INTRAOCULAR BIOPSY: AN EVALUATION

BY T. E. Sanders, M.D.*

Biopsy is the surgical removal of a tissue specimen for histologic diagnosis. Its role in the diagnosis of neoplastic disease has become increasingly important. Ackerman (1) has said, "It is imperative that pathologic verification of malignant tumors be present before any therapy for them is instigated." The sole means of doing this is with biopsy. Only histologic examination of tissue can differentiate a chronic inflammatory lesion simulating a neoplasm from true tumor or can give an exact diagnosis of the origin and the type of neoplasm with some idea as to its malignant potentialities.

Techniques of obtaining tissue by biopsy vary with the site of the lesion. Biopsy methods may be quite simple or very specialized and ingenious. The commonest and most useful method is the incisional or surgical biopsy, in which a specimen is removed by incising into the tumor mass (2). In many instances aspiration techniques, in which a large needle with syringe suction is employed, are satisfactory (3). In small discrete lesions, excisional biopsy in which the lesion is removed in toto are applicable. This type of biopsy is very useful in the skin (4). In certain sites, specialized techniques have been devised, as the vaginal smear (Papanicolaou; 5), sedimentation of pleural and abdominal fluids (6), and the use of endoscopic methods, such as the bronchoscope. Sternal marrow puncture has become an invaluable aid to the hematologist (7). At times such major procedures as exploration of the abdominal, thoracic, or cranial cavities are employed.

The purpose of most of these procedures is to obtain a tissue specimen, although at times complete removal of the lesion is also accomplished. It is the responsibility of the surgeon to obtain an adequate and representative specimen by proper choice of the site,

* From the Department of Ophthalmology, Washington University School of Medicine, and the Oscar Johnson Institute, St. Louis.
the extent, and the method of biopsy. As the pathologist can diagnose only on the actual tissue presented, it is essential that there be close cooperation between the clinician and the surgical pathologist (1). This is particularly true in the eye.

A notable exception to this increased use of biopsy is the intraocular tissues. It is feasible to perform a biopsy on any of the intraocular tissues: iris, ciliary body, choroid, retina, or lens. The intraocular tissues are not, however, easily accessible, and the iris and lens are the only ones that are usually excised.

As will be discussed later, there are in the literature only a few scattered case reports of choroidal or ciliary body tumors in which biopsy was performed (8-12). Several series of iris tumors as well as many individual cases have been reported in which some of the specimens were obtained by biopsy. There are no reports of retinal or lens biopsy. I have been unable to find in the ophthalmic literature a comprehensive discussion, with evaluation, of the role played by biopsy in intraocular disease.

Obviously there must be some reasons for this other than the apparent lack of interest of the ophthalmologist in accurate tissue diagnosis. As will be shown, there are several excellent reasons that obviously tend to limit the enthusiasm of the ophthalmologist for intraocular biopsy.

In view of the present-day status of biopsy in other surgical fields and the relative lack of information on intraocular biopsy in the ophthalmic literature, it is believed that the role of intraocular biopsy in ophthalmic diagnosis needs evaluation concerning its indications, the available techniques, the dangers and contraindications, the accuracy of the results, and the clinical applications. This can best be achieved through analysis of a series of patients on whom intraocular biopsy has been performed.

In the files of the Laboratory of Ophthalmic Pathology, Washington University School of Medicine, there are 48 instances of intraocular biopsy. There are 40 cases of iris biopsy, 6 of choroid and ciliary body, and 2 of lens material, with no instance of retinal biopsy. The clinical aspects, the biopsy methods, and the pathologic lesions of these various tissues are so different that they will be discussed separately.
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CHOROID AND CILIARY BODY

Apparently biopsy of a ciliary body or a choroidal lesion is a very unusual procedure. In 1951 Veasey (8), in reporting his case, stated that it was unique. However, in 1944 Alvis (9) recorded the first case of the present series. Veasey's patient, a white male, aged 71, complained of monocular diplopia due to a translucent mass in the ciliary body. Because of the possibility that the mass was a cyst, a 24-gauge needle was passed into the mass through a sclerotomy opening, in the hope of collapsing the cyst and of aspirating some tissue. A core of tissue was obtained, which was diagnosed histologically as "sarcoma." In the enucleated eye a large, non-pigmented, malignant melanoma of the ciliary body was found.

Other instances of aspiration biopsy of a choroidal malignant melanoma have recently been recorded. In April, 1951, Kauffman (10) presented a case before the Section on Ophthalmology of the College of Physicians of Philadelphia. In 1950, Gonzalez, Pateyro, and Grosso (11) reported two cases of aspiration biopsy of malignant melanoma of the choroid confirmed by enucleation. They were impressed with the rarity of this tumor as the two reported cases were the only instances of malignant melanoma in 100,000 patients. Although not reported several other instances of choroidal biopsy are known to have been performed in this country (12).

There are several recorded instances of the use of the intraocular fluids for tumor diagnosis. Tumor cells were found in the subretinal fluid in five of six cases of choroidal melanoma by Meissner (13) in 1923. Rintelen (14) reported two similar positive cases in 1938. Reese (15) doubts the diagnostic value of such examination: proliferated epithelial cells are not uncommon in the subretinal fluid, and the differentiation of such cells from true neoplastic cells is difficult; there are no tumor cells in the subretinal fluid in many cases of early malignant melanoma in which the lamina vitrea is unbroken. Oxilia and Pizzetti (16) in 1950 reported two cases of malignant melanoma of the ciliary body which were diagnosed by aspiration of the aqueous humor, tumor cells being found in the aqueous by the Papanicolaou technique. Cibis (16) in 1940 tested the subretinal fluid for melanin with iron
chloride in five cases with a positive result in each. The test was negative for aqueous, vitreous, and subretinal fluid in ideopathic detachment. Although his belief was never confirmed, Cibis believed that this test possessed real value.

Because there was no tissue for examination, I have not included in the present series one case of proved malignant melanoma of the choroid, in which there were two withdrawals of subretinal fluid. The fluid was sent to the laboratory as dried film on a slide. The interpretation was most difficult: only blood cells could be identified. It should be remembered that in the accepted techniques, using body fluids for cytologic diagnosis, an examination is made of the centrifuged sediment of a relatively large amount of fluid. In the eye, in which the amount of fluid is necessarily minute, this concentration is impossible, and the technique, therefore, is much less dependable.

Considering the rarity of reported cases of biopsy of a choroidal or a ciliary body lesion, our series of six cases is surprisingly large. As these six cases constitute the chief reason for this attempt to evaluate intraocular biopsy, they will be reported in some detail. Three of the six cases are choroidal malignant melanoma (Cases 1, 3, and 4), one an interesting false positive (Case 2), and two are neurofibroma of the ciliary body. These two cases of neurofibroma (Cases 5 and 6) are so interesting and unusual that they will be reported in detail elsewhere. The pathologic diagnosis of all six cases was done by the author, and in three of the cases (Cases 4, 5, and 6) the biopsy was also done by him. Dr. B. Y. Alvis performed the biopsy on Cases 1 and 3, and Doctor H. R. Hildreth on Case 2. These cases are reported with their permission.

REPORT OF CASES

Case 1. H. B., white male, aged 53 years, was referred to Dr. B. Y. Alvis on February 25, 1943. The patient reported that at the age of five years his right eye was punctured by scissors point. Since that time vision had been poor in this eye, but there was no other difficulty. About five weeks prior to the report, he had noted some hazy vision in his left eye, which grew worse. About two months before admission, he was told by an ophthalmologist that he might have a tumor. One month later the diagnosis was changed to retinal detachment, and the patient was referred to Dr. Alvis for operation.
Vision: Right eye, 20/200; left eye, 6/200.

Right eye: Dense corneal opacity in central area of cornea in which lower margin of iris is incarcerated. Some anterior lens opacity. Left eye: Externally normal. Ophthalmoscopic examination showed extensive bullous detachment throughout lower half from 2 to 8 o'clock extending to disc. At 4 o'clock 30 degrees outward are two tears with some pigment proliferation around them. Tension (Schiötz) was right 20 mm. Hg., left 17 mm.

On February 27, 1943, a scleral diathermy operation was done after resecting the inferior rectus muscle. After the diathermy punctures were completed, there was no appreciable flattening of the detachment. A sclerotomy was done and no fluid escaped, even though the sclerotomy was about 3 mm. deep. In the wound some dark tenacious tissue was seen. This was scraped with a blunt iris hook and smeared on a slide.

When this smear was stained, it was found to contain many large spindle cells with a clear ovoid nucleus with definite nucleolus. These cells were thought to be typical of malignant melanoma, subtype Spindle B.

Postoperatively, a large inferior detachment remained, and in the
FIGURE 2. CASE 1, ENUCLEATED GLOBE SHOWING EXTENT OF TUMOR

FIGURE 3. CASE 1, TUMOR SHOWING EFFECT OF DIATHERMY
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inferior temporal quadrant there was a pigmented mass elevated about 15 D. Enucleation was done on March 2, 1943, and a relatively large flat malignant melanoma was found to be present in the inferior temporal quadrant. This extended from the optic nerve to the equator. It was limited to the choroid with no tendency to rupture the lamina vitrea. The tumor mass consisted of Spindle B cells chiefly, but a few Spindle A were also present. Around the sclerotomy opening there was much necrosis, secondary to the deep diathermy punctures.

It is reported that the patient died in 1945 from cancer of the liver, probably metastatic from the choroidal tumor.

Case 2. L. W., white male, aged 65, was first examined by Dr. H. R. Hildreth on May 21, 1943. About six months before, he had noted in the left eye some fine floaters which had persisted. For the past two weeks there had been increasing visual loss in the left eye.

Vision without correction: right eye, 20/25; left eye, 20/100.

The right eye was externally and internally normal. The left eye was externally normal. Superior residual field. Ophthalmoscopic examination showed hazy vitreous. The retina was detached throughout the upper half from 10 to 3 o’clock. The detachment extended to the disc, where the elevation was 10 D. There were many fine

FIGURE 4. CASE 2, BIOPSY SHOWING UNSECTIONED BIT OF TISSUE
FIGURE 5. CASE 2, ENUCLEATED GLOBE SHOWING AREA OF REACTION TO DIATHERMY

FIGURE 6. CASE 2, AREA OF SCLEROTOMY SHOWING PROLAPSE OF RETINA
folds over the detached area, but the peripheral margin was smooth. Two tears with some secondary retinal proliferation were localized 50° out at 1 o'clock.

On May 23, 1943, a scleral diathermy was done over the superior sclera after resecting the superior rectus. The diathermy points were placed with a ½ mm. point from 10 to 4 o'clock. Sclerotomy was done at 2 o'clock. There was some bleeding, but no fluid was presented. Sclerotomy was repeated at 12 o'clock and some gelatinous tissue was presented in the wound. This tissue was excised and placed on a slide.

After the tissue on the slide was stained, it was found to consist of a solid mass of round cells with some blood. Because of drying, the tissue did not stain well, but the round nuclei of a solid mass of cells could be easily seen. Although the mass could not be sectioned and the cells could not be studied adequately, it was thought that the cellular mass was a bit of prolapsed choroidal tumor, as this was thought to be the only possible cause of a solid mass of tissue under a detached retina.

Clinically the eye did poorly postoperatively, there being much reaction in the vitreous. The retina was hazily seen, but was apparently still detached. Because of the finding of solid subretinal tissue and the poor postoperative response, the eye was enucleated on May 26, 1943.

Pathologic examination of the eye showed no evidence of tumor. About one half of the retina was involved in a relatively flat detachment. Much of this detachment was adherent to an area of choroid thickened several times by edema, hemorrhage, and diffuse chronic cellular infiltration. In section through the sclerotomy, the retina was found to be prolapsed into the wound with part of the outer layers excised.

The final diagnosis was simple idiopathic detachment of retina with prolapse of the retina through the sclerotomy wound.

CASE 3. E. S., a white female, aged 25, was first seen by Dr. B. Y. Alvis on December 14, 1948. She had no trouble with her eyes until blurring of the right eye was noted three weeks previously.

Vision: right eye, 20/200; left eye, 20/15.

Externally the eyes were normal. Ophthalmoscopic examination revealed: left eye, normal; right eye, retinal detachment from 2 to 9:30 o'clock inferiorly extending to edge of disc. The nasal side looked a little dark. After several days' bed rest, the retina of the right eye flattened, leaving two elevations, a smooth solid detachment nasally, and a bullous translucent one temporally. No tear was noted.

On December 21, 1948, sclerotomy was done in the area of the trans-
FIGURE 7. CASE 3, APPEARANCE OF BIOPSY TISSUE

FIGURE 8. CASE 3, APPEARANCE OF TUMOR IN GLOBE
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lucent detachment with recovery of blood fluid. Through a sclerotomy over the nasal detachment, solid tissue was recovered with a sharp curette.

The solid biopsy material was sectioned and stained. Typical malignant melanoma of the epithelioid type was found.

On December 24, 1948, enucleation was done. The specimen showed a large choroidal malignant melanoma, extending from the equator to the disc about 12 x 6 x 8 mm. in size. It was extremely vascular. The tumor was also made up of epithelioid cells.

In 1950 the patient developed carcinoma of the breast, which recurred after surgical removal of the breast. The patient died in 1951 of carcinoma, which might have been metastatic either from the choroidal or from the breast lesion.

CASE 4. C. S., white male, aged 36, first admitted to the Washington University Clinics on September 10, 1951. At the age of twelve he had been struck in the right eye with a glass fragment. The eye was enucleated two days later. About six weeks prior to admission, the patient noted unusual lights and colors in the left eye. These grew progressively worse, and were accompanied by much flashing and wave-like motion. For two weeks there had been increasing blurring of vision.

Vision: right eye, 20/70+.

The external appearance was normal. Ophthalmoscopic examination showed detachment of the lower third, with a sharp line of demarcation running horizontally. No tear was noted.

On September 13, 1951, a scleral diathermy operation for detachment was done, the conjunctiva incised inferiorly, and the inferior rectus resected. Transillumination showed a localized opaque area in the inferior nasal quadrant. Diathermy punctures were placed over the lower half. Sclerotomy, with an attempt to remove tumor tissue, was done by the Resident. The tissue diagnosis was indeterminate.

Postoperatively, a solid mass could be seen in the inferior nasal quadrant. This was localized by the Stine technique.

On September 24, 1951, the area of previous sclerotomy was exposed by me. The mass was again localized by transillumination. Near the previous sclerotomy the sclera was again incised. In this area there was definite resistance to palpation with strabismus hook. A sharp 1 1/2 mm. trephine was passed into this area. No fluid escaped, but a solid core of tissue was obtained.

This biopsy definitely showed malignant melanoma of the mixed type.

Enucleation was done on September 27, 1951. The vision of the
FIGURE 9. CASE 4, TUMOR TISSUE IN BIOPSY

FIGURE 10. CASE 4, TUMOR IN GLOBE
eye had deteriorated to 10/200 because of the increased retinal detachment. The vitreous was hazy, but there was no marked hemorrhage.

The specimen showed a large malignant melanoma of the choroid about 12 x 6 x 8 mm. in size, extending from the pars plana back past the equator. The retina was adherent to the tumor surface, with the remaining retina completely detached. Histologically, the tumor was the mixed type. There was some hemorrhage in the biopsy defect, but none had spread into the cavities of the eye.

CASE 5. G. D., white female, age 31, was referred to me on January 24, 1952, with the diagnosis of cyst of the ciliary body of the left eye. About eighteen to twenty-four months prior, she had first noted "flashing and quivering of vision" in her left eye which was present intermittently. For the past six to eight months she had noted constant progressive loss of vision.

Vision: right eye, 20/20; left eye, 12/200, eccentric.

Externally both eyes were normal. Tension: O.U., 22 mm. Hg. (Schiotz) Residual eccentric field inferiorly.

Ophthalmoscopic examination revealed that the right eye was normal. The left eye had a dilated pupil, a large, brown, smooth,
rounded mass filled all the anterior, inferior, nasal quadrant. The upper edge of this mass impinged on the lens in the pupillary area. The disc could be seen and was of normal color with sharp outline. The superior retina was normal, but all the inferior retina was detached, but only moderately elevated.

Slit lamp examination: With widely dilated pupil, the mass could be seen almost in contact with the posterior lens surface. There was some scattered pigment on the surface of the mass, but the slit-lamp beam penetrated the mass, giving the appearance of a thin-walled cyst. No vessels were noted on the surface.

Transillumination through the dilated pupil showed the mass to be practically transparent. Gonioscopic examination showed the iris angle to be open with no evidence of invasion in area of the mass.

The clinical diagnosis was a cyst of the ciliary body. Because of the detachment of retina, it was thought that the lesion could be a cystic malignant melanoma or an epithelioma of the ciliary body.

On January 31, 1952, a cyclodialysis incision was made over the area of the mass. A 1½ mm. trephine was then passed in the direction of the cyst for about 6-7 mm. When the trephine was removed, it was filled with a plug of solid white tissue about 6 mm. long. No fluid escaped when the plug was removed. Under direct observation through the pupil, a probe was passed into the central area of the mass, which
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FIGURE 13. CASE 5, GROSS APPEARANCE OF TUMOR IN CILIARY BODY

did not collapse. This procedure was carried out, not only to obtain a biopsy, but also to attempt to collapse the mass if it were cystic.

From the biopsy a diagnosis of neurofibroma of the ciliary body was made.

On February 4th, the eye was enucleated. On March 15, 1952, Dr. A. H. Conrad, Jr., a dermatologist, reported that the patient had three tumors of the skin that were clinically typical of neurofibroma.

Examination of the specimen showed a solid tumor replacing the ciliary body about 5 x 5 x 4 mm. in size. This extended inward to impinge on the posterior lens surface. The retina in the lower half was detached by a solid coagulum. Histologically, this tumor was identical with the tissue obtained by biopsy. The tumor mass was solid with no evidence of cyst. The final diagnosis was neurofibroma of the ciliary body.

CASE 6. V. T., white female, aged 10, was referred to me on April 8, 1952, because of a tumor of her left eye. About five months earlier, the child's mother had noted a lump on her left upper lid. On investigation, she found that this was a lump on the the eyeball. This grew progressively larger, but with no discomfort, inflammation, or defect in vision.

FIGURE 14. CASE 6, GROSS APPEARANCE OF BIOPSY SPECIMEN—5 MM. BETWEEN SPOTS

FIGURE 15. CASE 6, MICROSCOPIC APPEARANCE OF BIOPSY
Right eye: Externally and internally normal.

Left eye: The left upper lid looked full. When the globe was rotated downward, an oval mass was seen in the superior sclera at 12 o'clock. This mass measured 10 x 12 mm. in size, extending backward from just outside the limbus. It was well circumscribed and elevated about 5 mm. There was no inflammation or injection. The surface of the mass was slightly dark, but was crossed by many translucent bands of stretched sclera. At 12 o'clock in the angle opposite the edge of the tumor there was a reddish mass about 3 mm. broad, which extended about 2 mm. on the posterior surface of the cornea. Slit-lamp examination showed the mass to be very vascular and slightly translucent, with no pigmentation. The anterior segment was otherwise normal. Fields were full. Tension, right, was 15 mm. Hg. (Schiotz), left 17 mm.

Ophthalmoscopic examination: Media clear; fundi normal. No mass could be seen anteriorly. Mass did not transilluminate. There was no take-up in tumor of either radioactive iodine or phosphorus as shown by Geiger counter.
Gonioscopic examination could not be done, as the mass prevented placing the contact lens.

The diagnosis was tumor of the ciliary body, of undetermined type. The possibilities considered were malignant melanoma, ciliary epithelioma, lymphoma, neurofibroma, hemangioma, or tumor of the superior rectus tendon.

On April 11, 1952, a biopsy was done. The conjunctiva was incised radially along the nasal edge of the mass. The next tissue incised was definitely scleral fibers. As incision was completed, a bright red, plaque-like mass presented in the wound. As this tissue was excised with scissors, much vitreous was lost with marked bleeding. Incision was closed with two scleral sutures.

The biopsy was identical with that of Case 5 and was diagnosed as neurofibroma. No evidence of neurofibromatosis of the skin was found by Dr. A. H. Conrad, Jr.

Enucleation was done on April 15, 1952. A tumor 7 x 5 x 5 mm. in size was found replacing the ciliary body on one side. This extended from the ora serrata into the iris angle and invaded the iris root. It had caused an elevation of the overlying sclera, which is extremely thin. There was hemorrhage in the vitreous, under the retina, and under the choroid. The tumor tissue was very vascular and was histologically a neurofibroma.

**COMMENT**

It is apparent that the ophthalmologist has neglected intraocular biopsy for several reasons: the lack of an accepted technique; belief that the biopsy procedure might be excessively damaging to the eye; fear of dissemination of the tumor from manipulation during the biopsy; and the apparent lack of real value of the procedure in the usual case of intraocular suspected tumor.

Although there is no routine technique for intraocular biopsy, that used in the few previously recorded cases was almost exclusively aspiration. It is surprising that in none of our six cases was this method used. In Case 1 a smear technique was used, but in the other five some variation of the incisional biopsy was performed. Actual incision was done in Cases 2 and 6, curettage in Case 3, and a tissue core was trephined in Cases 4 and 5.

In the first two cases the biopsy was done more or less by accident during an operation for retinal detachment in which abnormal tissue was presented in the sclerotomy wound. Nevertheless,
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these cases are true biopsies, as the tissue removed represented a surgical biopsy. In Case 6 the original operation was also primarily a scleral diathermy for retinal detachment with the tumor mass found by transillumination. In the remaining instances the procedure was a planned biopsy.

After considering the technical problems involved in these six cases, it is apparent that there are two essentials in obtaining a proper biopsy of a posterior uveal lesion. In ciliary body lesions the problem is simpler as these lesions are more accessible.

First, the site of the biopsy must be carefully chosen by accurate localization of the lesion. This was accomplished in all the present cases by using several methods. In all cases a careful ophthalmoscopic examination was done, not only for diagnosis, but also because this examination is essential for localization of the lesion. In certain instances the Stine technique of localization of retinal tears can be used with value. Transillumination is also essential, particularly by the transscleral method, after incision of the conjunctiva. However, it should be remembered that a negative transillumination does not necessarily rule out tumor (Case 5). Often the base of a solid tumor can be palpated through the sclera as an area of resistance to a tip of a strabismus hook. This procedure was valuable in Case 4. This method has been previously described (18).

Second, the technique must be such as to obtain an adequate specimen. Except for the first attempt in Case 4, this was accomplished very satisfactorily in all of our cases. In each case a small but very adequate piece of tissue was obtained except in Case 1. Although aspiration biopsy is apparently a simple, non-traumatizing technique, it does not recover an actual piece of tissue, so that the diagnosis must be made more on the appearance of the individual cells, as the architecture of the tissue is destroyed. This is also true of the smear technique as used in Case 1. Undoubtedly, some variation of the incisional biopsy is probably the most effective method of obtaining a specimen, the exact technique being adapted to the clinical findings in the individual case. The greatest potential hazard in any biopsy is the inadequate specimen that gives rise to a false negative.
If the biopsy is to be accepted clinical procedure, the operative injury following it must be a minimum. Although incisional biopsies were used in all our cases, damage from the biopsy occurred in only one (Case 6). In this case there was extensive, intraocular hemorrhage in the vitreous, under the retina, and in the choroid. This was not so much due to the method of biopsy as the extreme vascularity of the tumor. Although no eye in this series was saved, the eventual loss was due to the type and extent of the pathologic lesion and not to any damage inflicted by the biopsy procedure. Even in Case 2, when the eye was removed following a false positive report, the eye was already surely lost. The prolapse of retina through a sclerotomy wound in detachment operation is an unusual occurrence, but the incarceration of retina itself would probably have led to loss of the eye even if the prolapsed tissue had not been removed for biopsy.

Dissemination of the tumor by metastasis, as well as local extension following rupture of the capsule following the manipulation of biopsy, has long been a subject of discussion. This was the chief objection to biopsy in its early stages of development. However, at present there is a general feeling that, if properly done, biopsy does not particularly increase the chances of metastasis (1,2). Reese (19) has stated that, almost surely in any malignant melanoma of the choroid, tissue cells have gained entry into the circulation, but it is the ability of these cells to undergo independent growth that is the chief factor in metastasis. Even in cases of malignant melanoma that have undergone extrascleral extension before enucleation, orbital recurrence of the tumor is rare. Therefore, it would seem unlikely that the biopsy incision would be a factor in local spread, particularly since the globe is promptly enucleated if the biopsy is positive. However, although possibly a coincidence, it is hard to disregard the fact that two of these patients died of liver metastasis.

From this experience with biopsy of posterior uveal lesions, it must be concluded that the procedure has few, but definite, indications. Biopsy probably should be an essential procedure in most cases with a suspected tumor in the only seeing eye (as in two of our patients). In certain individuals who refuse enucleation on
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clinical examination only, it might be the means of forcing a necessary removal of an eye with tumor, this also being so in Cases 1 and 3. Biopsy is also useful in establishing an accurate diagnosis in tumor-suspect patients who present unusual clinical findings, as surely was the case in all six of these patients. In an occasional case the clinical picture is so obscure that every resource, including biopsy, may be necessary to obtain a true diagnosis. It must be emphasized that biopsy should never be a routine procedure and should only rarely be advised, depending on the clinical findings in the individual case.

From the standpoint of actual clinical value, it probably will never become a common, or possibly even an accepted, procedure. It is difficult to see how this procedure could save a globe. A positive finding, of course, will always lead to an immediate enucleation. In a case with negative biopsy findings, a reasonable doubt as to the accuracy of the biopsy might force an enucleation because of fear of a retained malignant tumor. The value of the procedure is also markedly reduced because most eyes in which biopsy might be considered are so damaged by the original lesion that enucleation is inevitable. In these cases, a biopsy merely subjects the globe to an unnecessary procedure. As will be seen, in contrast to iris lesions, the value of biopsy in posterior lesions is minimized for none of these lesions can be excised.

The ideal case for this procedure would be a lesion that could be destroyed, as the small, circumscribed tumor of the posterior choroid with excellent vision. If proved to be one of the less malignant types of malignant melanoma, eradication by diathermy could possibly be attempted. This method has been described by Weve (20), and the extreme necrosis obtained by diathermy is demonstrated in Case 1.

A simple accurate microchemical test for melanin that could be run on small amounts of subretinal fluid routinely removed at all retinal detachment operations would surely be of much value.

IRIS

The iris has been the only intraocular tissue on which biopsy has been a generally accepted procedure. The indicated treatment
for most localized, discrete iris masses has been removal by iridectomy. This may be a true excisional biopsy, as complete removal of the mass is often accomplished. A great variety of pathologic lesions have been removed by iridectomy. However, no evaluation of such a procedure for these various lesions could be found in the literature.

The present series of iris biopsies consists of 40 specimens: malignant melanoma, 11; inflammatory pseudo-tumor, 3; leiomyoma, 1; epithelial implantation cyst, 8; intraepithelial cyst, 1; and incidental removal, 16.

The last group consists of iris specimens removed by iridectomy during other surgical procedures, such as cataract extraction or glaucoma operation. Often there was a history of preexisting iritis. The histologic examination proved to be of no particular value or interest either clinically or pathologically. Unless there is some specific reason for sending such a specimen to the laboratory, it is probably a waste of time for both surgeon and pathologist.

The most important lesion in this group is the malignant melanoma. Of 17 malignant melanomas of the iris in this laboratory, 8 had removal of the tumor by iridectomy. This compares with Reese’s (21) series of 23 cases with 19 enucleations and 4 local excisions. In our series of 8 excisions, subsequent enucleation was necessary in 4, as from the examination of the iris specimen it was evident that the removal was incomplete. The remaining four cases have remained well. Reese divides these tumors into three types: a localized tumor mass; a localized tumor mass with one or more benign foci; and a diffuse growth with widespread involvement. Although the last type must be enucleated, the first two types are suitable for excision.

Leiomyoma is represented in this series by one case. Heath (22) states that these tumors are always benign and that they arise near the pupillary border from the iris sphincter. For both these reasons they are ideal for local excision.

Cysts are represented in this series by one case of intraepithelial cyst of iris formed by a splitting of the pigment epithelium of the iris and by eight cases of implantation cyst, three of which followed surgery and five of which followed perforating injury. Three of
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these cases had subsequent enucleation because of recurrence. As both types of cysts are benign, attempted local removal is usually indicated.

Of particular interest are the three cases of inflammatory pseudotumor. One case was granulomatous, probably sarcoid, while the other two were non-specific inflammations. These cases probably represent globes that without local excision and subsequent histologic examination would have been enucleated. Irvine and Irvine (23) have recently used aspirated aqueous in the study of anterior uveitis; this is comparable to the use of subretinal fluid mentioned previously.

The technique of removing an iris tumor by iridectomy has recently been well described by Reese (24) and by Heath (22). Both stress a large incision that can be separated so that the tumor does not touch the wound edges while it is being delivered. After delivery, radial incisions on either side are placed well out in the normal iris stroma. The base is then torn free.

After the tumor is excised, it is helpful to the pathologist if the tumor is spread on filter paper or on a cork. This keeps the iris flat until fixed so that the sections can be made radially. In two of our cases this orientation was most important in determining complete removal, as tumor tissue was found in the cut base of the iris.

From both the clinical and pathologic aspects, the only real contraindication for this procedure is the presence of other tumor tissue in addition to the localized discrete lesion. This can be diffuse spread in the iris stroma, extension posteriorly into the ciliary body, or the presence in the angle of separate disseminated tumor nodules.

In general it can be concluded that iris lesions are ideal for excisional biopsy for four reasons. First, they can be accurately examined not only with the slit lamp, so that the nature can be evaluated, but also with the gonioscope to determine the involvement of the iris base and ciliary body. Secondly, they can be easily and completely removed without damage to the surrounding tissues. Thirdly, the site of removal is easily observed for evidence of recurrence. And in the fourth place, tumors of the iris are
relatively benign, many being cysts and pseudo-tumors. Also there is excellent evidence that the malignancy of malignant melanoma of the iris is definitely less than that of this tumor elsewhere in the uvea. Callender, Wilder, and Ash (25) in a series of 32 cases found a mortality of only 9.4 percent. Only three of their cases had local excisions, but these were successful. Reese (26) believes that this low mortality is due not only to the nature of the tumor, as some of them are probably benign melanomas or nevi, but also to earlier detection.

From this series the value of excisional biopsy in the proper management of an iris lesion is evident. A number of eyes were retained which without this procedure would probably have been removed. Conversely, several enucleated eyes with excellent vision have been examined by me which could have been saved by a simple excisional biopsy. Among these are a small malignant melanoma involving only the pupillary border of the iris, an intraepithelial cyst of the ciliary body which was removed as a malignant melanoma and a malignant melanoma of the iris, removal of which had been suggested, but refused, twenty-five years prior.

RETINA

There are no instances of retinal biopsy on record. It is inconceivable that any attempt at biopsy would be made on any retinal lesion other than a large mass. On a very small lesion the problems of localization and damage could be most difficult, the knowledge gained through biopsy probably being not worth the risks. Theoretically, biopsy might be considered for exact diagnosis in a massive lesion resembling retinoblastoma.

There are several reasons why biopsy should not be attempted on such lesions. Retinoblastoma is a rapidly growing malignancy that tends to remain localized inside the globe until the optic nerve is invaded. Any sclerotomy made for biopsy might well be the path of invasive spread into the orbital tissues. Even if the lesion were not a retinoblastoma, I have shown that in such pseudogliomas the globe is hopelessly damaged by the process causing the pseudo-tumor (27).
Intraocular Biopsy

It is generally and correctly accepted that any such eye should be promptly removed. This attitude of not temporizing with such lesions is the reason for the complete lack of retinal biopsy. It must be concluded that biopsy of any suspected retinoblastoma is definitely contraindicated.

LENS

It was early recognized that no worthwhile information was gained from the histologic examination of cataractous lenses removed at operation. Much information has been gained by the chemical examination of such lenses, but this is not biopsy.

In the present series there are two biopsy specimens of lens remnants. Both of these were removed by capsulotomy following an original difficult and complicated cataract extraction. In neither case was any information of value derived from the histologic study. The recent work of Irvine and Irvine (25) suggests that study of surgically removed lens remnants might be useful in the study of lens-induced uveitis.

Biopsy is of particular value in neoplastic disease, which is characteristically absent in the lens. The reasons for this have been discussed by Sachs and Larsen (28).

CONCLUSIONS

As would be expected, the various aspects of intraocular biopsy vary with the tissue involved. The procedure is extremely valuable in the management of iris lesions, of very limited use in the choroid and ciliary body, usually useless in lens material, and definitely contraindicated in retinal lesions.

If the iris lesion is discrete and localized, excisional biopsy is the treatment of choice. This is true in all types of iris lesions, even the malignancies, if complete removal is feasible on clinical evidence and if pathologic examination confirms the accomplishment of this.

Although biopsy of a choroidal or ciliary body lesion is technically more difficult, it usually can be accomplished without undue damage to the eye. The lesion must be accurately localized and a technique employed by which an adequate specimen is ob-
tained. It may be indicated in one-eyed individuals, in patients with a clinically unusual lesion, and in patients in whom histologic confirmation of tumor is essential to obtain permission for enucleation. Its value is limited, as no choroidal or ciliary body tumor can be removed from the eye, even if removal is indicated by the biopsy findings, and as the original lesion is usually so damaging that enucleation is inevitable.

REFERENCES

12. Personal communications.
Intraocular Biopsy


DISCUSSION

Dr. Algeron B. Reese. The feeling among general pathologists interested primarily in cancer work is that the removal of biopsy material from cancer lesions does not alter the course of the disease. There is a great deal of clinical and statistical evidence to confirm this. Only recently a large series of patients with a cancer of the breast in whom biopsy was removed was compared with a large series in whom no biopsy material was taken, and the fate of the patients was comparable in the two groups. Now does this same principle hold in regard to melanomas of the choroid? I think there is no doubt that it does. I think we must assume in practically every case of malignant melanoma of the choroid that cancer cells get into the blood stream. You are familiar with the common picture of the large vascular channels throughout melanomas of the choroid in which the walls of the channels are composed of cancer tissue, and free cancer cells are seen in the lumina. Certainly one must say these cells do get in the blood stream. The factor which determines metastasis is whether or not these cells can remain viable at distant sites.

In most instances of melanoma of the choroid the diagnosis is quite obvious from the ophthalmoscopic examination. There are difficult cases, though, in which we need all the aid we can get, and certainly this is true in one of Dr. Sanders’s cases where there was a hole in the retina similar to that seen in serous detachment of the retina. When these difficult diagnostic problems arise we must call on all the resources we have in order to make a correct diagnosis. In the rare case it is possible that a biopsy would be in order.

In regard to biopsy of suspected melanomas of the iris, I think that an excisional biopsy has a definite place. This is true because in the iris there are several more or less benign, simulating lesions such as leiomyoma, nevus, or intraepithelial cyst. In a good percentage of these cases a cure can be effected by local excision and thus unnecessary enucleation is prevented. Therefore, it is in the iris that excisional biopsy has its greater application.
Dr. John McLean. Dr. Sanders's contribution is particularly interesting because it touches on a phase of surgical pathology which is not widely used in ophthalmology. Although, as Dr. Reese has pointed out, the risk of biopsy of malignant tumors is probably very slight, I still feel that some potential risk exists. If I thought I had a malignant melanoma in my eye I would be very loath to have someone poking around in it with a trephine or an aspiration needle unless I felt sure it was necessary to substantiate the diagnosis.

In confirmation of what Dr. Reese and Dr. Sanders said about subretinal fluid, in the last few years we have been routinely supplying Dr. Papanicoloau, who has been studying the cytology of exfoliated cells of various body fluids, with subretinal fluid, both in cases of intraocular tumor with separated retina, and in cases of separated retina without tumor. We have felt it wiser to enucleate the eyes with tumor first before aspirating fluid. The results of his studies, which I think I can cite briefly without trespassing on his later report, have been very discouraging. Cells resembling tumor cells were found in non-tumor fluid, and sometimes no cells were found where small tumors were present. However, occasionally, as Dr. Sanders has pointed out, it may be necessary to settle a disputed diagnosis, as for example in a recent case which came to our Out-Patient Department, which we felt had an intraocular tumor. The patient, unwilling to accept this opinion, consulted three other New York ophthalmologists, who told him that he did not have a tumor, and was persuaded to have detachment operation. He wandered back to our Clinic subsequently and finally agreed to settle the dispute by aspiration of supposed subretinal fluid. The aspiration needle was introduced; no fluid was obtained, the retina did not settle. Of the slides herewith exhibited the first is a low power view of the stained smear of the few drops that were extruded from the tip of the needle. The next two are two high power fields of the tumor cells extruded from the needle onto the slide, and the last shows a high power section of the tumor of the choroid in the subsequently enucleated eye, showing the similarity of the cells in the eye to those obtained with the needle.

Dr. E. V. L. Brown. In a recent article in the Archives of Ophthalmology, 7 cases were reported on the use of the Geiger counter with \(^{32}\)P. In at least 5 of the 7 cases this was contributory to the diagnosis. In the last week we have had a case of glioma that Dr. Krause and Dr. Vail saw in one eye removed at the age of two. The patient is now 11, and has had a very stormy course for the last 6 months. The Geiger counter reacted on the side of the remaining eye.

Dr. W. L. Benedict. I am sure we all have seen extension of malignancy following puncture of an encapsulated tumor. While opening
the capsule may not make any difference in the rate of growth, it
does permit the extension of tumor cells into tissues which otherwise
would not have been invaded. Another thing we must bear in mind is
that we do not know the rate of growth of a malignant tumor, par-
ticularly melanomas of the eye. Some years ago a boy of six who had
a melanosis of his conjunctiva, of the nares, the buccal cheek, and
the tongue was seen by Dr. E. V. L. Brown. This boy was also seen by
several nationally known surgeons, who for some reason or other,
which I think was good, did not perform a biopsy. When the boy was
twelve, a biopsy was made at the Mayo Clinic and the report from the
pathologist was inflammatory tissue full of blood vessels, probably a
type of hemangioma, and the exophthalmos and fullness of the lid
were due to aneurysm. Consequently the carotids on that side were
ligated. Some ten years later there was an extensive malignant de-
generation of all the tissues in the orbit and exenteration was done.
The wound healed, and the man lived to be 36 or 37 years old, until
finally, through an invasion of the brain, the tumor caught up with
him. It was a melanomasarcoma.
Seven years ago a 50-year-old schoolteacher from Canada was seen
in our office with a bilateral tumor of the choroid. In one eye the
vision was reduced to hand movements, in the other it was 20/20.
We removed the eye with the reduced vision, and the diagnosis of
malignant melanoma was confirmed. The tumor in the other eye
was of the same appearance. But she had 20/20 vision in that eye.
She had no relatives and was entirely dependent on herself for sup-
port. She was able to carry on her work as a teacher as long as she
had vision, but without any vision she could only become a charge
on the state. I have followed the case for five years. There has been
no appreciable change in the size of the tumor. I wish to make the
point that if we had disturbed the tumor by biopsy I think we might
not only have precipitated its rate of growth, but might have invited
its extension in some other direction. We know that many malignant
melanomas grow so slowly it is not necessary to remove immediately
an only eye that is useful.
Another factor to bear in mind is that a person who has a malignant
disease may have two or three different kinds of tumor, not necessarily
of the same organ: a sarcoma in one place, a carcinoma in another,
and a different type in a third location. I recall an individual who had
a melanoma of the conjunctiva for which an exenteration was done,
and a few years later he died of an extensive astrocytoma of the brain
which could have no connection with the melanoma. We have seen
persons with tumors of the eye of a sarcomatous nature who had car-
cinomatous lesions of the breast or elsewhere.
There is difficulty in making a diagnosis by smear, even by tissue,
and in most pathological specimens we get from the eye I would say that the pathologist's opinion is questionable in at least 10 percent and it is wrong in 2 to 5 percent. With that possibility of error I think we should only disturb a tumor, intraocular or intraorbital, with a great deal of caution and have a good reason besides curiosity for cutting in on it.

Dr. Bennett Y. Alvis. Since I was responsible in a way for the first of these cases, I think perhaps it might be well to give the reason for the procedure. The patient in question came to me because of a detachment of the retina. There was no question about the man having a detachment of the retina and to my mind no question that he had an intraocular tumor. However, he was loath to have his eye removed, and refused, so we compromised on the matter. I promised we would examine the eye at the operating table, and if we found incontrovertible evidence of tumor he would consent to have the eye removed. If we found no such evidence we would proceed with the operation for the detachment of the retina. The opening was made through the sclera with some trepidation because of the fact mentioned by Dr. Benedict: that if we opened the capsule we might introduce or permit the cells to grow in the orbit which they might not do if we simply did an enucleation. Therefore the opening was made in the sclera at the point where we felt sure the tumor was; the tumor was found and some of it removed with a sharp curette. The tissue was submitted to Dr. Sanders, who made the diagnosis of a malignant tumor. The eye was enucleated and the patient was satisfied, so I feel in this case that we were justified in our procedure. I have seen many cases since then of tumors of the eye but rarely one in which sufficient doubt existed to justify operating for diagnostic purposes.

Dr. T. E. Sanders. Many of these questions are answered in the full paper. I want to thank Dr. Reese for his defense in stating in his opinion there was a lack of danger of metastases following biopsy. That is always the chief objection of the clinician to the procedure.

As to Dr. McLean's statement that he would not want this done on himself, it is definitely a calculated risk. I think we all must take calculated risks in ophthalmic surgery. If we don't, we may not be doing the best thing for the patient.

I agree that the examination of subretinal fluid for cells is unsatisfactory although the examination of fluid by biopsy methods from other cavities, such as the abdomen and chest, may be successful. I suspect that if we could eventually get accurate chemical tests subretinal fluid biopsy might be worth while. Case 6, the 10-year-old girl, was tested with radioactive iodine and radioactive phosphorus with no pick-up, with the Geiger counter. That was an ideal case, be-
cause the mass was practically in contact with the Geiger counter. This is the result expected in this type of tumor. I think in the future this might be one of our best tests.

As to Dr. Benedict’s objection to biopsy of an encapsulated tumor, an orbital recurrence of a malignant melanoma is very rare, even when the tissue specimen shows a large nodule of malignant melanoma externally on the sclera. There is no good explanation for this. I do not think that in malignant melanoma local extension is a particular danger. I object to the same procedure in retinoblastoma, in which the opposite holds true. As far as this tumor being a relatively benign one, as Dr. Benedict mentioned, I think the statistics of the Registry are quite accurate: they show in 10 years 59 percent of the people are dead, which means at the time of enucleation they had metastases.

In regard to Dr. Benedict’s remark about curiosity, I think we have to be curious to find out facts. My curiosity has been worthwhile, because, although I do not know whether I will ever do another intraocular biopsy, at least I am satisfied that I have learned something about them.