LEIOMYOMA OF THE IRIS: REPORT OF A CASE

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The subject of leiomyoma of the iris has been confined largely to the realm of academic conjecture, discussion, and controversy. Very few cases have been reported in the literature, and in most of these the pathologic diagnosis is questionable. The existence of such a tumor in the iris or ciliary body has, therefore, been postulated for the most part on the basis that leiomyoma does occur in other types of smooth muscle tissue. Most textbooks on the eye do not mention the possibility of such a growth, and the only references to this form of tumor are in a few comprehensive treatises on pathology and histology.

Henke and Lubarsch,[1] in their Handbuch, make the following comment: "Myomas and myosarcomas of the uvea have been described many times, but the diagnosis is still not without question. In the first place, when smooth muscle is found in sarcomas it has not been shown that this takes part in the building of the new formation, that it is not merely rests of preformed muscle fibers. Secondly, it does not seem definite that the structure in question always shows smooth muscle cells. As Mitvalsky has shown, the differentiation of pathologic smooth muscle fibers from other kinds of spindle elements in sarcomas is extraordinarily difficult."

Parsons[2] merely mentions the possibility of myoma of the iris, and refers to the case, described by Thompson, in which Griffith suggested this diagnosis in 1899.

According to Stengel and Fox,[3] leiomyoma occurs most often in the uterus, gastro-intestinal tract, and ovaries. The growth is found less commonly in the walls of the vessels,

the skin, the bladder wall, the kidney, and the nipple. It always springs from pre-existing unstriped muscle fibers. Its characteristic structure consists of bundles of muscle cells running in different directions. Longitudinal sections show cylindric nuclei and indistinct cell outlines. The protoplasm stains deeply with eosin. Between the muscle cells are collagen and the so-called myoglia fibrils. The whole picture resembles that of sarcoma, from which it can be distinguished by the greater regularity in the direction of the cells in the different bundles and the distinctly cylindric nucleus.

Mallory's[4] description of leiomyoblastoma or leiomyoma is quite similar to that of Stengel and Fox. Mallory defines this type of tumor as of mesenchymal origin, with a tendency for the tumor cells to differentiate into smooth muscle cells. He describes the long, spindle-shaped cell with the rod-shaped nucleus and the dense acidophilic cytoplasm. In the cuticle of the cytoplasm are longitudinal striations (myoglia fibrils) which are brought out by special staining. The fibrils are fine and separate, except at the ends of the cells, where they fuse and form coarse fibrils. The smooth muscle cells are always surrounded by numerous collagen fibers, which bind them together and appear to be largely responsible for the density and toughness of the smooth muscle tissue. The rate of growth of leiomyoma in any situation is slow. If mitotic figures are present, the tumor is clinically malignant and capable of infiltration and metastases.

The description of leiomyoma in other standard works on pathology does not differ from those just given.

The studies of Ida C. Mann[5] on the embryology and development of the human eye leave little doubt but that the dilatator and sphincter muscles of the iris are derived from the neural ectoderm. This marks them as being extremely primitive in type. They possess the power of contraction to light when all nerve paths have been blocked. The earliest development of the sphincter muscle takes place about the fourth month of embryonic growth. The dilatator fibers ap-

pear at about six months, or after the sphincter is definitely formed. Some difference of opinion exists as to whether these fibers arise from the sphincter and grow over the anterior epithelial layer or whether they are developed in its surface *in situ*. The fibers extend to the root of the iris, and fine longitudinal striations appear in the anterior third of the anterior layer of cells. These latter form a definite layer which never becomes vascularized, and is never separated from the ectoderm by a layer of mesoderm. This layer of epiblastic cells remains in a more or less embryonic state.

Verhoeff[6] is the only observer in this country who has reported a case of leiomyoma of the iris. This was the first case in which differential staining was used (Mallory's phosphotungstic hematoxylin), and hence it was the first instance of this type of tumor in which the diagnosis could be verified histologically. According to Verhoeff, leiomyoma is characterized by the long spindle-shaped appearance of the cells, with their typical rod-shaped nuclei, the tendency of the cells to occur in bundles with the nuclei arranged in rows (palisade arrangement), and the presence of myoglia fibrils coursing along the cells and coalescing to form large fibrils at their terminal processes. This writer called attention to a characteristic difference between myomas and spindle-cell sarcomas. "This," Verhoeff says, "consists in the fact that myoma cells are truly spindle-shaped, whereas the cells of a uveal spindle-cell sarcoma are seldom if ever distinctly spindle-shaped, but terminate in or send off laterally several ill-defined irregular processes which anastomose with neighboring cells and thus form a more definite syncytium." Verhoeff also stressed the benign character of leiomyoma.

In a review of the literature at that time Verhoeff found three cases that had been reported as myoma of the iris and six cases diagnosed as myoma of the ciliary body. In addition, a case which Dreschfeld[7] in 1875 described as sarcoma of the iris was cited as a probable instance of myoma. After a careful study of these cases Verhoeff reached the following

conclusions, which are more authoritative than any I could make from my own review of the same cases. Hence I quote:

"In regard to the question as to whether any of the tumors previously described as myomas of the iris or ciliary body were really such, it is impossible, in the absence of differential staining, to arrive at a positive conclusion. It is reasonably certain, however, that the tumor described by Thompson[8] and examined microscopically by Griffith was a true myoma. The spindle cells were arranged in bundles and possessed rod-shaped nuclei. While many such nuclei may often be found in spindle-cell sarcomas, the nuclei are not predominantly rod-shaped. In addition to this, the illustration of this tumor shows that there was a definite tendency for the nuclei to be arranged in rows, leaving zones free from nuclei. There is some probability that the tumor described by van Duyse[9] was also a myoma of the iris, owing to its long duration, twenty years, and to its not having produced glaucoma or affected vision. From the meager histologic description of this tumor, however, it cannot be differentiated from a spindle-cell sarcoma.

"Owing to the fact that the ciliary body consists largely of smooth muscle, it would seem that a myoma was more likely to occur here than in the iris. In none of the six cases of supposed myoma of the ciliary body reported, however, is it possible, from the histologic description given, to be reasonably sure that the tumor was not a spindle-cell sarcoma. In fact, I regard it as almost certain that the tumors were all spindle-cell sarcomas."

I have reviewed all these earlier cases, and, of course, cannot add anything to Verhoeff's conclusions regarding them. Since Verhoeff's report, two cases described as leiomyoma have been reported in the literature. The first was a case of leiomyoma of the ciliary body reported by Velhagen[10] in Germany, and the other, described by Bossalino[11] in Italy, was called leiomyoma of the ciliary body and of the iris. In neither of these instances does the pathologic

picture described quite justify the diagnosis, according to the description of leiomyoma given by most general pathologists and to the criteria set forth by Verhoeff.

Velhagen's patient was a woman, aged fifty-seven years, who consulted him because of a cataract in the left eye. In addition to the cataract he observed some distortion of the pupil. A closer examination revealed the presence of a black tumor, which seemed to extend from the periphery of the inner surface of the iris, but continued definitely inward along the wall of the globe. The growth was diagnosed clinically as a melanotic sarcoma of the ciliary body and the eye was enucleated.

In his pathologic report Velhagen states that the tumor had its origin in the ciliary muscle and finally included the entire ciliary body. It consisted principally of a basic fibrous tissue, which took on almost the same hue, when subjected to the van Gieson stain, as did the healthy portions of the ciliary muscle. The tissue was irregularly interspersed with cell nuclei, which only rarely showed protoplasmic substance, but otherwise greatly resembled, in size and formation, the normal muscle nuclei of the ciliary body. The nuclei of the region which corresponded to the pars circularis of the ciliary muscle were often round; those belonging to the region of the pars radialis and base were spindle-shaped. The chromatin design was quite clear; cell division formations did not appear anywhere. In addition, Mallory's method of differential staining was used, with negative results.

Despite these findings, after excluding sarcoma and other tumors, Velhagen justifies his diagnosis of leiomyoma in the following terms: "Consequently the only remaining possibility is to describe this tumor as a leiomyoma of the ciliary body. Even though no specific reaction has so far pointed to this conclusion, still the similarity of the coloring of the tumor fibers with those of the normal pars meridionalis of the ciliary muscle was significant. Moreover, one had the

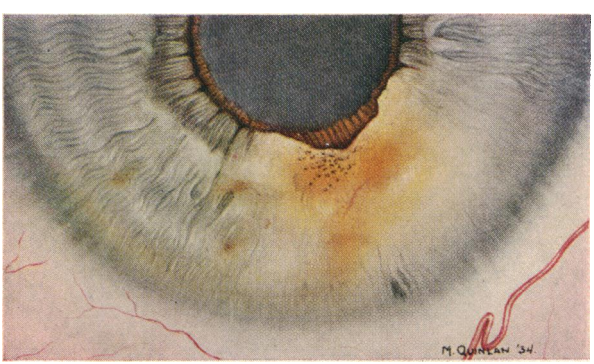

Fig. 1.—Leiomyoma of the iris. The appearance of the left eye, showing the extent of the tumor and ectropion of the uvea.

definite impression that these portions of the growth lying within the pars circularis were the oldest."

In the case reported by Bossalino[11] in Italy the evidence for the diagnosis of leiomyoma is even more vague. His patient was a woman, aged sixty-eight years, who had had a number of hemorrhages into the anterior chamber of the right eye, and finally consulted the oculist because of annoying, although not severe, pain in the right eye and forehead. Examination revealed the presence of a large nodule in the lower internal quadrant of the anterior chamber. The growth seemed to be connected with the iris, and extended until it occupied the region corresponding to the iridocorneal angle; toward the center it extended from 2 to 3 mm. beyond the edge of the pupil. It was yellowish-pink in color. The anterior surface, which was flattened out, did not adhere to the posterior surface of the cornea. The portion of the iris not invaded by the neoplasm appeared to be normal. The eye was enucleated.

Bossalino reports that the whole mass of the tumor apparently consisted mainly of fairly wide bands of tissue, forming larger or smaller spirals, some of which surrounded zones less elongated in appearance and having irregular borders. Elongated or round spaces full of blood were observed in the midst of this newly formed tissue. The predominating cells are described as fibroblasts, and certain degenerative and necrotic changes were noted. Since this tumor was apparently not subjected to differential staining methods, the diagnosis of leiomyoma cannot be accepted without question.

The following is the report of the case recently observed by me:

The patient was a married woman, aged forty-six years. I had examined her eyes periodically for six years. The tumor was first noticed in August, 1934. It was a small, circumscribed nodule, yellowish-gray in color, the surface near the pupillary border being dotted with pigment. There was also an ectropion of uveal pigment at this point, producing a somewhat pear-shaped pupil. This

ectropion was about 1 mm. in width, and showed the radial columns of dark brown pigment of the posterior surface of the iris. It suggested that the iris had been turned inside out by the contracture of the tissues in the anterior layers. The growth appeared to have increased the thickness of the iris about 1 mm., and extended from the pupillary margin to a little more than half the width of the iris (fig. 1).

The mass was somewhat wedge-shaped, with its apex directed toward the pupillary margin, and extended from about 4 to 6 o'clock. The thickest portion was nearer the pupillary margin, and gradually grew thinner toward the root of the iris. Small blood vessels were visible in the stroma, making their way in the iris tissue from the periphery toward the mass. A dilated and tortuous anterior ciliary vessel was seen in the same sector as the tumor. There were no precipitates on the posterior surface of the cornea, and no evidences of active inflammation were present. The fundus in both eyes appeared to be normal.

The patient had no pain or other symptoms and there was no impairment of vision. The tumor gradually increased in size until, in six months, it was about twice as large as when it was first noticed. During this time the patient was seen by a number of consultants, of whom Dr. Clarence King was the first. Dr. King believed that the growth presented many of the characteristics of an exudate. Hence exhaustive physical and laboratory tests were made, but since all the findings were normal, this belief was abandoned by him.

In November, as the patient was to be in New York, I advised her to see Dr. John M. Wheeler. Dr. Wheeler believed the growth to be a sarcoma, and advised that its progress be watched carefully. Three or four months later, on her return from Florida, she consulted Dr. Alan C. Woods, who was of the opinion that it was a malignant sarcoma, and that the eye should be enucleated at once. He strongly advised against an iridectomy for biopsy.

In March, 1935, I removed the patient's eye. Needless to say, her anxiety during the period of observation was great, and the removal of the eye and the pathologic report relieved her fears, so that she was much happier than she would have been if the eye had been retained and the malignancy of the growth uncertain.

Dr. A. B. Reese and Dr. John M. Wheeler, of New York, collaborated in the histologic studies. Dr. Reese's description of the specimen was as follows:

"The cornea shows an irregularity in the thickness of Descemet's

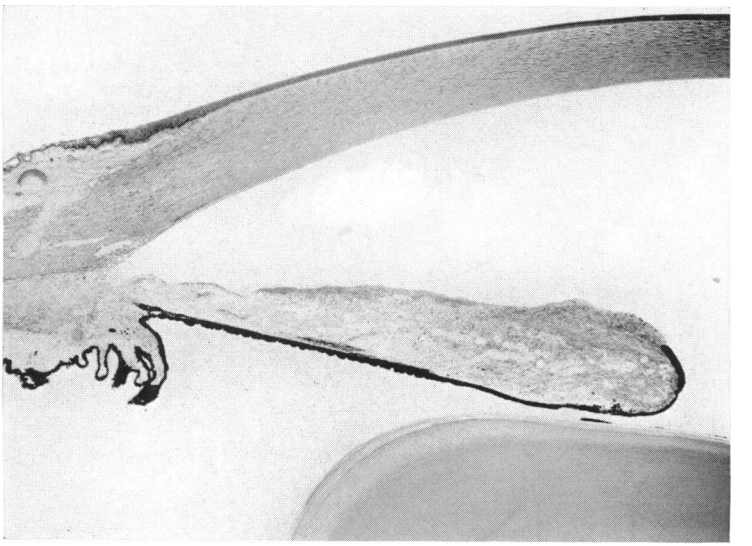

Fig. 2.—The tumor tissue infiltrating the iris stroma, with greatest thickness in the sphincter area.

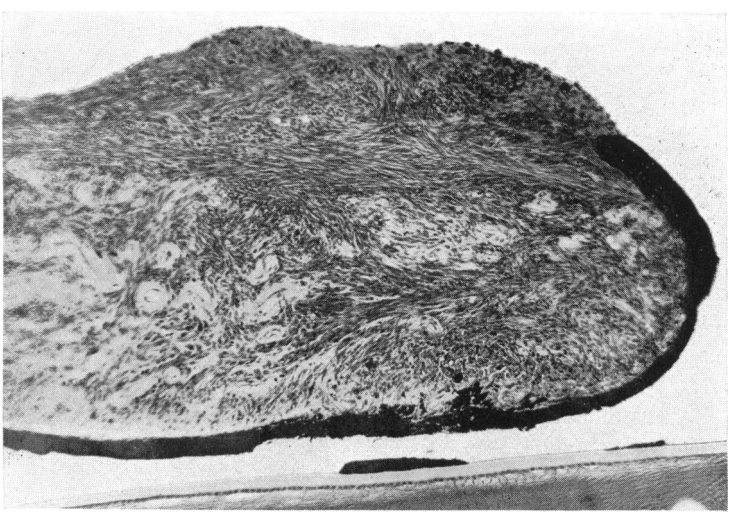

Fig. 3.—Low power, showing interlacing bundles of tumor cells invading the sphincter area. The position and direction of the bundles suggest that their contraction has produced the ectropion.

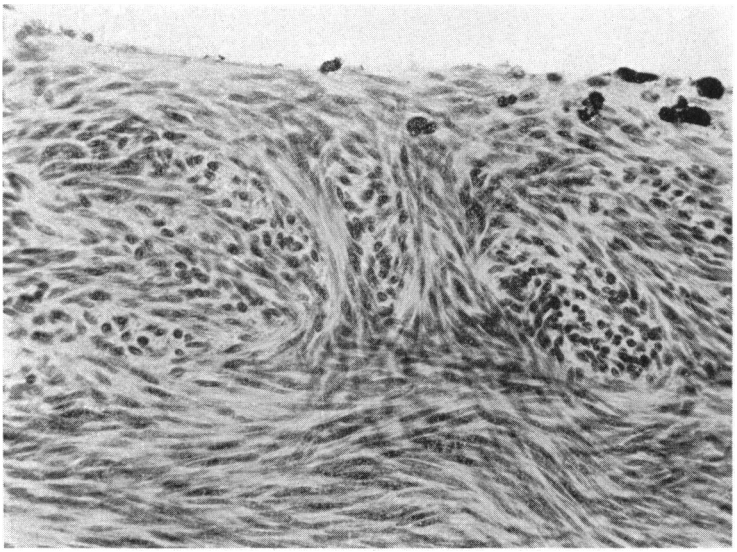

Fig. 4.—High power. Cell bundles cut longitudinally and transversely. Rod-shaped nuclei with palisade arrangement.

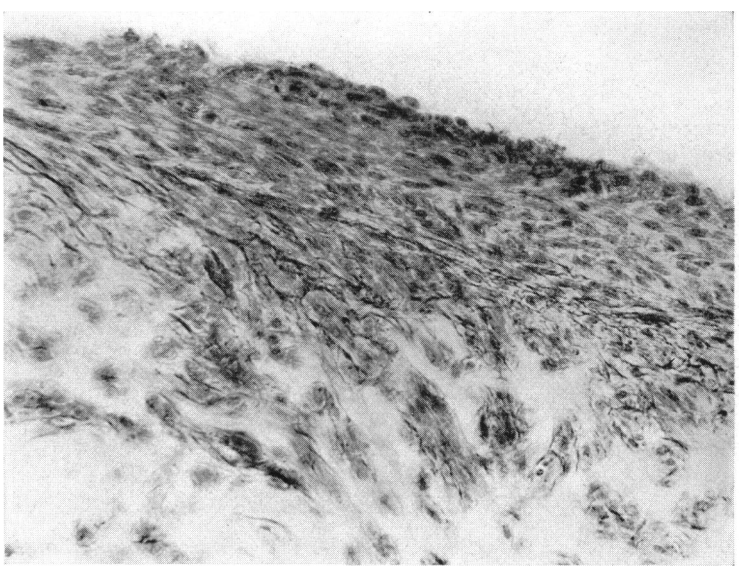

Fig. 5.—Showing myoglia fibrils by gold impregnation method.

membrane peripherally, with the appearance of posterior excrescences (Henle's warts). The sclera inferiorly is pierced by a large intrascleral nerve loop at the level of the posterior portion of the ciliary body. The anterior chamber is of normal depth and the angles are well open. Schlemm's canal is dilated and of good size. The pupillary two-thirds of the iris below is occupied by a rather dense, moderately vascularized tumor which extends on the anterior surface of the iris nearly to the iris root (fig. 2). The tumor is composed of interlacing bundles of closely packed elongated spindle-shaped cells with considerable granular eosinophilic cytoplasm and long oval nuclei. In cross-section the nuclei appear round. The tumor is of greatest thickness at the level of the sphincter iridis, with which it appears to be continuous (fig. 3). There are a few scattered chromatophores in the tumor tissue. No mitotic figures were seen (fig. 4). At the iris root below there is a compact group of cells containing brown granular pigment. There is a small degree of ectropion uveae. The ciliary body and choroid show no abnormalities. There is peripheral cystic degeneration of the retina. The optic disc and nerve are normal."

Differential staining by the gold impregnation method (fig. 5) also revealed the presence of the characteristic myoglia fibrils, and a diagnosis of leiomyoma of the iris was made. A section was sent to Dr. Verhoeff, and he concurred in this diagnosis. In his opinion, the close relationship of the tumor to the pupillary border and the sphincter muscle suggests that it arose from the latter, but, on the other hand, this evidence cannot be regarded as conclusive because the tumor cells may simply have invaded and intermingled with the cells of the sphincter. However, in any case, if Mann's conclusions regarding the development of this tissue are correct, the tumor must be regarded as of epiblastic origin.

With our present knowledge it is impossible to make a clinical differentiation of leiomyoma from sarcoma. The diagnosis can be made only as the result of microscopic study, and even then it may be difficult to determine definitely whether the tumor had its origin in smooth muscle fibers. Whether the factor of iris ectropion can be considered as a valuable clinical sign in the diagnosis of leiomyoma can be determined only by observation of other cases. The question to be determined is whether these modified smooth muscle fibers retain their contractility, presumably without a nerve supply, and thus cause the ectropion.

SUMMARY

1. A case which must be regarded as a leiomyoma of the iris is described. This is the second case in which the pathologic findings are sufficiently definite to justify this diagnosis. The other case was reported in 1923 by Verhoeff, who reviewed the literature and contributed an excellent description of the pathologic histology of this lesion.

2. Two cases since reported as leiomyoma by Velhagen and by Bossalino are questionable, for neither of these authors demonstrated the presence of the characteristic myoglia fibrils by differential staining.

3. Clinically, leiomyoma is relatively benign. Its outstanding pathologic characteristics include a structure of interlacing closely packed bundles of spindle cells with rod-shaped nuclei in palisade arrangement, displaying eosinophilic cytoplasm and myoglia fibrils.

I wish to express my appreciation to Dr. Wheeler and his staff for the preparation of the excellent colored drawing and the photomicrographs. My thanks are also due the other consultants.

REFERENCES

1. Henke and Lubarsch: Handbuch der Speziellen Pathologischen Anatomie und Histologie, Julius Springer, Berlin, 1928, xi, p. 535.
2. Parsons: The Pathology of the Eye, G. P. Putnam's Sons, New York, 1904–1908, i, p. 326.
3. Stengel and Fox: A Text Book of Pathology, W. B. Saunders Company, Philadelphia, 1915, Ed. 6.
4. Mallory: The Principles of Pathologic Histology, W. B. Saunders Company, Philadelphia, 1914.
5. Mann: The Development of the Human Eye, Cambridge University Press, 1928.
6. Verhoeff: Arch. Ophth., 1923, lii, p. 132.
7. Dreschfeld: Lancet, 1875, i, p. 82.
8. Thompson: Tr. Ophth. Soc. U. Kingdom, 1899, xix, p. 49.
9. van Duyse: Arch. d'opht., 1911, xxxi, p. 13.
10. Velhagen: Klin. Monatsbl. f. Augenh., 1933, xci, p. 456.
11. Bossalino: Boll. d'ocul., 1934, xiii, p. 332.

DISCUSSION

DR. F. H. VERHOEFF, Boston: This case interests me greatly, because so long a time has elapsed for another case of leiomyoma of the iris to be described. As the essayist said, I examined the

sections, and they convinced me that this was a true case of leiomyoma, but I am not sure as to whether or not the tumor was epiblastic in origin. In my case the tumor arose from the anterior surface of the iris, and was not connected in any way with the sphincter or dilatator. I was of the opinion that it was probably mesoblastic in origin, and that it arose from the stroma cells of the uvea, just as do the ciliary muscles.

The day after Dr. Standish removed the tumor, he asked me if I had ever seen a "ghost" tumor. I said that I was not familiar with them, but when we looked at the eye, the growth appeared to be unchanged, and yet I had the tumor in a bottle. What he had evidently done was to pull out the tumor and leave its capsule behind. We knew that a part of the growth was left in the eye. The patient went on for sixteen years before he developed glaucoma and the tumor increased enough in size to necessitate enucleation of the globe. I am sorry to say that I have not seen the patient since. The fact that it was a leiomyoma does not prove that it was not malignant. We believe that neoplasms having the characteristics of Dr. Frost's tumor and of my tumor are leiomyomas, but we cannot affirm that other tumors are not simply because they do not present these characteristics. This was illustrated very well by a case of leiomyoma of the orbit which Dr. Terry reported, and the specimens of which I saw. In the first place, this patient had had an operation on the uterus, and no one knew the nature of the tumor that was removed; some years later she developed a tumor in the orbit in relation with Müller's muscle, so that we cannot be sure whether this growth arose from Müller's muscle, or whether it was metastatic in origin. We believe that it arose from Müller's muscle. The first specimens showed the typical picture of leiomyoma. The tumor recurred several times, and each time it resembled less and less a leiomyoma. Finally it lost all semblance to a leiomyoma and presented the appearance of a malignant sarcoma so that evidently these growths can assume a character that will not permit their recognition. This brings up the question of whether some of the spindle-cell sarcomas of the choroid may not really be of the same nature. Evidence is apparently growing that all these melanomas are neurogenic in origin, but we cannot be too dogmatic about anything of that kind when we realize that we can obtain from pigment epithelium muscle cells that look exactly like those of mesoblastic origin. It is conceivable, therefore, that some of these tumors of the choroid may really be essentially leiomyomas, but I have never been able to prove this. I have

examined a number of choroidal tumors and tried to find myoglia fibers in them, but have never been able to do so. I believe that we can be sure we have a leiomyoma only when the tumor presents all the typical characteristics and we find myoglia fibers, as in this case.

The essayist showed me part of his paper, in which he gives credit to Ida Mann for demonstrating that the sphincter and the dilatator muscles are of epiblastic origin. It is my recollection that this fact was definitely demonstrated and accepted many years ago.

DR. CLARENCE KING, Cincinnati: I saw this patient through the kindness of Dr. Frost about a month after he first observed the peculiar changes in her left iris. When a detailed general examination and laboratory tests proved negative, it was obvious that the lesion in the iris was not due to an inflammation. I was unable to arrive at a definite conclusion as to its nature. If it was not due to an inflammation, it could be only a neoplasm. Theoretically, since benign tumors of the iris are very rare, this growth should be malignant. Objectively, it did not present the appearance of malignancy. It was sharply circumscribed. The iris tissue around it was normal. It was not markedly pigmented. The area involved functioned, as was manifested by its contractility. During the period in which I observed it it showed no tendency to increase in size. The lesion in the iris did not appear to be sufficiently atypical to indicate marked possibilities of independent development. The fact that it might be a myoma never occurred to me. As the patient had excellent vision, it appeared to me that no harm would be done by keeping her under observation before deciding on radical intervention. It is generally agreed that the partial removal of such a growth for purposes of biopsy is contraindicated. As the growth later showed signs of extending, I am convinced that Dr. Frost was fully justified, in the best interests of the patient, in enucleating the eye. When I saw the patient, an excision of the iris beyond the limits of the area involved would have necessitated an iridectomy extending from 3 to 7 o'clock. A coloboma down and out, of this extent, might have been very disturbing to vision.

This case again raises the question as to whether an iridectomy is ever indicated in sarcoma of the iris. Wintersteiner maintains that iridectomy is indicated in cases in which the visual acuity is good, and in which there is some likelihood that it will remain useful after the operation. The tumor must be small, circumscribed, solitary, and free, and be situated in the pupillary zone of

the iris. He believes that iridectomy is contraindicated in those cases in which the tumor involves the angle of the chamber, when it impinges on the cornea, or when it is adherent to the lens. According to Wintersteiner, of 31 cases in which a sarcoma was removed by iridectomy, 18 were cured and 13 were not cured after a two-year period of observation. As to the technique, a number of authors recommend, when there is danger that the point of the keratome may engage in the iris, that a conjunctival flap be prepared and a peripheral incision be made with a scalpel. Using a fine iris hook, the iris is incised on each side of the tumor. The tumor itself is drawn out by means of a sharp hook and excised peripherally.

DR. ALAN C. WOODS, Baltimore: I saw this patient at a much later date than did Dr. King. At the time I saw her the tumor was not circumscribed, but was very definitely invasive. It did not involve the angle of the anterior chamber. To my mind, it presented the characteristic appearance of a sarcoma. It so happened that just before that we had seen several sarcomas of the iris, and the appearance in this case was practically identical with one or two other early cases that I had seen. When the sections came back from Dr. Frost, I was frankly amazed at the picture. Dr. Jonas S. Friedenwald examined the sections, and it is my recollection that after he saw them he concurred fully in the diagnosis of leiomyoma made by Dr. Reese and Dr. Wheeler.

DR. ALBERT D. FROST, closing: I appreciate the discussion that has followed the paper. I neglected to say that without the help of Dr. Wheeler and the members of his staff I do not believe that I would have been able to arrive at this diagnosis, so I claim no credit for it. I merely wished to bring the case before the Society for discussion and consideration.

Concerning Dr. Verhoeff's remarks in regard to the epiblastic origin of this tumor, I concluded that since the sphincter and the dilatator fibers of the iris are of epiblastic origin, we might assume that this tumor, since it appears to have come directly from those fibers, may have had the same origin. I did not mean, and I did not state in my paper, that I believed that Ida Mann was the first to show that the muscles of the iris are of epiblastic origin—I simply quoted her as an authority on the subject.