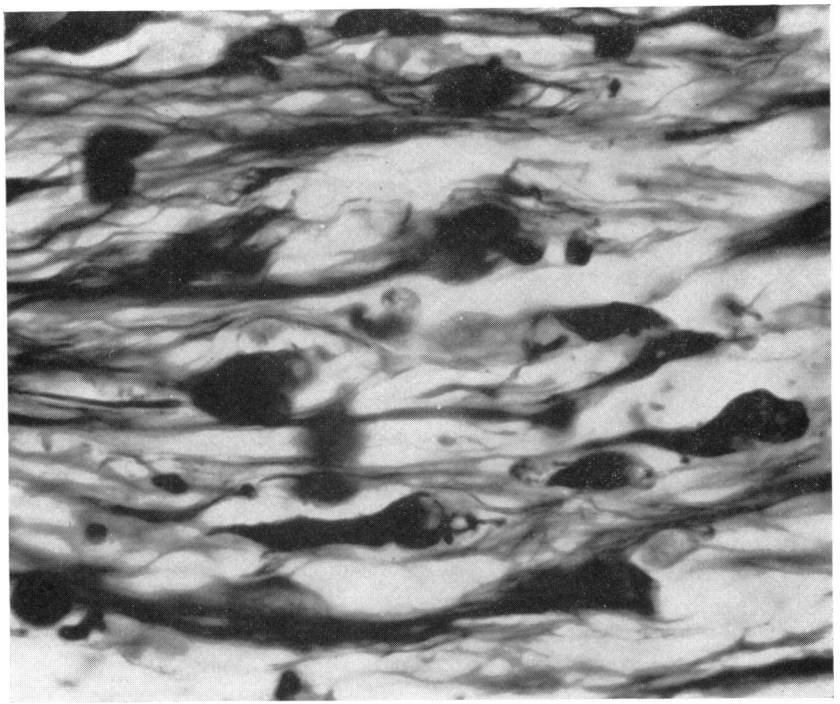


FIGURE 3

A group of nerve stumps with cytoid bodies pointing towards the disk in the nerve fiber layer (Case 1). Frozen flat section, Hortega stain, photomicrograph × 800.

swellings were understood to represent the earliest morphologic expression of the local nerve fiber damage that could progress to interruption of neurites and cytoid body formation.

A well-developed pseudoprotoplasm and a pseudonucleus were observed in some of the terminal swellings (Figure 5A). A similar arrangement was often seen in the free cytoid bodies that were no longer connected to a nerve stump (Figure 5B). However, not all the cell-like elements in the regions of the cytoid body reaction of this nerve fiber layer were terminal nerve swellings. Fat-laden macrophages (microglia, gitter cells) were also present in the regions of the most severe nerve fiber destruction (Figure 6). These macrophages usually had a small round eccentric nucleus while the pseudonucleus of the typical cytoid bodies was usually in the center.

CASE 2

This 62-year-old white female died on December 16, 1966, of respiratory arrest secondary to acute intermittent porphyria. This diagnosis had been

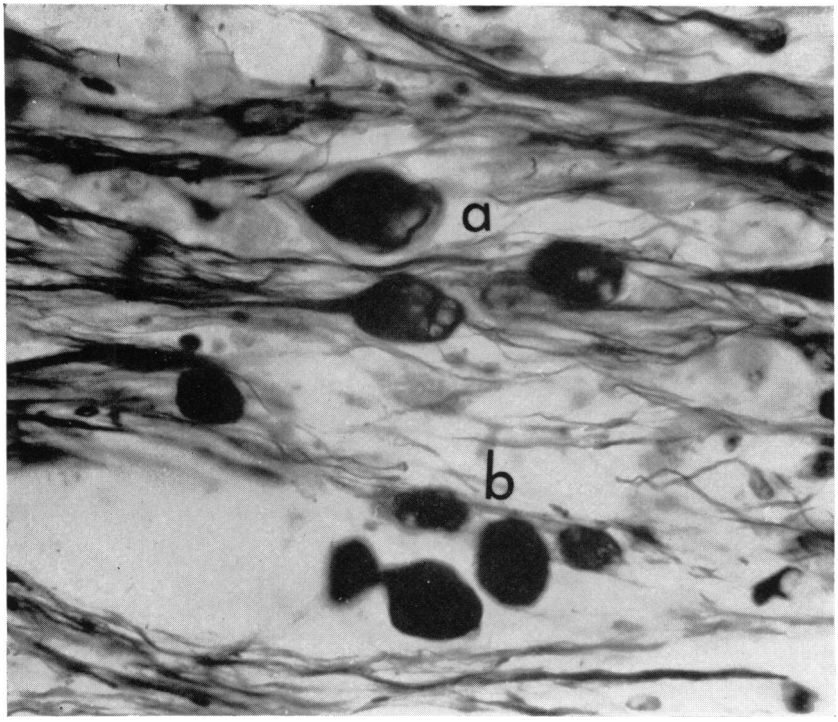


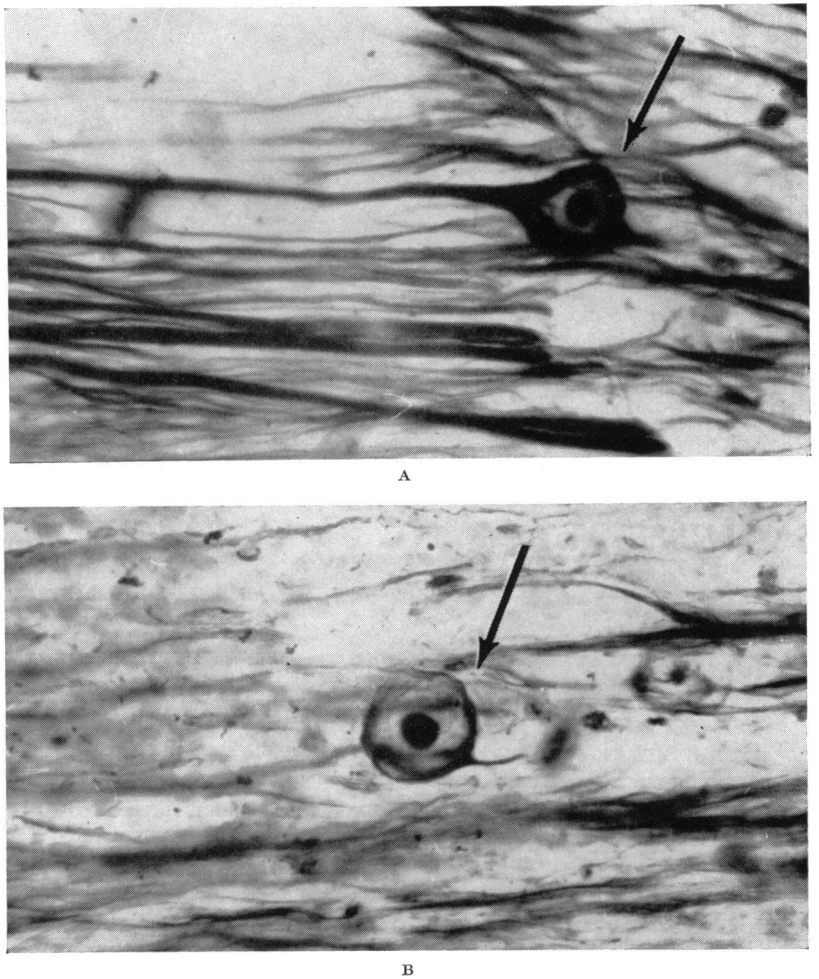
FIGURE 4

Nerve stumps with cytoid bodies (a) and free cytoid bodies (b) after retrograde degeneration of their nerve stumps (Case 1). Frozen flat section, Hortega stain, photomicrograph × 800.

made in 1961 and in 1966 the patient also exhibited secondary polyneuropathy, flaccid quadriplegia, hypertension, and aortic ejection murmur, and a left cataract.

Both normal-sized eyes were obtained at autopsy. Red fluorescence under ultraviolet light was clearly seen in all tissues of both eyes, but this was most outspoken and impressive in the vitreous and retina. Vascular abnormalities of the unstained retina were visible by their strong fluorescence under the fluorescence microscope.

Histologically both eyes exhibited narrowed retinal arterioles with extensive thickening and hyalinization of their walls as well as diffuse degeneration of retinal neurons with some cystic degeneration in the left eye. This diffuse degeneration of neurons was more pronounced in the left eye than in the right. The left eye also had a cataract and several cotton-wool spots were seen in the central portion of the nerve fiber layer of the retina.



A

B

FIGURE 5

A, nerve stump with cytoid body exhibiting pseudonucleus and pseudoprotoplasm. B, free cytoid body with pseudonucleus and pseudoprotoplasm. Both from Case 1. Frozen flat sections, Hortega stains, photomicrographs, × 800.

Flat sections stained with the nerve fiber method of del Rio Hortega allowed a demonstration of the arrangement and details of one of these cotton-wool spots (Figure 7). More or less bizarre swollen nerve fiber stumps were recognized as its components. Thick stumps with large terminal swellings were seen in the peripheral aspect of the lesion, while other

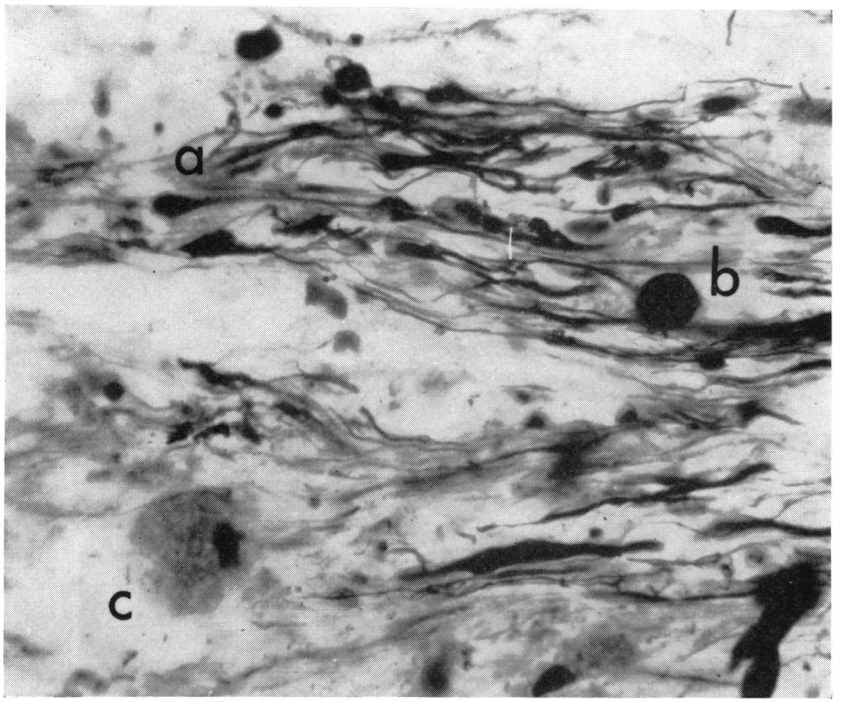


FIGURE 6

Case 1, small cytoid bodies at the end of centrifugal nerve stumps (a), one larger cytoid body on an afferent nerve stump (b), and two faintly visible large macrophages (c). Frozen flat section, Hortega stain, photomicrograph × 800.

stumps of thin fibers with smaller terminal swellings were found in its central aspect (Figure 8). Serial sections through this cotton-wool spot showed it to be distinctly swollen and elevated over the surrounding retina. This swelling appeared to be due to an accumulation of intercellular edema in the area that pushed the nerve and glial elements apart.

CASE 3

Nerve regeneration secondary to the development of cytoid bodies is very rare in adults. Thus, the eye of a baby is used in this study to demonstrate attempts at nerve regeneration occurring secondary to interruption at the ends of neurite stumps in the nerve fiber layer. This one-year-old white male baby had his left eye enucleated on November 9, 1956, for retinoblastoma. This tumor had been discovered shortly before by the parents. There was a negative family history and the right eye of the baby was normal.

Gross examination of this eye showed it to measure 19 × 20 × 20 mm.

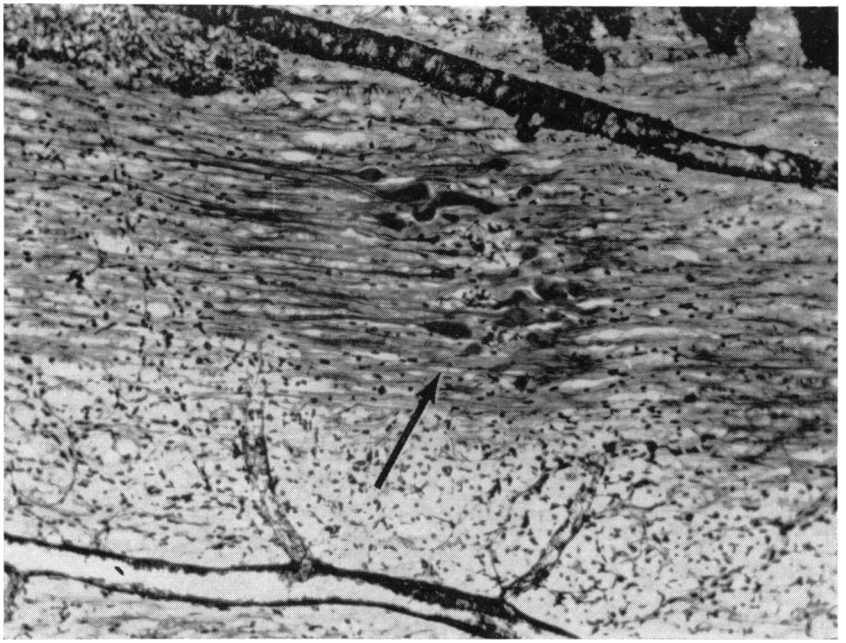


FIGURE 7

Low-power view of flat section of retina of left eye in patient with porphyria. A cotton-wool spot is seen in the nerve fiber layer (arrow). Artery (above) and vein (below) are clearly seen. Frozen section, Hortega stain, photomicrograph × 250.

The anterior chamber was shallow, the lens was pushed forward, and a large white tumor filled the vitreous chamber. Microscopic study of routine sections revealed closure of the anterior chamber angle. The retina was pushed forward into the retrolental space by an exophytic retinoblastoma with rosettes.

Pieces of the detached central retina were isolated from the tumor and cut into flat sections on the freezing microtome. The silver carbonate nerve fiber stain of del Rio Hortega was used to study the neurons of this retina. Much degeneration was found especially in the outer retinal layers. Interrupted neurites with terminal swellings (cytoid bodies) were seen in the nerve fiber layer. Many of these nerve stumps exhibited new growth of delicate axons with a distinct swelling (growth bulb) at the end (Figures 9 and 10). These were typical abortive attempts at nerve regeneration.

CASE 4

The fourth case, spinal nerve fiber changes secondary to a cordotomy, is used to show that the cytoid bodies of the retina actually represent a non-

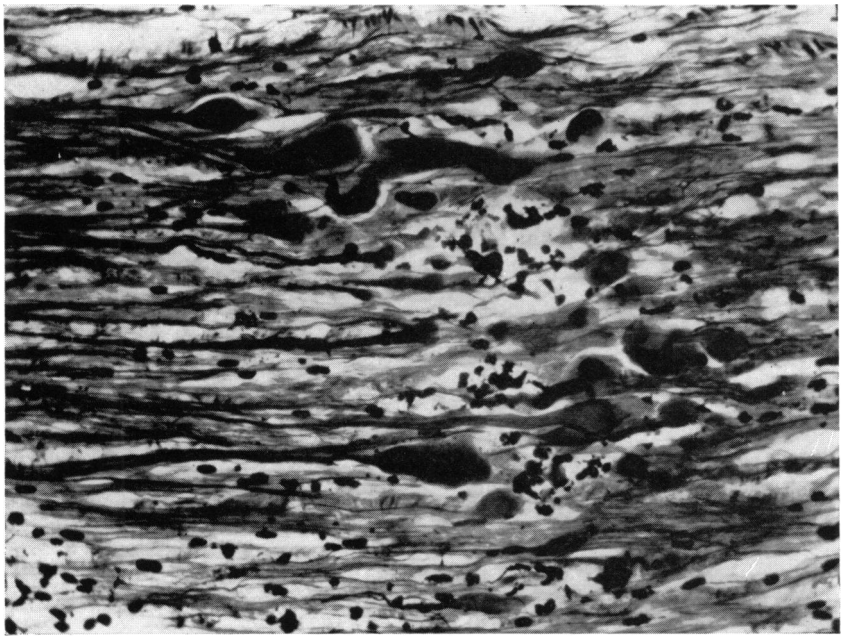


FIGURE 8
Higher power of the cotton-wool spot seen in Figure 7 with thick nerves forming large terminal swellings on the peripheral (left) aspect and thin nerves forming smaller swellings on the central (right) aspect of the lesion. Frozen section, Hortega stain, photomicrograph × 800.

specific nerve fiber reaction that may be observed in other parts of the nervous system and is well known to neuropathologists.

This 42-year-old white female had a high thoracic cordotomy done on April 27, 1960, for pain due to a recurrent squamous cell carcinoma of the cervix with bone metastases. She died on May 5, 1960. A piece of spinal cord including the area of the cordotomy wound was obtained at autopsy. Longitudinal frozen sections were made of the white matter next to and inferior to the cordotomy. These sections were stained with the nerve fiber stain of del Rio Hortega.

Interrupted neurites with typical terminal swellings were seen to point towards the cordotomy (Figure 11). There also were many isolated terminal swellings which were no longer connected to nerve stumps (Figures 11 and 12). Some of both types of terminal swellings exhibited well-developed pseudonuclei and pseudoprotoplasms and closely resembled the cytoid bodies of the retina (Figure 12).

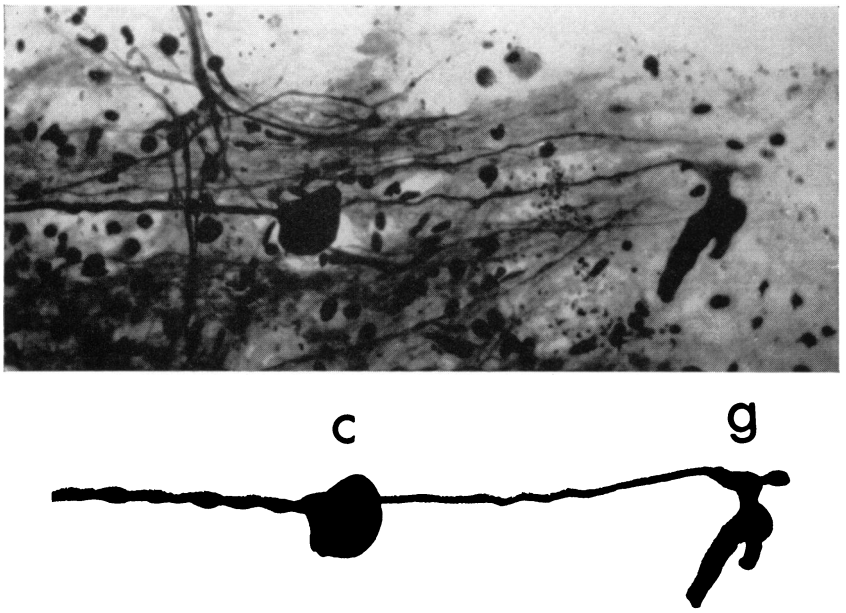


FIGURE 9

Top, abortive nerve regeneration starting from the cytoid body of a nerve stump and pointing toward the optic disk in the nerve fiber layer of a one-year-old child. Flat frozen section, Hortega stain, photomicrograph × 400. *Bottom*, drawing to explain the photograph: c, cytoid body; g, growth bulb at the end of regenerated fiber.

DISCUSSION

Cytoid bodies are a common histologic finding in the nerve fiber layer of the human retina in many ocular and general diseases.[1,2,4,5] The present study once more confirms the view that cytoid bodies in general are reactive formations of single neurites composed of nerve substance. They typically develop after interruption at the proximal end of neurite stumps. In the literature these formations are also known as Cajal's end bulbs,[6] terminal swellings, or ganglioform swellings. The causes of the interruption of neurites which in turn leads to cytoid body formation can be various in nature. Ischemia or direct trauma are good examples. Cytoid bodies may be found as isolated occurrences, but there also may be a great many in a diffuse or focal arrangement. Patches of densely accumulated cytoid bodies are typically seen in areas of localized retinal ischemia and appear clinically as cotton-wool spots.

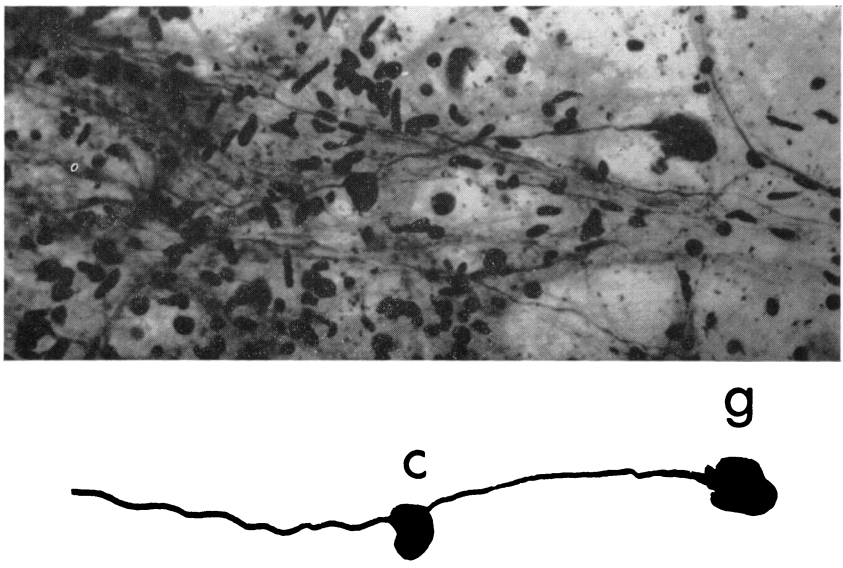


FIGURE 10

Top, regenerated fiber with growth bulb on nerve stump with cytoid body in the nerve fiber layer of a one-year-old child. Frozen flat section, Hortega stain, photomicrograph × 400. *Bottom*, drawing to explain the photograph: c, cytoid body; g, regenerated fiber with growth bulb.

Cotton-wool spots are typically slightly swollen and elevated as compared to the surrounding retina, and resemble little pillows. This swelling appears to be due to accumulation of intercellular edema in the region. The swollen neurites, however, may have a part in causing this elevation. Conditions in which cytoid bodies of the retina are commonly seen are hypertensive or diabetic retinopathy, occlusion of retinal veins, papilledema, anemia, hyperoxemia, leukemia, lupus erythematosis, and dermatomyositis. Under normal conditions isolated cytoid bodies in a diffuse distribution may also be seen in senility.[7] Foci of cytoid bodies occur in tumor involvement of the retina, following direct trauma—including photocoagulation[8] or diathermy, and in retinal detachment. The observation of cotton-wool spots in the retina of a patient with acute intermittent porphyria reported here is an interesting new finding.

Observation, after special stain, of different stages of cytoid bodies in the retina of numerous cases with many different diseases allows an understanding of the basic phases of this nerve fiber reaction. First,

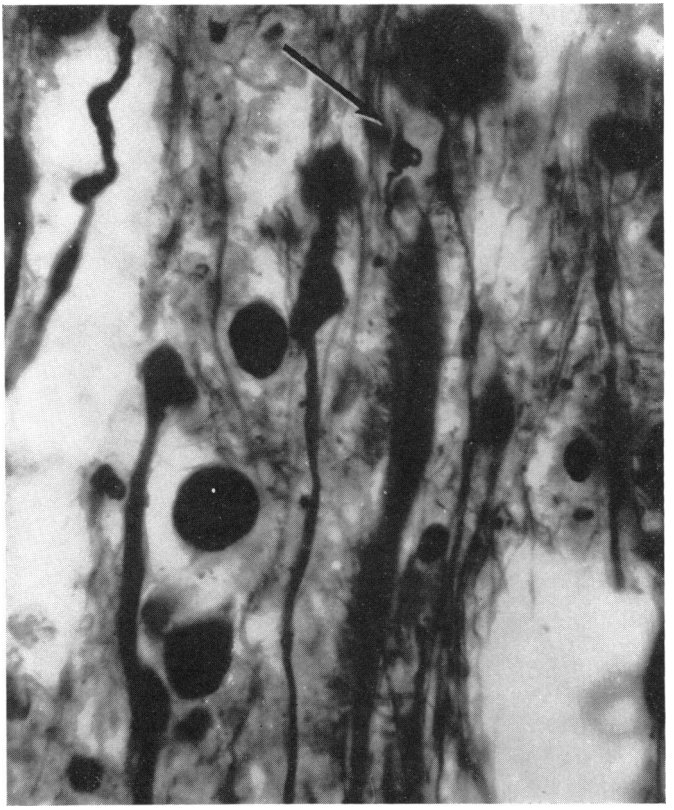


FIGURE 11

Nerve stumps with cytoid bodies and free cytoid bodies next to cordotomy wound of spinal cord. Abortive regeneration is seen on one terminal swelling (arrow). Frozen section, Hortega stain, photomicrograph × 800.

localized nerve fiber swelling is usually seen at the site of the injury (Figure 13b). This kind of local swelling seems to be reversible, and thus will either disappear or interrupt the nerve fiber permanently (Figure 13c). In the latter case that part of the neurite that is no longer connected with the ganglion cell body will disintegrate and disappear within a few days, while the neurite stump that is connected to the cell will form the cytoid body (Figure 13d). In the retinal nerve fiber layer most cytoid bodies are usually seen at the end of afferent nerve stumps. These stumps are always directed towards the optic disk. However, the less numerous efferent (centrifugal) nerves of the

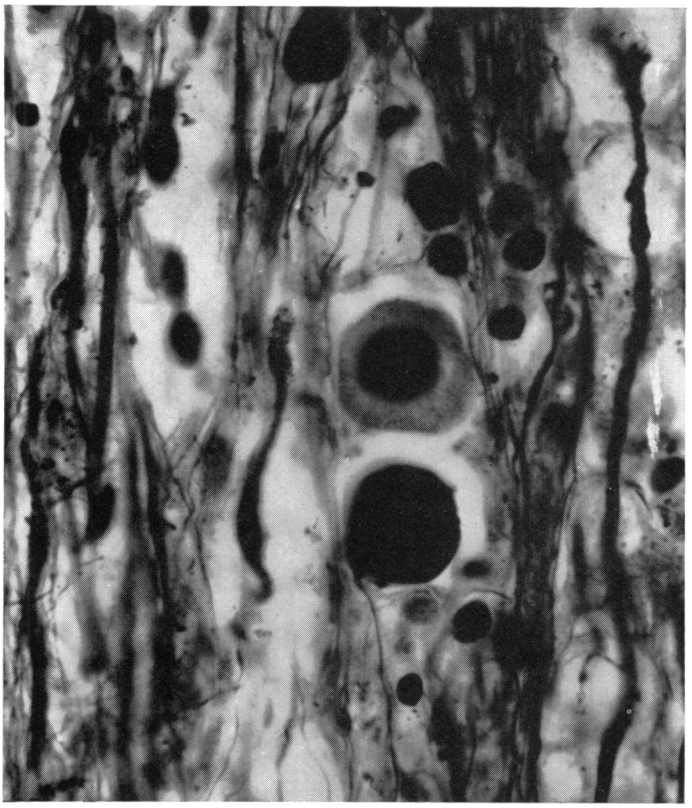


FIGURE 12

Small and large cytoid bodies next to the cordotomy wound of the fourth case. Cytoid bodies with well-developed pseudonuclei and pseudoprotoplasms are seen. Frozen section, Hortega stain, photomicrograph × 800.

nerve fiber layer also form cytoid bodies at the ends of their stumps. The stumps of the centrifugal nerves are always found to point away from the disk and their cytoid bodies are usually smaller.[9-11] The cytoid bodies (also known as terminal or ganglioform swellings) may show great variations in shape and size. Cytoid bodies may or may not exhibit a well-developed pseudonucleus and pseudoprotoplasm. In general, the thickest nerves will have the largest cytoid bodies, while smaller cytoid bodies will develop on the thin nerves. However, one may sometimes see very large cytoid bodies at the ends of very delicate nerve stumps or small cytoid bodies on thick nerves. Nerve stumps with

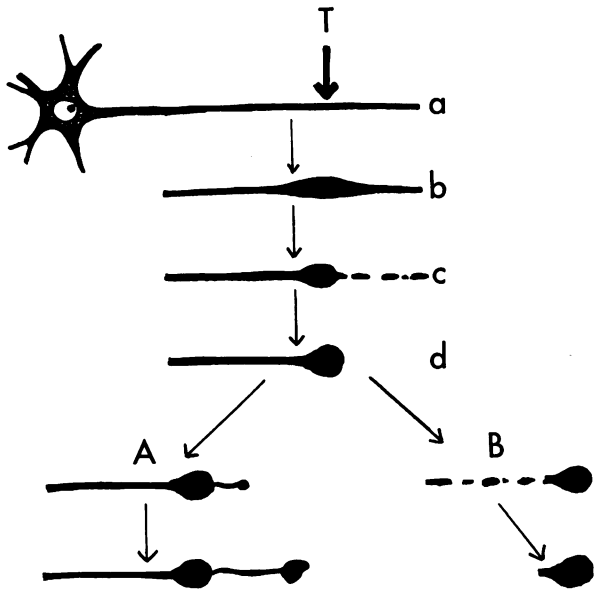


FIGURE 13

Drawing to show the phases of the cytoid body reaction in the human retina. a, local trauma (T) is acting on the neurite; b, localized swelling develops; c, interruption of the neurite at the site of the trauma with degeneration of that portion of the neurite that is no longer connected with the cell; d, formation of a cytoid body at the end of the nerve stump. The two possible further changes involving cytoid bodies are shown. A, abortive regeneration; B, retrograde degeneration of nerve stumps with isolation of the cytoid bodies which in turn may persist for some time or disappear.

cytoid bodies seem to remain in the retina at least for a few weeks. In the long run, however, one of two reactive processes set in: regeneration or retrograde degeneration.

Abortive regeneration of nerve fiber stumps in the retinal nerve fiber layer must be very rare in the adult, but it has been seen occasionally.[12] Attempts at regeneration are rather commonly seen at the end of nerve stumps in the retinas of children. It does not seem that this fact—demonstrated in the third case of this paper—has been reported before in the literature. However, abortive regeneration of centrifugal nerve stumps in the optic nerve of children has been described.[13,14] Regeneration begins from the cytoid bodies and usually represents new growth of a neurite with a so-called growth bulb at its

end (Figure 13A). Only early attempts at regeneration have been seen so far in the retina and the optic nerve and it is not known how extensive this process can become.

Retrograde degeneration of the nerve stumps is the most common reaction in the adult retina.[5] This causes the nerve stumps themselves to disappear while the terminal swellings may remain in the nerve fiber layer as isolated and usually very irregular bodies (Figure 13B). These bodies may or may not exhibit pseudonuclei and pseudoprotoplasms. Retrograde degeneration of the nerve stumps and of the cytoid bodies occurs, for example, along with the clinical disappearance of cotton-wool spots after a few weeks. I have so far found no way to estimate the length of time the isolated bodies may stay in the retina. Most of them finally disappear, but some become hyalinized and I would guess that these remain for long periods.

Macrophages filled with fat and debris may also occur within areas of densely accumulated cytoid bodies (cotton-wool spots, for example), as the first case of this paper shows. This is not surprising since retinal microglia are known to be attracted by the debris of broken-down tissue and would thus be expected to be active in areas of nerve fiber destruction.[15,16] These large phagocytes may look somewhat like the cytoid bodies with some staining methods and this fact may in part explain the difficulties that eye pathologists have had in agreeing about the nature and origin of cytoid bodies.

The fourth case of spinal cord nerve changes after cordotomy demonstrates clearly that the cytoid body reaction is not a specific change of retinal neurites. Interrupted nerve stumps with the terminal swellings of Cajal, as well as isolated bodies with and without pseudonuclei and pseudoprotoplasms, were beautifully seen next to the cordotomy wound. All the characteristics of the retinal cytoid body reaction may be seen in this and in many other pathologic conditions of most parts of the nervous system. At this point I would like to ask whether it is sufficient just to understand the nature of the so-called cytoid body reaction or whether it would be even better to discontinue the use of the confusing term, cytoid body, in ophthalmologic language and literature. The basic central nervous system reaction that it describes has never been anything new or special to our field.

SUMMARY

Three cases are used to show that cytoid bodies of the nerve fiber layer of the human retina are a reaction of interrupted nerve fibers.

Attempts at nerve regeneration starting from the cytoid bodies of nerve stumps are demonstrated in the retinal nerve fiber layer of a child. The reactions of the neurites of the spinal cord after cordotomy show that the cytoid bodies of the retina are a non-specific nerve fiber reaction that may occur in most other parts of the human nervous system.

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DISCUSSION

Dr. A. Edward Maumenee. Dr. Wolter's presentation today is another example of how the application of a different technique and persistence will contribute to our scientific knowledge in medicine. On numerous occasions in the past, Dr. Wolter has applied his special technique of silver staining of nerves to the eye and adnexa. With this technique, he has made new observations and confirmed many old ones regarding the extraocular muscles,

cornea, uveal tract, retina, sclera, and optic nerve. His persistence is illustrated by his presentations of material on cytoid bodies in several different languages in 1956, 1957, 1959, 1960, 1961, 1965, and 1966. It had been previously suggested on numerous occasions that cytoid bodies were due to swollen axon fibers in the retina, but in 1957 Dr. Wolter was able to clearly demonstrate these changes in the axons of the human optic nerve with his silver technique. The observation that cytoid bodies are swollen and degenerated axons has been confirmed by electron microscopic and other studies by Ashton, Okun, Collins, Zimmerman, and others.

Again today, Dr. Wolter has beautifully demonstrated the presence of axonal changes as the cause of cytoid bodies in the retina, and in addition has illustrated similar lesions in the spinal cord. Since ophthalmologists, and even ophthalmic pathologists, do not study lesions in the central nervous system frequently, I asked Dr. Lindenberg, our neuropathologist at Hopkins, to supply me with illustrations of degenerated axonal fibers in the central nervous system. [Slides] The first slide illustrates a fat embolus in the pons and degeneration of the surrounding nervous tissue. The second slide shows the active gliosis occurring in this area. In the third slide, a silver stain shows the swollen axonal fibers, cut both longitudinally and in cross-section. The final slide illustrates that these swollen fibers may enlarge to ten to fifteen times the size of undamaged axons. Pentschew and Swartz, in *Acta neuropathologica* (1:313, 1962), have beautiful illustrations of these lesions produced by Vitamin E deficiency in adult rats. These sections are taken from the fasciculus gracilis. [Slides] The first slide shows these lesions cut in longitudinal sections and illustrates a pseudonucleus and multiple areas of swelling along one axon. The second slide is from the lateral cuneate nucleus and is a Mallory stain. The reddish stain surrounding the swollen axon represents the residual myelin.

I would like to ask Dr. Wolter several questions. One, have you observed swollen axons in the central nervous system to occur in clusters as they do in the retina? Secondly, in some instances where the cytoid bodies are fairly large and occur next to the disk, it would appear that almost all of the axons are interrupted. This is illustrated in the next slide. [Slide] It would seem that such extensive damage should create a visual field defect, but I have never observed one. I wonder if Dr. Wolter has observed visual field defects from cytoid bodies? Finally, since Dr. Wolter does not like the name cytoid bodies, and since the name axonal bodies has been used to indicate the destruction of the axons with the development of pseudocells, I wonder if he would prefer axonal bodies to cytoid bodies?

DR. LORENZ E. ZIMMERMAN. I am pleased to have been invited to participate in the discussion of Dr. Wolter's paper for several reasons. First of all, it gave Mrs. Zimmerman and myself a marvellous excuse to come to Hot Springs; secondly, it is always a pleasure to be invited to discuss a paper that is so technically excellent and beautifully illustrated as the one we have

just heard. Finally, it afforded me an opportunity to correct some misunderstandings I had had with respect to the historical aspects of the lesions Dr. Wolter has described so well. As he pointed out these lesions—called cytoid bodies by ophthalmic pathologists—are usually referred to as "end bulbs of Cajal" in the neuropathologic literature, and I, along with many others, have long been mistaken in the belief that it was Cajal[1] who first described them. My probing into the early ophthalmic literature was stimulated by a desire to find out who introduced the term "cytoid body" (a term that I would like to see dropped for several reasons). I had suspected that Verhoeff introduced the term, but he denied it and suggested that it was Parsons.[2] In reading Parsons' textbook, *Pathology of the Eye*, published in 1905[3] I was astonished to find that cytoid bodies were first described in albuminuric retinitis by Heymann and Zenker[4] who regarded them as degenerated ganglion cells. That was in 1856! Two years later, H. Müller[5] confirmed their presence in albuminuric retinitis but he correctly interpreted them as swollen, varicose, or ganglionic nerve fibers. By the time that Parsons had written his book,[3] it was well known that cytoid bodies are also observed in many other conditions, including experimental injury to the retina which Parsons himself had studied.

Thus the theory for the histogenesis of "cytoid bodies" originally advanced by Müller[5] was accepted by Parsons[3] and subsequently proved by Leber[6] who dissected them from the retina and showed them to be swollen club-shaped bodies, which he believed to be hydropic nerve fibers, and by the monumental work of Cajal[1] who studied the patterns of nerve fiber degeneration throughout the central and peripheral nervous system as well as in the retina and optic nerve. Strangely, subsequent workers, including some of the great names in American ophthalmology, had different ideas.

In 1921, Verhoeff[7] unfortunately confused the varicose swelling of degenerating axons in the retina and optic nerve head with hyalinized astrocytic fibers observed in gliomas of the optic nerve (Rosenthal fibers[8]). Since the latter may be observed in the meninges where there are no axons, Verhoeff considered this as proof that cytoid bodies could not be derived from axons. In retrospect Verhoeff should have concluded that since the structures he labelled as "cytoid bodies" in gliomas of the optic nerve may be observed in the meninges where axons are not present, this proves that the "cytoid bodies" of gliomas are different from the "cytoid bodies" observed in the retina and optic disk. Verhoeff's authoritative opinions undoubtedly must have misled others. This led to a search for a new and better explanation.

Friedenwald[9] collected a series of cases of albuminuric retinitis in order to study the origin of cytoid bodies. In 1929 he wrote: "the lesion begins with a small hemorrhage in the nerve fiber layer, with resulting necrosis of the tissue and cellular reaction. When the accumulation of wandering cells becomes sufficiently dense, those at the center of the lesion become necrotic, and are seen in the sections only as faint shadows." He concluded that the

cytoid bodies are therefore "large, swollen, necrotic mononuclear wandering cells." In 1952, when the first edition of *Ophthalmic Pathology*[10] appeared, Friedenwald had apparently changed his mind, for the macrophagic theory was replaced by the glial concept that had been previously suggested by Verhoeff's observations on the optic nerve gliomas.

Finally, in 1956, one hundred years after cytoid bodies were first described by Heymann and Zenker, Reimer Wolter[11] published the first of a series of papers[11–14] in which he has clearly and (in my opinion) unequivocally re-established the axon as the source of cytoid bodies. He has confirmed the original observations of Cajal, as have experimental neuropathologists, using electron microscopy[15,16] as well as more conventional neurohistologic methods. Moreover electron microscopy has recently been employed in the study of cotton-wool spots.[17–19] Whether occurring in the course of natural diseases in man or produced experimentally in animals, cotton-wool spots are focal ischemic lesions of the inner retinal layers in which cytoid bodies are characteristically present. By electron microscopy the cytoid bodies are observed to be the terminal bulbous swellings of severely damaged axons. The dense basophilic area contained within the cytoid body (the pseudonucleus) is the result of an aggregation of cytoplasmic organelles which become clumped into a relatively homogeneous mass within the swollen portion of the axon.[19] In the early "reactive" stages mitochondria and dense bodies predominate.[16] Later with attempts at regeneration neurofilaments and vesicles become conspicuously numerous.[16] Whether these accumulations of cytoplasmic organelles in the markedly swollen portions of the axons are the result of a cytoplasmic flow of organelles from other regions within the axon or a consequence of rapid synthesis of new organelles at the site of axonal damage is not yet known.

These electron microscopic observations also provide a good cytologic explanation for the accumulation of oxidative enzymes that occurs in the bulbous stumps of severed axons.[20,21]

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DR. THOMAS R. HEDGES, JR. One is struck by the similarity of these findings in cytoid bodies of the retina with Dr. Wolter's contribution in 1956 regarding hyaline bodies of the optic nerve. If retinal cytoid bodies are similar findings to what one finds in the central nervous system, I would like to ask him to comment about what he termed then as "tombstones" of neuronal degeneration in the optic nerve or hyaline bodies of the optic nerve and whether their pathogenesis is really similar.

DR. DAVID O. HARRINGTON. I would like to answer Dr. Maumenee's question as to why these cytoid bodies do not produce field effects. They do.

In the first place, most of these patients are not examined perimetrically because the findings are so obvious ophthalmoscopically that nobody bothers to do fields on them. When fields are done and done carefully, and particularly where there are lesions close to the optic nerve head, they will produce field defects; and, as I have reported in the past, they produce typical nerve fiber bundle defects or scotomas sometimes confused with glaucomas. I have had a number of patients referred to me with a diagnosis of glaucoma, in

whom the lesions which produced the field defect were the lesions Dr. Wolter describes.

DR. P. J. LEINFELDER. I would like to emphasize that from the clinical point of view it is probable that all cotton-wool areas are not the "cytoid bodies" described by Dr. Wolter. There is variation in the clinical appearance of cotton-wool areas, and their occurrence in many conditions, such as diabetes, carcinoma of the bowel, multiple myeloma, the peptic ulcer syndrome, and collagen diseases, makes it difficult to explain them with a single hypothesis. It is particularly interesting to me that in the course of a year we see on the medical wards at least ten patients with cotton-wool areas in whom we suggest a diagnosis of carcinoma of the bowel prior to the medical diagnosis. How explain these lesions?

DR. WOLTER. I am very happy to have so many excellent discussers add important points to my paper. I certainly agree with everything Dr. Maumenee said, and I would like to thank him.

That terminal swellings are commonly arranged in clusters has to do, I believe, with the fact that the retinal arterioles are true end-arterioles, and that these clusters of terminal swellings (cotton-wool spots) are caused most often by a vascular involvement. In other cases it may be due, for example, to the photocoagulator burn in one spot or to a similar local insult.

Dr. Harrington was kind enough to answer Dr. Maumenee's second question in part. There are cotton-wool spots, in my opinion, which do have a field defect, but there also are cotton-wool spots which do not. This may be because some of the nerve fibers in a cotton-wool spot may be continuous, and I have commonly found these fibers histologically to run right through their center. Furthermore, the cotton-wool spots, of course, are located in the inner layer of the retina and the rods and cones are in the outer layers, while there are many very complex nerve networks in between which could make up for quite some defects in parts of the retinal system.

May I also thank Dr. Zimmerman for his valuable comments and additions. It is news to me that it was not Cajal who first understood this type of nerve fiber reaction. All I did was to apply the accepted view on the reaction of interrupted nerves in the central nervous system to ocular pathology. It has to be stated, furthermore, that most ophthalmologists in Europe always have believed that cotton-wool spots are caused by axonal changes. When I came to this country I did not really know what people were talking about when they used the term cytoid body.

I am very happy that Dr. Zimmerman brought electron microscopic photographs of axonal enlargements in the central nervous system, and I am sure that there is much more that can be done with this technique. It seems to be possible, for example, to show the difference between reactive and degenerative terminal swellings. This should be studied in the retina.

One would need a whole new paper to answer Dr. Hedges' question con-

cerning the bodies in the optic nerve. Terminal swellings may develop in the optic nerve after any type of nerve fiber interruption and there definitely are round bodies of nerve fiber origin in the human optic nerve. Hyaline bodies everywhere in the eye, and especially in the retina and optic nerve, however, may be of very different origin. Almost everything can hyalinize, and you never know where one particular kind of bodies came from unless you can observe all the stages of their development. As far as the drusen in the optic nerve head go, I am not prepared to say what their origin is. I do not know that much about it.

Dr. Leinfelder's statements were very interesting, and again I certainly agree. Liddicoat, Wilkinson, and I published a paper on retinal metastasis of a malignant melanoma (*Am. J. Ophth.*, 48:172, 1959), and this certainly looked clinically like a cotton-wool spot. I am sure that there must be many things that can look clinically like a cotton-wool spot and actually be a combination of different changes or an entirely different change. Cotton-wool spots may occur in many systemic diseases and these do not need to be severe. In such cases eyes are not commonly enucleated and, thus, there may be much to be learned about details of their possible composition.

I have probably forgotten to answer some of the other questions because there were so many. Again I would like to thank you very much for this opportunity. Finally, it may be stated that axonal enlargement is suggested as a new term to replace that of cytoid body. All other terms which are known to and understood by neuropathologists, like terminal swelling, axonal degeneration, or neuronal body end swelling are, of course, also acceptable.