TUMORS OF THE IRIS MUSCLE

BY *Parker Heath,* M.D.*

In a comprehensive general study of iris tumors for the 1950 de Schweinitz lecture, the primary new growths arising from iris muscles offered sufficient interest for a separate report (1). This material, available for microscopic study from the Massachusetts Eye and Ear Infirmary, contained 10 mucle tumors amongst 230 examples of new growth in the iris. To this material has been added for a composite study 9 examples of neuroectodermal muscle tumor supplied by the Armed Forces Museum of Pathology. About one third of these 19 examples have been reported elsewhere as individual case reports.

The intrinsic iris muscles commonly show limited hyperplasias. They are altered in various ways by inflammations, glaucoma, and the process of aging. Furthermore, benign proliferations or cysts may accompany the primary iris muscle tumor. Among these possibilities I have selected to discuss only the new growths arising from the sphincter and dilator structures of the iris.

Published case reports concerning neuroectodermal tumors of the iris usually apply to individual cases. A few of these publications are found in the list of references (2-15).

The tumors arising from the ectodermal iris muscles, sphincter, and dilator myoid are not familial, and usually differ in appearance. A simple classification based upon the tissue of origin is possible when differentiation has progressed far enough. Subdivisions in classification are then a matter of interpretation of atypical forms. Since both sphincter and dilator originate from the anterior of the two neuroectodermal layers, the more primitive or reversionary the tumors the more they resemble each

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other; and the term used for this is embryonal leiomyoma. By terminology I have attempted to indicate differences in morphological and developmental states. The classifications adopted are as follows:

IRIS, NEUROECTODERMAL TUMORS

Sphincter Muscle Type
- Benign:
  - Leiomyoma
- Malignant:
  - A. Malignant leiomyoma
  - B. Leiomyoblastoma

Dilator Myoid
- Benign:
  - A. Benign epithelial proliferations; cysts
  - B. Leiomyoidoma
- Malignant:
  - A. Malignant leiomyoidoma
  - B. Leiomyoidoblastoma

Embryonal leiomyoma, which contains some myoid elements (or a medullary epithelioma with teratoid and retinal elements)

The frequency of this series of sphincter tumors is 2.6 percent and the dilator myoid frequency is 1.73 percent. The relative importance in the over-all possibilities of the iris so far as frequency of these neuroectodermal tumors is concerned is well down the scale.

SPHINCTER TUMORS

The early clinical appearance of the sphincter tumor is usually that of a compact, small gray, sometimes yellowish mass, not ordinarily accompanied by pigment, occurring in the lower half of the iris. Some, however, are masked by an envelope of pigmented stromal tissue. This is more commonly noted in deeply pigmented races in which the anterior boundary layer of the iris is heavily pigmented. Ectropion uveae may occur. The iris thickness is increased. The vascular components are not conspicuous clinically, but are well developed. The tumor originates in the pupillary zone, grows slowly, and may not reach the base of the iris for years. The tumors do not become circumferential and follow the iris ring.

Microscopically the sphincter contributes a well differentiated tumor in which relatively regular-sized spindle cells are arranged in whorls and in interlacing bundles without secondary inflammation. The strands of cytoplasm drawn around the central nuclei are eosinophilic. The short rod-shaped and slightly pointed oval nuclei containing moderately granular and clumped chromatin do not characteristically possess mitotic figures. Nuclei are circular in cross section and possess well-defined boundaries. A palisade arrangement may occur. The muscle cells do not branch and are free from pigment. Fibrous nonbranching myoglial elements are characteristically present, and in parts of some sections may be increased (Fig. 3). Neither the capsule nor extensive reticulum was found. Differentiation is aided by various stains, Mallory's phosphotungstic, analine blue, van Gieson's and others. With the hematoxylin and eosin stain the cell cytoplasm and processes and fibrile take eosin; with Mallory's phosphotungstic acid hematoxylin stains, they are dark violet; with Mallory's connective tissue stain, red; with the van Gieson, yellow; with gold chlorid, black. The tumor is relatively free from reticulum. It is quite proper to refer to the predominantly fibrous type of this tumor as a leiomyofibroma or a leiomyoglioma.

Metastasis does not occur, but neglect of local growth permits extension, followed in turn by pressure atrophy. Other complications are cataract, secondary glaucoma, and recurrent hemorrhages, all very rare.

The rare malignant manifestations are suggested microscopically by richer blood supply, more fusiform round cells in a loose irregular arrangement, the presence of some mitotic figures, and more coarse granular chromatin in hyperchromatic nuclei. Sometimes these tumors show marked pleomorphism and atypical giant cells. Relatively little stromal change is noted in what seems a malignant conversion of this tumor. The potential for teratoid epithelial growth exists in the iris. These embryonal tumors occur in the ciliary body and have been reported to this society by Verhoeff (17) and by Fralick and Wilder (18). None of this form of growth has been reported as primary in the iris, with the possible exception of the case of Hirschberg and Birnbacker (19).

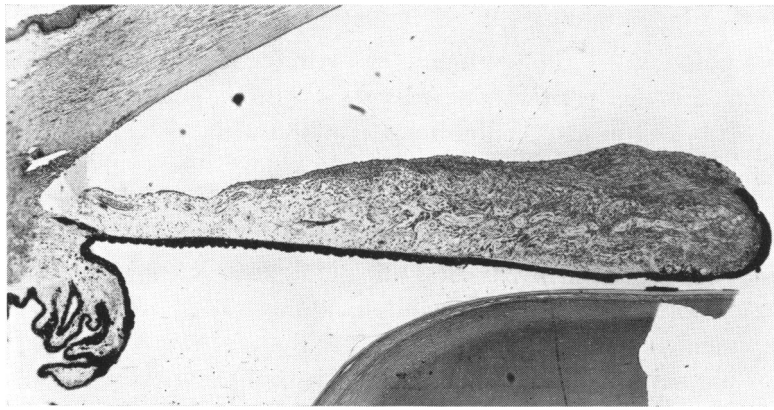

FIGURE 1. TYPICAL LEIOMYOMA OF IRIS, SPHINCTER ORIGIN, OF SLOW GROWTH

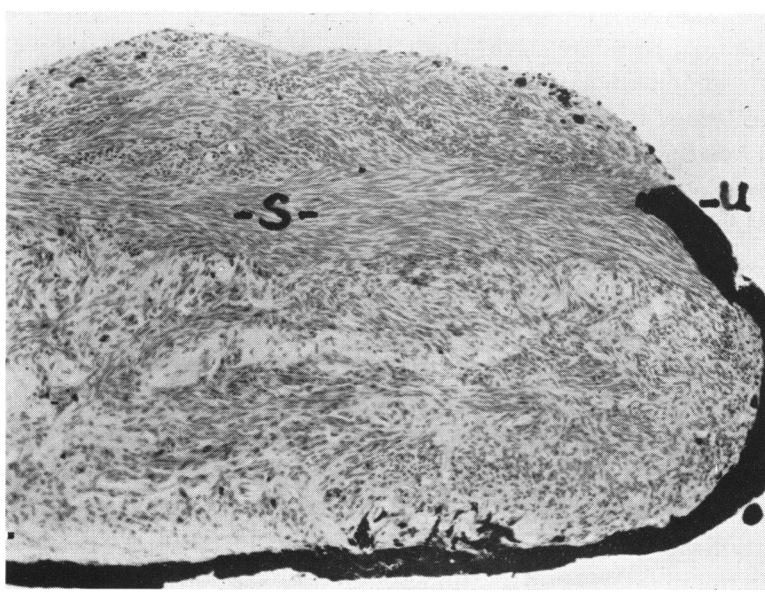

FIGURE 2. HIGHER-POWER DETAIL OF LEIOMYOMA SHOWING PUPIL BORDER Strata arrangement, S. ectropion uveae, U.

While metastasis would seem likely to occur in the atypical-cell forms, this has not been known to occur in this series. Infiltration does occur into the angle and the ciliary body, where the growth is accompanied by cellular inflammation. Examples of some types of leiomyomas are seen in Figures 1, 2, 3.

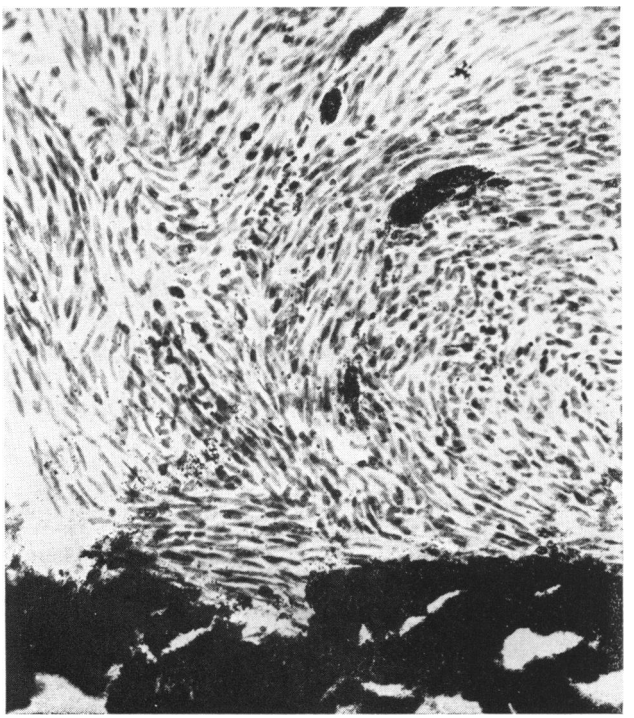

FIGURE 3. ROD-SHAPED CELLS, MANY WITH POLAR SPINDLE PROCESSES

It is exceptional for stromal structures of the iris to proliferate with the sphincter type of tumor. In 1923 Verhoeff (16) reported a leiomyoma of the iris which he considered had a mesoblastic origin. His case showed a small base attached to the iris surface near its root and apparently not connected with the iris muscles. He suggested that it arose from stromal cells of embryonic uvea, ordinarily part of the ciliary muscle. Other possible origins are from smooth muscle of the walls of blood vessels and from the neuromuscle cells of the ciliary anchor of the dilator. Benign prolifera-

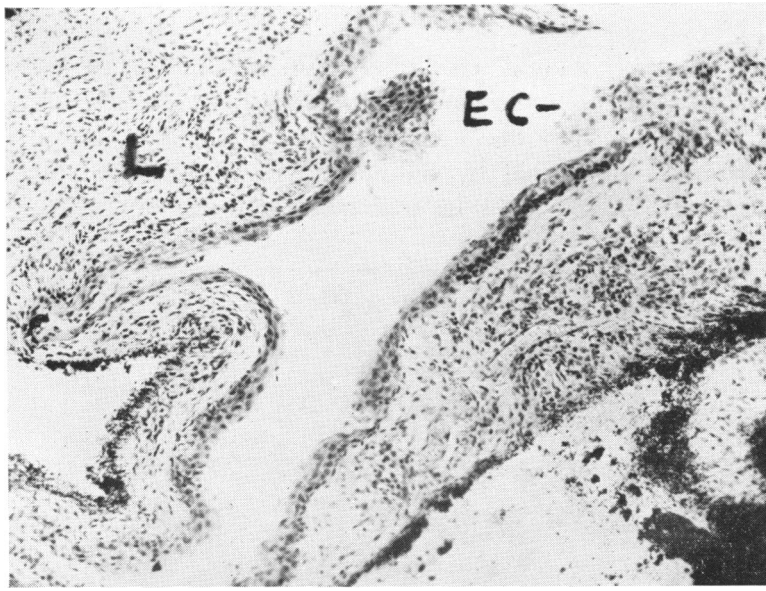

FIGURE 4. PRIMARY EPITHELIAL IRIS CYST (FOLDED) AND LEIOMYOMA
Leiomyoma, L. Epithelial cyst, EC.

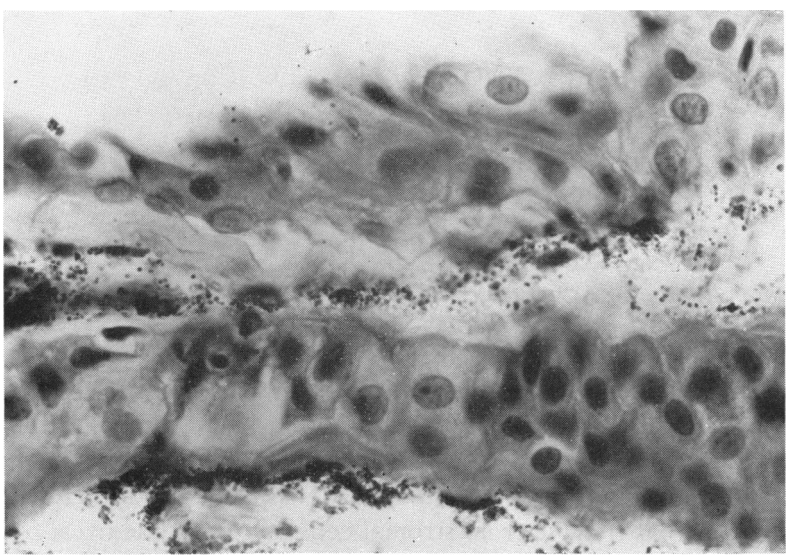

FIGURE 5. HIGHER-POWER DETAIL OF EPITHELIAL CYST WALL

tions here have been described by Klien (20). In my series the tumor cells did not grow individually free in the anterior chamber, as is the case of epithelial new growth and some melanomas. Simultaneous growth of another kind of tumor can occur, however, and is very rare. Such a bizarre cogrowth with a leiomyoma is that of a congenital ectodermal cyst. The simultaneous presence of an exceedingly rare primary ectodermal cyst and a rare sphincter tumor is explainable only on theoretical grounds, which are vulnerable to criticism. It is not known whether pressure, chemical, or vascular influences are related to some embryological injury, for example, and whether other factors are concerned which control collateral growth. Such an ectodermal cyst may represent heterotopic tissue and this could be malignant or otherwise, depending on its nature. The sphincter tumor itself could be classified as a hamartoma; namely, congenital tissue in a normal environment but exaggerated in amount (Figs. 4, 5). One example of a leiomyoma occurred which was associated with, and not much altered by, an incidental iritis from another cause. From microscopic examinations alone it is not always ascertainable whether a neoplastic manifestation of a sphincter tumor had these qualities at the beginning or acquired them later.

No relationship could be established in this series between the neuroectodermal iris myomas and hormonal disturbances or derangements. This is quite unlike the situation in the endometrium where estrogens, for example, are important factors in hyperplasias and show a correlationship with later carcinoma.

DILATOR TUMORS

The embryological origins and development of the posterior pigmented layers and the iris muscles are described and depicted in Bach and Seefelder's atlas (21) and by Mann (22). Clinically, tumors of the dilator, which also origniated from the more anterior of the pair of pigment layers of the iris, appear as pigmented growths away from the pupillary zone. They sometimes exhibit an undifferentiated state and tend towards bizarre forms. The growth is usually in an anterior direction and may be accompanied by proliferation of the posterior pigment layer, and is

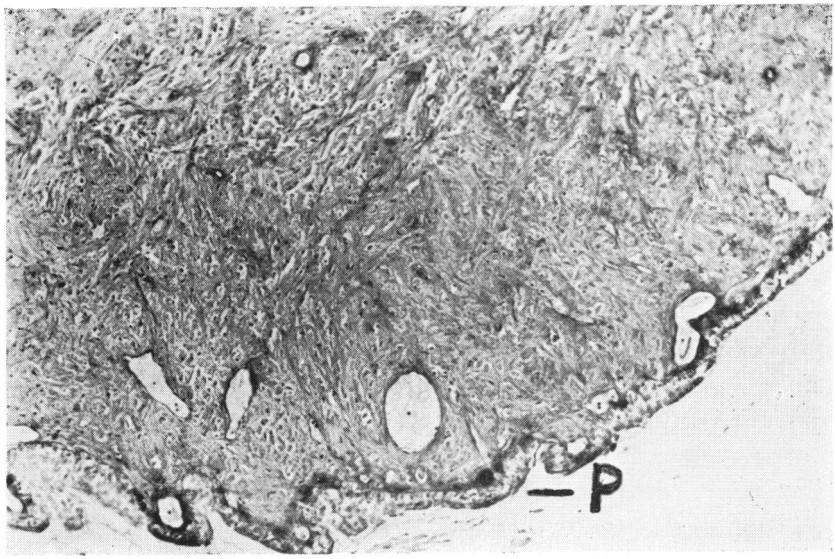

FIGURE 6. LEIOMYOIDOMA, DILATOR ORIGIN, FROM ANTERIOR PIGMENT LAYER OF IRIS; BLEACHED
Posterior pigment layer. P.

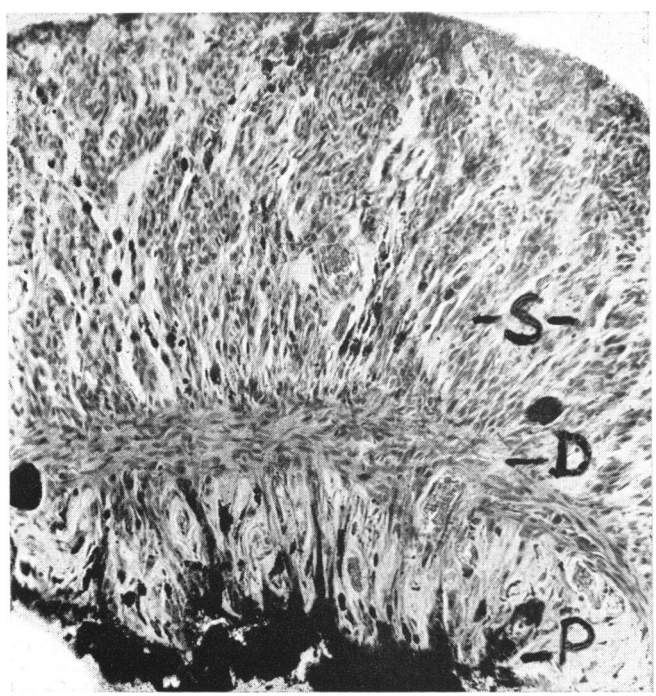

FIGURE 7. IRIS CUT OBLIQUELY SHOWING DILATOR ORIGIN
Dilator, D. Proliferating strands, S. Posterior pigment layer, P.

less circumscribed than the sphincter growth (Figs. 6, 7). Atypicality in size, nuclear structure, fibrous cell processes, and cell arrangements occur. Sometimes the neuroepithelial cells are or tend to be arranged in single rows or coils, and acinoid formations may be found (Fig. 8). The nuclei are large, oval, or round and contain a granular chromatin. Nucleoli are common. A limited fibrous stroma is found in dilator tumors after reticular stains. Benign growths of this structure may properly be spoken of as myoidomas, as leiomyoidomas, or as neuroepitheliomas, while malignant counterparts may be described as leiomyoidblastomas or as malignant neuroepitheliomas (Figs. 9, 10, 11, 12). If undifferentiated and atypical, the new growth may properly be listed as embryonal myoidoma or medullo-epithelioma. Local invasiveness is common and may be described as sarcomatous, if in this case the word is not limited to mesoderm. One manifestation of a dilator tumor exhibits excessive fibrous whorls and fibrils which partly surround and isolate pockets or cuboidal cells (Figs. 13, 14).

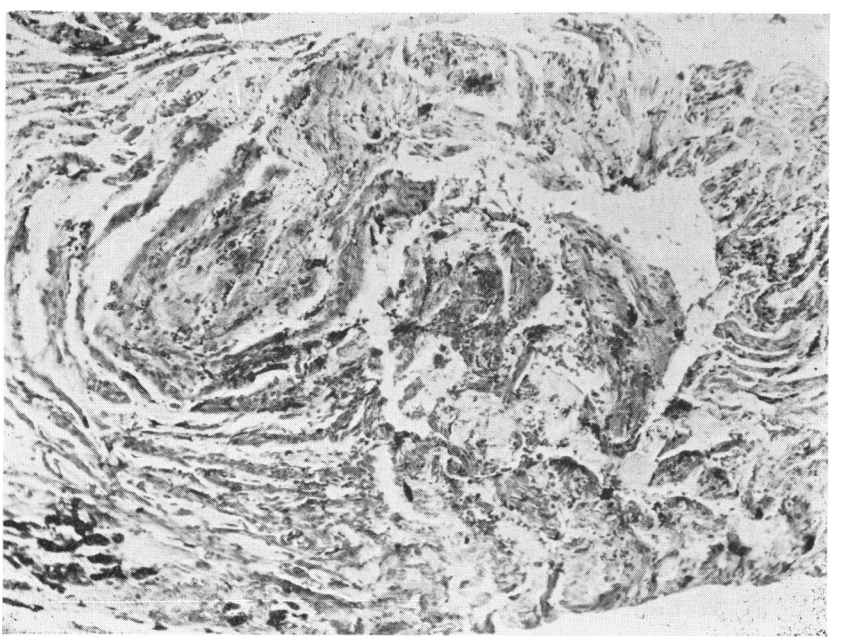

FIGURE 8. PROLIFERATING STRANDS DEEP IN TYPICAL LEIOMYOIDOMA

Differential stains and depigmentation are necessary to show conclusively the presence of myoglial elements. The latter may be and usually are patchy and varicose. This variety of primary tumor may be confused with a metastatic iris growth.

Pigment from these cells of retinal ancestry is irregularly found in the tumor, and may be extensive. In the latter case the growths

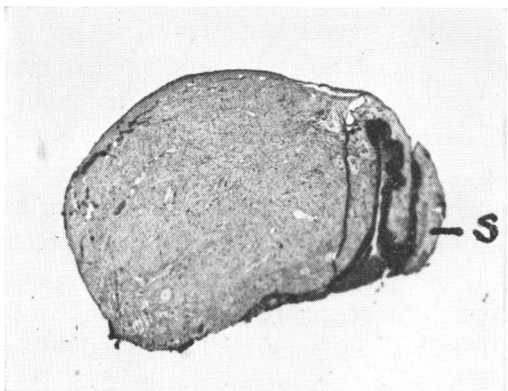

FIGURE 9. LOW MAGNIFICATION OF LEIOMYOIDBLASTOMA IRIS TUMOR AS REMOVED

The sphincter portion of iris coiled and normal, S.

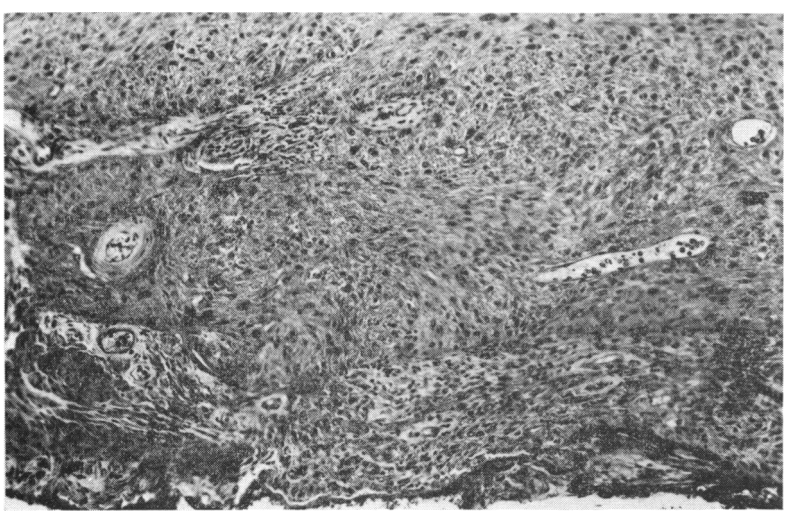

FIGURE 10. HIGHER POWER DEPICTS DILATOR ORIGIN AND HYPERCHROMATIC BIZARRE CELLS

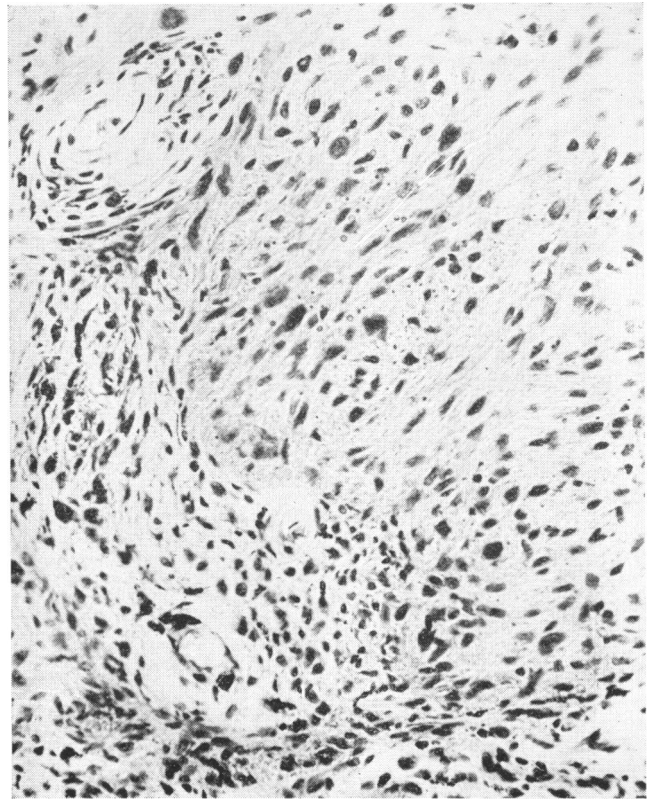

FIGURE 11. LOW-POWER DETAIL OF LEIOMYOIDBLASTOMA SHOWING HYPERCHROMATIC NUCLEI IN MYOID STROMA

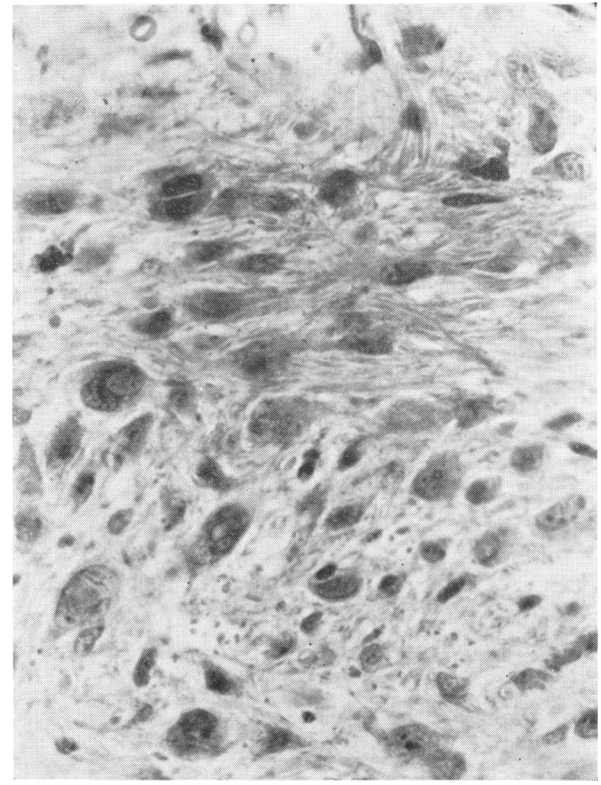

FIGURE 12. HIGH-POWER DETAIL OF ATYPICALITY OF CELLS

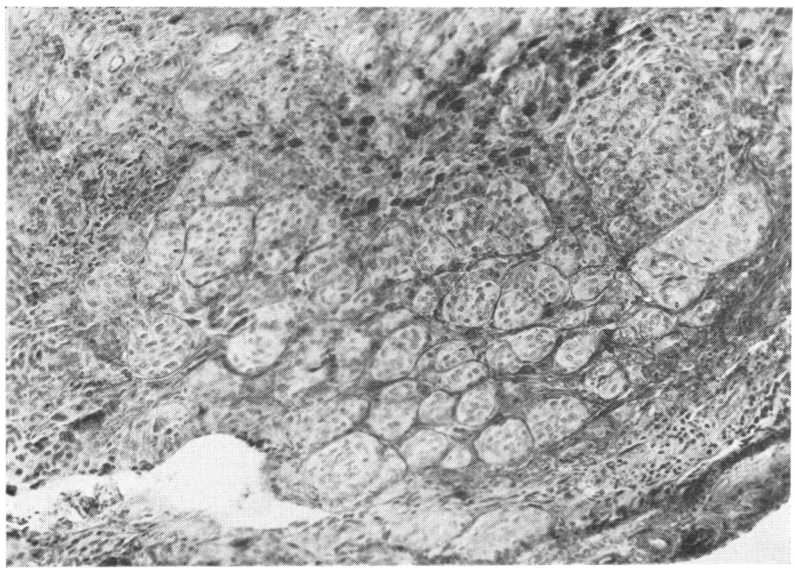

FIGURE 13. ATYPICAL FORM OF MYOIDOMA, NESTS OF CUBOIDAL CELLS OUTLINED BY FIBRILLAE

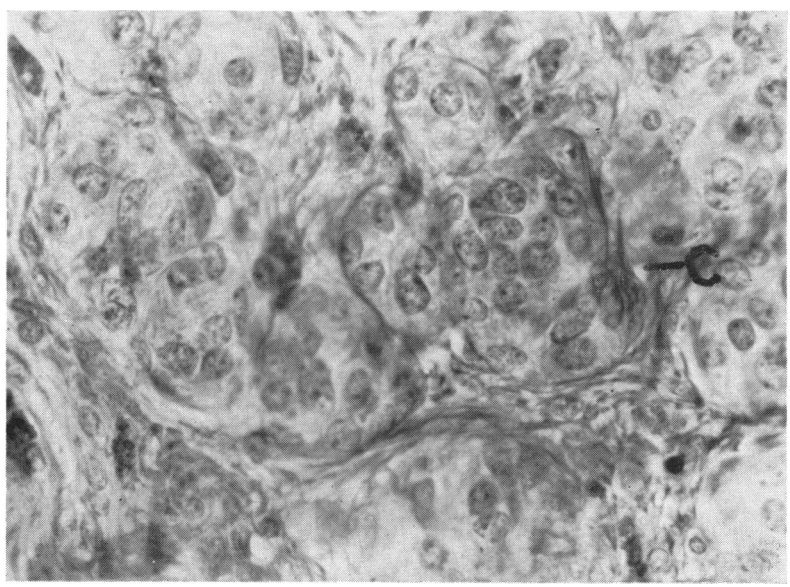

FIGURE 14. HIGHER POWER OF FIG. 9
Cells with processes, C.

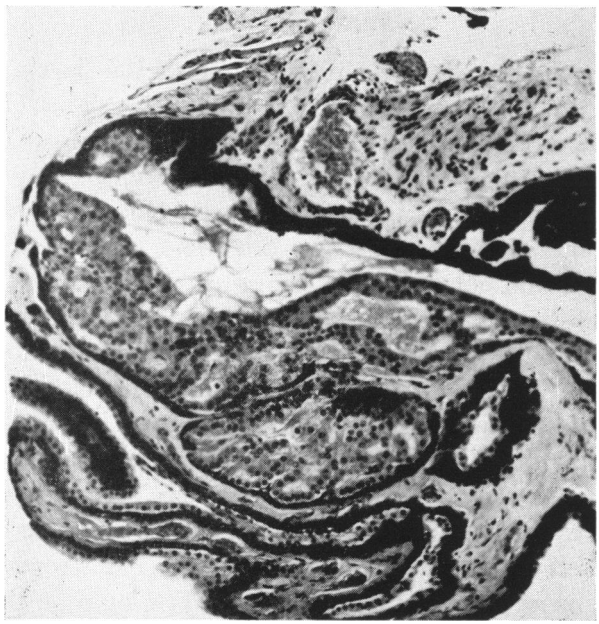

FIGURE 15. BENIGN NEURO-EPITHELIAL GROWTH WITHIN IRIS, RESEMBLING CILIARY PROCESS EPITHELIUM IN WHICH BOTH PIGMENTED AND UNPIGMENTED STRANDS PARTICIPATE

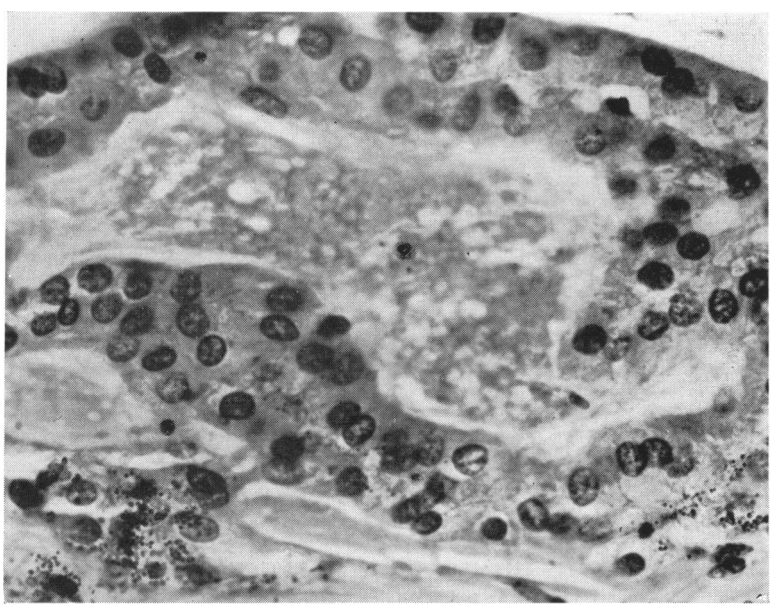

FIGURE 16. HIGHER-POWER DETAIL OF STRANDS

arising from the posterior pigment epithelial layers resemble somewhat malignant melanomas of anterior origin. Careful inspection after depigmentation and differential stain may disclose some myoid elements. Some pigment phagocytosis may be noted. The less they are differentiated, the less evidence is there of myoid elements and pigment, while the cells tend to become columnar with large round polar nuclei without nucleoli. These cells are not found free in the anterior chamber. After technical depigmentation there can sometimes be traced a connection indicating an origin from the anterior pigment layer. The close embryonal relationships of the dual pigment layers of the iris and the masking properties of the similar pigment structure make discrimination otherwise difficult. These myomas may occur in young children and the aged. It is not always clear in the case of a large tumor whether it arose from the anterior iris stroma, or from which pigment layer it took its origin. The more anterior layer would seem to have the potential for medullary differentiation. It is very likely that iris tumors now classified in a group as malignant melanomas include some arising from the dual pigment layer.

A confusing benign tumor in the iris arises from a ciliary-process

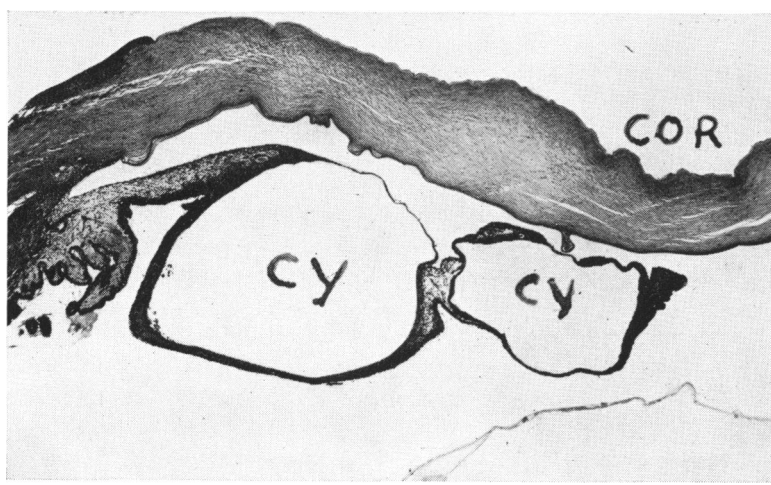

FIGURE 17. IRIS CYSTS FORMED FROM SEPARATION OF THE TWO IRIS PIGMENTED LAYERS AND PROLIFERATION OF THE POSTERIOR
Cornea, COR. Cysts CY.

type of epithelium. The proliferation is usually by cuboidal pigmented and unpigmented cells with large rounded and granular nuclei (Figs. 15, 16). The pigmented part of the strands is less proliferative. The coiled strands of cells may present an adenoid appearance. A connection with a ciliary process may or may not be demonstrable. These tumors when primary in the iris arising from the posterior epithelium are labeled benign epithelioma and have been described by Asbury (2) for the iris, Fuchs (23), Zentmayer (24), Klien (25), and Keyes and Moore (26) for the ciliary body. Not uncommonly cysts are seen in the laboratory arising from separations of the two posterior pigment layers and accompanied by proliferation of the more posterior layer (Fig. 17). In general, dilator tumors grow more rapidly, in some instances very rapidly, than those arising from the sphincter. They tend to appear in younger people and are more plastic or embryonal.

SOME PRACTICAL CONSDERATIONS

In general, tumors originating from the sphincter are more benign than those arising from the dilator myoid, as evidenced by morphology and rate of growth. The sphincter tumors show a slow local extension and consequently are relatively benign. Periods of over twenty years of local growth occur in this series. The more rapid a noncystic growth occurs in the iris the more suspicions should arise of neoplastic change. But apparently these tumors of the iris muscle are additionally sheltered by the same factors tending toward benigness which are found with other iris tumors. Some of these factors I have listed before, namely, growth occurring in a loose open tissue without compression, thick-walled blood vessels, early discovery and treatment (1). An environment with a lower temperature has also been suggested as a contributory factor. The pigmented neuroepithelium of the iris, like that of the retina, rarely becomes invasive.

In general, the myoid tumors are somewhat more rapid in growth. They occasionally are congenital and appear in a wide range of ages. They are more pigmented and variable in cell structure than sphincter growth and, though morphologically atypical enough to suggest malignancy, are compact and contained.

In this they differ from stromal malignant melanomas which frequently have multiple origin and satellite melanomas and which rarely arise before the age of fifteen.

An important principle to be kept in mind in considering the best treament for these solid iris tumors is that local removal, properly performed, is usually successful. The instance of recurrence following surgery, before the growth has reached the angle, is very low. And this circumstance indicates prompt surgical treatment. The best surgical technique calls for a wide section of the cornea so that the tumor will not be dragged against the lips of the wound during its removal and thereby cause recurrences from seeding. The surgeon should be able to work down upon the tumor with the cornea well retracted. The iris should be grasped to one side of the growth, and once fixed in the forceps, should not be released.

STATISTICAL SUMMARIES

Age range: Birth to 66 years; average age 31.
Sex: No significant differences.
Location of tumor: Predominately in the lower half of iris.
Size of tumor: From 1½ mm. to 9 mm.
Color: Leiomyoma, whitish, yellow, or pink; leiomyoidoma, mostly pigmented.
Eye side: Left twice as frequent as right.
Genetic or familial characteristics: None.
Rate of growth: Sphincter type is slow, some over 20 years; dilator type variable, month to years.
Metastasis: None (two eyes lost by growth of tumor).
Frequency: Among 230 primary and secondary new growths in the iris: sphincter origin, 2.6 percent (6 cases); dilator origin, 1.73 percent (4 cases); total, both types, 4.34 percent (10 cases).
Origins and types: Sphincter, leiomyoma, 10 (one with primary epithelial cyst); sphincter, leiomyoblastoma, 1. Dilator, leiomyoidoma, 7 (two with auxillary serous cysts); dilator, benign epithelioma, 1.
Complications: Hemorrhage 2/19; glaucoma 2/19; cataract 1/19.
Operations: Iridectomy ratio to enucleation 9 to 5; local recurrences, 2.

CONCLUSIONS

A report is given of the histopathology found in a group of 19 neuroectodermal tumors of the iris. The frequency of these tumors in a large series of primary and secondary new growths

in the iris is found to be 4.34 percent. A classification by histologic types is given and illustrated. Comment is made on the nature, the differences, and the common properties of growths originating from the neuroectodermal muscles of the iris. Some practical considerations in the management of these tumors are mentioned.

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DISCUSSION

DR. F. PHINIZY CALHOUN, JR. Dr. Heath has analyzed and classified 19 cases of primary tumors arising from the iris muscles. This is the first time such a large and comprehensive study of these tumors has been carried out, and the resultant contribution to our knowledge of their histopathology is great. When it is realized that this type of growth comprises only 4 percent to 5 percent of all iris tumors, and that the literature contains only about 5 proved and 5 unproved cases, then the present study becomes even more valuable.

The generally accepted criteria for the histopathological diagnosis of tumors arising from the iris muscles have been enumerated by Dr. Heath, but there exist many unreported iris tumors which do not completely fulfill these criteria and which cause great diversity of opinion among ocular pathologists. As shown by the present study, many such tumors, some of which have been considered malignant melanomas, can be traced to an origin in the iris muscles. The bizarre cases especially belong probably to the dilator myoid group.

The sphincter muscle is fully differentiated and unpigmented. The dilator muscle consists only in a partial differentiation of the outer aspect of the cells forming the outer layer of neuroectoderm. Fleming (*Brit. J. Ophth.,* 1948) has stated that "Muscular and pigmentary functions co-exist in the dilator muscle cells, and it might be that further degrees of muscular differentiation, corresponding to that seen in the sphincter iridis muscle, would definitely exclude the melanoblast function."

The problem of tumors arising from the iris muscle is by no means purely one of histopathology, however; it has a definite clinical importance. It is still true, as Frost has stated, that it is impossible definitely to differentiate clinically between a leiomyoma and a malignant melanoma of the iris. However, it must be emphasized that tumors from iris muscle usually grow slowly, occur more commonly in the outer lower quadrant of the iris (according to Moulton's analysis of 10 cases), and are usually described as being flesh-colored, salmon-pink, or "lightly pigmented."

Although some cases can be considered malignant histologically, there is no record to my knowledge of any case in which distant metastases or death occurred from such tumors. To some degree this may be due to easy recognition and treatment of iris tumors, but in a large part it is due to the characteristic lack of invasive spread which these tumors show.

It is quite proper, therefore, to entertain a more favorable prognosis

in tumors arising from iris muscle when they are amenable to complete excision. Complete local excision was performed in 6 of the 10 reported cases collected by Moulton, and in Fleming's one case, which incidentally was large and heavily pigmented. There was no recurrence in any of these cases.

We are indebted to Dr. Heath for his detailed study and classification of this group of tumors. It will help to place in their proper category many tumors which heretofore have been of obscure etiology. Especially important is his clinical and pathological differentiation of the sphincter and dilator types.

I would like to ask Dr. Heath if he has seen any case of leiomyoma of the iris which appeared to have a mesoblastic rather than epiblastic origin, as did the original case of Verhoeff.

It has been a pleasure to be able to read and to discuss this fine paper.

DR. JOHN S. MCGAVIC. Dr. Heath has permitted me to read his paper in advance of its presentation and I appreciate this because the subject matter, as you saw, is rather complex.

I had had the erroneous idea that leioyomas were a simple group of benign tumors whose clinical and histologic features could be rather readily listed. Now I find there are several types and that malignant characteristics not uncommonly are present. This shows the value of a detailed study of a large number of cases. Dr. Heath's classification is a new one, and has had to be made up to cover the various bizarre formations of these tumors.

I have been unable to find in the literature of the past 10 years any reference to metastasis or death from leiomyoma of the iris. Twenty percent of women over 40 are said to have uterine fibroids, so that these are quite common. The gastrointestinal tract commonly harbors leiomyomas, and these have had some proven metastatic lesions. They are probably the most malignant of all leiomyomas. They are not ununcommon in the kidney and bladder and are found in the prostate. Although they can arise in the large vessels from the muscle wall, this is rare. Leiomyomas of the skin correspond most closely to those in the iris, arising from the erectores pilorum muscles. They usually remain stationary, but may grow to 1 mm. in size and sometimes regress. The general pathologist regards them as hamartomas.

In general, we find leiomyomas are a well-behaved group of tumors, and it would therefore seem wise to place the term "leiomyo-sarcoma" in the uterus as a potential classification, at least until one proven instance of metastasis has been presented.

A tumor arising from any structure which has functions different from its embryonal matrix, may be expected to behave erratically,

and this is what Dr. Heath has shown. The tumors from the dilator muscle retain some structural connection with the two epithelial layers of the iris, are more variable and more bizarre in structure and pigmentation, and have tendencies which are not found in the sphincter. This is better separated structurally, is a stronger muscle, and has no fraction of nonmuscular tissue in it.

It is interesting to note that the outer layer of the optic vesicle gives rise to the leiomyomas, whereas the majority of tumors coming from the ectoderm arise from the inner layer.

The term "teratoid" was used to denote muscle and epithelial proliferation in Dr. Heath's classification. I am sure he did not mean to imply they are real teratomas, and the emphasis is on the "oid." I believe that if we go back over the tumors of the iris which we have which are now called melanomas, either benign or malignant, and do the detailed study which Dr. Heath has done, we will find a higher incidence of leiomoidomas in cases we have overlooked. I am sure we have all learned a great deal more about leiomyomas than we knew before Dr. Heath's talk, and when you read the paper you will find a great deal more information.

DR. E. V. L. BROWN. I think I may have reported a sphincter tumor, benign, under the title of "So-called Leuco-sarcoma of the Iris" (J.A.M.A., 47: 418, 1906). There were no metastases. It was removed through a corneal section with a good clinical result. I recall that in looking at these structures I could find some pigment in the epithelioid cells, but I questioned whether it was not absorption of pigment from the rest of the iris.

DR. PARKER HEATH. I thank the discussers for their support. They could very well have criticized more freely, I am sure, but they were very kind.

In answer to Dr. Calhoun's question, Verhoeff reported some years ago a tumor of the leiomyoma type which he thought originated from mesoderm because it arose in the anterior portion of the iris, near the base. I reviewed this material and restained it, and I think it originates from the anchor tissue of the dilator at its ciliary part. You may remember a paper by Dr. Klien some years ago in which she described benign proliferations of the ciliary portion of the dilator.

The term "embryonal" is used, in the classification, but the term "teratoid" also may be used in describing the characteristics of these tumors. They have the potential for showing medullary growth. We know one possible example of this in the literature (Hirschberg & Birnbacker). From the abstract it appears to have been a teratoid or embryonal tumor of the iris.