Malignant melanoma and rubeosis iridis

Histopathological and statistical study

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Although rubeosis iridis has been studied since the beginning of the 20th century (Coats, 1906), only comparatively recent publications describe its occurrence in eyes affected by malignant melanoma (Terry and Johns, 1935; Ellett, 1944; Duke-Elder, 1966). Scattered case reports have appeared in the literature (Howsam, 1963; Alexander and Shea, 1964), but little reference was made to rubeosis in several large series (Martin-Jones, 1946; Jensen, 1963). Terry and Johns (1935) observed rubeosis in 14 per cent. of their melanoma cases, and Font, Spaulding, and Zimmerman (1968) noted rubeosis in 11 per cent. of their series of diffuse melanomas. In a pathological study of rubeosis in various conditions, Schulze (1967) found only 5 per cent. of choroidal melanomas affected, but Yanoff (1970) mentioned only one case of rubeosis in his nineteen cases of melanoma with glaucoma.

The present study was undertaken in order to analyse in detail the relationship between melanoma and rubeosis, and to elucidate possible pathogenetic mechanisms.

Methods and materials

Specimens of uveal malignant melanoma were selected in a random manner from the records of the Pathology Department of the Institute of Ophthalmology, University of London. Cases with known systemic disease and tumours treated with radiotherapy were excluded.

Measurements of the cross-section area of each tumour were taken from sections judged to be representative of the central region of the tumour from examination of the embedded specimens. The areas were calculated in square millimetres using Simpson's rule. Grossly necrotic and diffuse tumours could be measured only approximately because of the difficulty in selective representative sections. An approximate assessment of the degree of retinal detachment was obtained by examining several sections for subretinal fluid, excluding any incomplete sections.

Tumours were classified as of ciliary body origin if the bulk of the tumour was located there. The position of choroidal tumours was recorded with respect to their relation to the equator of the globe. Tumours were graded according to the classification of Callender (1931), but fascicular tumours were included in the Spindle B group, since cell type rather than arrangement was of interest. For the purposes of this study, those tumours with necrosis affecting at least 20 per cent. of their cross-section area (assessed from several sections) were defined as necrotic. Tumours occupying at least one quarter of the uveal tract with maximum thickness of 3 to 4 mm. were defined as diffuse (Font and others, 1968).

Parameter incidence was analysed by means of the χ^2 test or, for small groups, an exact estimate was made of the probability that they were comparable (*i.e.* of the same normal population) (Goodman, 1957). Tumour size differences were examined by Student's "t" test, and grouped frequency comparisons by Cochran's test (Armitage, 1971).

Results

RUBEOSIS

Of the 303 cases included in this series, 46 (14.9 per cent.) manifested rubeosis iridis. New vessels were observed to arise almost at random on the iris surface, ranging from a small cluster of vessels to a fully developed fibrovascular membrane. Where serial sections were available, new vessels could be seen to course irregularly over the iris surface. In 26 cases peripheral anterior synechiae (PAS) developed from extension of the fibrovascular membrane into the angle, and a further eight showed ectropion uveae. In one case, the pupil was partially covered by fibrovascular membrane. Rubeosis was always associated with iris atrophy, which was very marked in some cases.

In one interesting case, in which there was a large posterior choroidal tumour, new vessels clustered around the pupil to form an angiomatic mass (Figure) and the iris and choroid were highly atrophic. The ciliary body showed degenerative changes, the retina was totally detached, and the lens was displaced forwards, but there was little evidence of uveitis.

FIGURE *Angiomatic mass on iris in eye with choroidal melanoma.* $\times 100$

POSITION OF TUMOUR, NECROSIS, AND DIFFUSE TUMOURS (Tables I and II)

The incidence of rubeosis was not affected by the origin of the tumour in the choroid or ciliary body, but more choroidal tumours associated with rubeosis ($P < 0.01$) involved the globe anterior to the equator. There were also relatively more necrotic tumours in the group with rubeosis ($P < 0.001$), as defined by the 20 per cent. criterion. Though only

Table I *Incidence and distribution of tumours*

Relative incidence and distribution $\chi^2 = 1.4$; $0.9 > P > 0.05$

Diffuse tumours $\chi^2 = 17.1$; $P < 0.001$

Necrosis $\chi^2 = 30.2$; $P < 0.001$

Site		Choroid	Necrotic choroidal	Diffuse choroidal	Ciliary body	Iris	Total
Type	Rubeotic	37	11	8	9	—	46
of	Non-rubeotic	215	9	8	45	2	262
tumour							
Total (per cent.)		82	—	—	17	1	

Table II *Position of choroidal tumours in relation to the globe*

$$\chi^2 = 7.48; P < 0.01$$

Site		Anterior to equator	Posterior to equator	Total
Type of tumour	Rubeotic	14	23	37
	Non-rubeotic	39	176	215

eleven cases with rubeosis and nine without fulfilled this criterion, necrosis was present in 70 per cent. of all eyes with rubeosis and in about 18 per cent. of the remainder as small foci scattered throughout the tumours. Seven tumours associated with rubeosis were almost completely necrotic, but those in non-rubeotic eyes were never more than half affected.

Relatively more diffuse tumours were associated with rubeosis (8 out of 46, compared with 8 out of 262), but the numbers are small. None of these tumours involved the ciliary body, and PAS were seen only in association with rubeosis.

CELL TYPE (Table III)

Excluding necrotic tumours, there was no significant difference between the frequencies of the different cell types in rubeotic and non-rubeotic eyes.

Table III *Cell type*

$$\chi^2 = 3.05; 0.95 > P > 0.5 \text{ (excluding necrotic)}$$

Cell type		Spindle A	Spindle B	Mixed	Epithelioid	Necrotic	Total
Type of tumour	Rubeotic	4	7	15	9	11	46
	Non-rubeotic	15	82	98	58	9	262

UVEITIS (Table IV)

Since uveitis was more frequently associated with necrotic tumours ($P < 0.001$), eyes with uveitis were divided into necrotic and non-necrotic groups. Though the necrotic group comprised relatively few cases, uveitis occurred more frequently in association with rubeosis than could be accounted for by chance ($P = 0.00465$). When necrosis was absent, uveitis and rubeosis were also seen together more frequently ($P < 0.01$).

Table IV *Incidence of uveitis related to necrosis*

$$\text{Uveitis with necrosis; } \chi^2 = 62.2; P < 0.001$$

Group	Type of tumour	Uveitis	
		Present	Absent
Necrotic	Rubeotic	11	0
	Non-rubeotic	2	7
Non-necrotic	Rubeotic	9	26
	Non-rubeotic	13	240

The manifestations of uveitis comprised a diffuse cellular infiltrate (mostly small lymphocytes) and posterior synechiae; PAS attributable to uveitis was evident in a few cases. In two eyes without rubeosis, PAS were observed in association with necrotic tumours, and in one case a frank hypopyon was present. Of the necrotic tumours with rubeosis, three had developed a severe panophthalmitis, one a marked scleritis, and one a hypopyon, and one was phthisical.

RETINAL DETACHMENT (Tables V and VI)

A greater degree of retinal detachment was seen more frequently in eyes with rubeosis than in eyes without ($P < 0.001$). Even the smallest tumours associated with rubeosis (less than 50 mm.² cross-section area) produced total detachments more frequently than tumours of a similar size in non-rubeotic eyes ($P = 0.000011$). Seven out of eight diffuse tumours with rubeosis caused total detachments compared with only one of the eight cases not associated with rubeosis.

Table V Degree of retinal detachment related to rubeosis

$\chi^2 = 90.0$; $P < 0.001$

Detachment	Nil	< $\frac{1}{3}$	$\frac{1}{3}$	$\frac{1}{2}$	$\frac{2}{3}$ to total
Type of tumour					
Rubeotic	—	—	3	10	33
Non-rubeotic	20	81	65	59	27
Total (per cent.)	6.6	27.0	22.6	23.2	20

Table VI Incidence of total retinal detachments associated with small tumours (50 mm.²)

$P = 0.000011$ (exact method)

Detachment	Total	Sub-total
Type of tumour		
Rubeotic	6	1
Non-rubeotic	7	145

SIZE OF TUMOURS (Tables VII, VIIIA, and VIIIB)

(a) Non-necrotic group

Significantly larger tumours arising from both ciliary body and choroid were observed in association with iris neovascularization ($P < 0.001$). Though a moderate variation in size was present within each group, the difference between means was highly significant. There is thus a correlation between degree of retinal detachment, tumour size, and rubeosis.

Table VII Mean size of non-necrotic tumours (mm².)

Site	Type of tumour	Mean $\pm$ S.D.	t	P
Ciliary body	Rubeotic	115.0 $\pm$ 49.5	} 5.05	< 0.001
	Non-rubeotic	42.5 $\pm$ 36.0		
Choroid	Rubeotic	118.8 $\pm$ 91.5	} 7.00	< 0.001
	Non-rubeotic	38.8 $\pm$ 33.8		

Whether uveitis was present or absent, eyes with rubeosis contained larger tumours than those without. Also, tumours in non-rubeotic eyes with uveitis were larger than in those without uveitis, but no difference in tumour size could be demonstrated in rubeotic eyes with or without uveitis. When tumours were grouped according to size and Cochran's test was performed (Table VIIIB), there was no significant difference in the relative frequency of tumours with uveitis between rubeotic and non-rubeotic eyes (Cochran, 1954). Thus, the increased frequency of uveitis in association with rubeosis is probably due to the predominance of large tumours rather than to a direct relationship between rubeosis and uveitis.

Table VIII A Mean size of non-necrotic choroidal tumours related to uveitis (mm².)

<i>Uveitis</i>	<i>Type of tumour</i>	<i>Mean ± S.D.</i>	<i>t</i>	<i>P</i>
Present	Rubeotic*	146.0 ± 61.0	} 3.18	< 0.01
	Non-rubeotic†	76.0 ± 37.3		
Absent	Rubeotic*	110.0 ± 61.0	} 10.26	< 0.001
	Non-rubeotic†	36.5 ± 30.2		

* All rubeotic tumours with and without uveitis: $t = 1.06$; $0.5 > P > 0.1$

† All non-rubeotic tumours with and without uveitis: $t = 4.60$; $P < 0.001$

Table VIII B Frequency of uveitis related to actual size of non-necrotic choroidal tumours

Standardized normal deviate $\frac{\bar{d}}{S.E.} = 1.64$; $P = 0.101$

<i>Type of tumour</i>		<i>Rubeotic</i>		<i>Non-rubeotic</i>	
<i>Uveitis</i>		<i>Total</i>	<i>Proportion</i>	<i>Total</i>	<i>Proportion</i>
Tumour size range (mm. ²)	1-40	1/5	0.2000	1/135	0.0074
	41-90	2/6	0.3330	7/49	0.1430
	91+	6/13	0.4660	5/14	0.3570

(b) *Necrotic group*

As already noted, assessment of tumour size in many of these specimens proved difficult, so that no exact statistics could be derived for this group. However, six out of the eleven eyes with rubeosis contained tumours large enough to fill the posterior segment, the others being of variable size. On average, non-rubeotic eyes contained smaller tumours and only one filled the posterior segment.

INVASION (Tables IX and X)

There was no significant difference in the invasive behaviour of tumours associated with rubeosis and those without, whether their site of origin was the choroid or the ciliary body.

Table IX Incidence of invasion (eyes with rubeosis in brackets)

Ciliary body $P = 0.5644$ (exact method)

All choroidal $\chi^2 = 0.92$; $0.95 > P > 0.50$

<i>Site</i>		<i>Ciliary body</i>	<i>Choroid</i>	<i>Diffuse choroidal</i>	<i>Necrotic choroidal</i>	<i>Iris</i>
Invasion	None	20(2)	151(13)	2(5)	7(7)	1
	Angle and iris	19(6)				1
	Intrascleral	4(0)	27(2)	2(0)		
	Extrascleral	2(1)	13(3)	4(3)	3(3)	
	Optic nerve		7(0)		1(1)	

Table X *Choroidal invasion by ciliary body tumours*

P = 0.143 (exact method)

<i>Invasion</i>		<i>Present</i>	<i>Absent</i>
Type of tumour	Rubeotic	8	1
	Non-rubeotic	26	19

Though there appeared to be an increased incidence of choroidal involvement in ciliary body tumours with rubeosis, the difference was not significant owing to the small numbers examined. A larger series might reveal a more definite relationship.

OTHER HISTOLOGICAL FEATURES

Haemorrhages were observed in four tumours in eyes with rubeosis, vitreous haemorrhage and also in two other eyes. Two other rubeotic eyes revealed cholesterol crystals enveloped by foreign body giant cells within the tumour mass. Two non-rubeotic eyes showed scanty haemorrhage in the tumours.

Discussion

It is of interest to compare the overall incidence of the parameters examined here with other published findings before analysing them with respect to their relationship to rubeosis. This series includes a higher proportion of ciliary body tumours and fewer iris tumours than the series quoted in Table XI, probably because of the method of selection. This difference does not affect the following discussion, which is concerned with the relationship of rubeosis to choroidal and ciliary body tumours. Neovascularization associated with iris tumours is well recognized, being usually found in the proximity of the tumours themselves (Rones and Zimmerman, 1958; Duke and Dunn, 1958; Kurtz and Zimmerman, 1963; Hogan, 1964), but involvement of the whole iris surface is uncommon (Ashton, 1972: personal communication). Pseudoangiomatous changes within iris melanomas have also been reported (Baghdassarian and Spencer, 1969; Hamburg, 1969). Unlike these cases, the angiomatous malformation reported in this paper was not associated with melanoma cells, but was a localized vascular proliferation in a rubeotic iris.

Table XI *Reported sites of melanomas (per cent.)*

<i>Author</i>	<i>Year</i>	<i>Site</i>		
		<i>Choroid</i>	<i>Ciliary body</i>	<i>Iris</i>
Martin-Jones	1946	92	6	2
Reese	1951	83	9	8
Ashton	1958	84	10	6
Jensen	1963	78	16	6
Cappin	1973	82	17	1

In this series, there was no difference in the incidence of rubeosis, whether the tumour originated in the choroid or in the ciliary body, but rubeosis was more common in cases with tumours involving the choroid anterior to the equator. Archila (1970) remarked that melanomas (and also retinoblastomas) associated with rubeosis in his series all involved the peripheral retina and choroid.

The relative incidence of tumour cell types is similar to that reported by Wilder and Paul (1956) and Jensen (1963) except for a slightly increased proportion of epithelioid tumours. However, analysis of this series reveals no significant difference in the incidence of cytological types in relation to rubeosis.

There have been variable reports of the incidence of tumour necrosis. Jensen (1963) quoted 20 per cent., Terry and Johns (1935) 68 per cent., and Samuels (1933, 1934) 79 per cent. Tumours classified as necrotic in the present series were only those satisfying the 20 per cent. criterion, and their incidence is not comparable with the above; however, 20 per cent. of the present series showed necrosis if minor areas were included.

Uveitis was evident in only 12 per cent. of this series, whereas Jensen (1963) reported a 20 per cent. incidence and Terry and Johns (1935) reported 76 per cent. The incidence of uveitis appears to be related to that of necrosis, as in the present series; differences between series may be related to tumour size.

The degree of retinal detachment can be measured only approximately, but if the parameters of this series are compared with the four grades of Jensen (1963) and Terry and Johns (1935), the overall distributions are not dissimilar, except for a slightly higher proportion of smaller detachments in this series (Table XII).

Table XII *Reported degrees of retinal detachment*

Authors	Year	Retinal detachment					Total
		Nil	+	++	+++	++++	
Terry and Johns	1935	0	7	20	33	25	85
Jensen	1963	7	16	23	28	26	100
Cappin	1973	7	27	23	23	20	100

Diffuse melanomas accounted for 5 per cent. of the eyes in this series, a similar incidence to that found by Font and others (1968) and Reese and Howard (1967), but a higher proportion had rubeosis than in Font's large series which included only 11 per cent. with rubeosis. In view of this discrepancy, a fair assessment of the relationship between flat melanomas and rubeosis is not possible on the present findings.

The reported incidence of extrascleral tumour spread is also variable. Jensen (1963) quoted 17 per cent. and Reese and Howard (1967) 13 per cent., compared with 10 per cent. in this series. No correlation between rubeosis and extrascleral spread was observed but, although there was a suggestion that invasion of the choroid by ciliary body tumours was more frequent in rubeotic eyes, the difference was not statistically significant (because of the small numbers). Together with the significantly frequent anterior uveal involvement by choroidal tumours when associated with rubeosis, there is evidence that intrauveal tumour spread into the junctional area between choroid and ciliary body may relate to iris neo-vascularization.

It is difficult to assess the size of an irregularly shaped tumour such as a uveal melanoma. Flocks, Gerende, and Zimmerman (1955) measured the dimensions in three planes with a micrometer and used the product as an index of tumour size. Others (*e.g.* Jensen, 1963) utilized the product of two-dimensional measurements, a less ideal index. Two-dimensional measurements must be taken in a plane representative of a median cross-section, obtained in this series by examination of the embedded specimens. The application of Simpson's rule produced a more accurate estimate of cross-section area than the product of linear dimensions.

By this means, tumours in eyes with rubeosis were found to be significantly larger than those in non-rubeotic eyes. The presence of large tumours and total retinal detachments together with iris neovascularization was noted by Schulze (1967), Archila (1970), and Yanoff (1970) in the few cases they examined, but no quantitative studies were attempted. My findings also corroborate the suggestion of a relationship between rubeosis and extensive retinal detachment, corresponding to increased tumour size, although six eyes with small tumours were found to have total retinal detachments and rubeosis.

Rubeotic eyes contained a significantly high proportion of necrotic tumours, and though it was difficult to assess the size of many of these tumours, a higher proportion of those associated with rubeosis compared with those in non-rubeotic eyes completely filled the posterior segment. Necrosis was significantly associated with uveitis, and uveitis with larger tumours. Uveitis occurred more frequently in rubeotic eyes, in the presence or absence of tumour necrosis, but this appears to be due to the relatively greater incidence of larger tumours in the group. Thus, on these findings, there is no evidence that uveitis is an independent stimulus to neovascularization of the iris though it may well be a contributory factor.

It is interesting to compare these observations on melanomas with those in a small study of retinoblastoma and rubeosis iridis (Walton and Grant, 1968). These authors reported an association between rubeosis, invasion of the optic nerve, choroidal penetration, and spread into the anterior segment. Greater age of patient and longer interval before enucleation correlated with iris neovascularization. Lack of accurate records made it impossible to ascertain these facts for the present series, but the finding of an associated increased size of melanomas suggests, as for retinoblastomas, that rubeosis is more likely to occur in eyes with long-standing tumours. The differences between melanoma and retinoblastoma are probably an expression of their respective invasive potential.

Numerous theories have been proposed to explain the pathogenesis of iris neovascularization:

- (1) Toxic products from intraocular haemorrhage (Inouye, 1910; Jones, 1958) are an unlikely cause, as haemorrhage is uncommon in melanoma.
- (2) Vasoformative substances may be produced by the tumour itself, possibly in quantities related to its size, and especially by necrotic tumours, but for this there is as yet no direct evidence.
- (3) Retinal anoxia may produce vasoformative metabolites (Smith, 1954, 1955, 1961). The retinal detachment associated with melanoma may result in retinal anoxia, long-standing detachments being frequently associated with rubeosis. It was not possible to demonstrate direct interruption of the central retinal vessels by tumour in the eyes examined in this series.

Ashton (1961) proposed three essential preconditions for neovascularization:

- (i) The presence of living tissue, in this case the iris;
- (ii) Low tissue oxygen tension;
- (iii) Poor venous drainage, whereby active vasoformative metabolites accumulate.

Anterior segment ischaemia produces rubeosis, readily demonstrated by the experimental occlusion of the anterior or long ciliary arteries (Pasino, 1958; Schulze, 1967; Anderson and Morin, 1971; Anderson, Morin, and Hunter, 1971). The presence of iris atrophy, evidence of iris ischaemia or anoxia, was universal in rubeosis iridis with melanoma. There are several possible mechanisms whereby melanomas may induce iris anoxia:

(i) Direct compression of the long or anterior ciliary arteries; this was seen in only one case. In this context, it is interesting that rubeosis is found more frequently in cases in which tumours involve the anterior choroid.

(ii) Increased intraocular pressure could produce diminished perfusion of the iris vessels. The perfusion pressure of the iris vessels is lower than the diastolic pressure in the ophthalmic artery, ranging from 30 to 60 mm. Hg (Rutkowski and Thompson, 1972). Jensen (1963) and Yanoff (1970) reported a high correlation between large tumours with total retinal detachments and glaucoma, similar to the relationship observed here with rubeosis. Thus a period of raised intraocular pressure might result in iris anoxia proceeding to rubeosis in some cases, especially if there was pre-existing poor ophthalmic artery perfusion.

(iii) A large tumour, with a high metabolic rate, may utilize an excessive proportion of the total oxygen supply to the eye, so inducing iris anoxia. The incidence of necrotic tumours could be regarded as evidence against this theory, but such tumours have outgrown their blood supply and must previously have had high oxygen requirements. A more cogent argument against this mechanism is the occurrence of rubeosis with the occasional small tumour and the slow-growing diffuse melanomas.

Poor venous drainage in eyes with melanomas can result from direct compression of the venous outflow channels, and is frequently observed clinically as the cause of congested scleral or episcleral vessels. Ashton's three preconditions can thus be satisfied.

No single mechanism suffices to explain the pathogenesis of rubeosis iridis in the presence of uveal melanoma. It is probable that several factors acting in combination are responsible, and that the longer they act the more probable it is that rubeosis will develop.

Summary

308 cases of malignant melanoma of the uvea included 46 with rubeosis iridis. The occurrence of rubeosis correlated with increased tumour size, involvement of the anterior choroid, tumour necrosis, extensive retinal detachment, and an increased incidence of uveitis. No relationship was found between rubeosis and extraocular tumour spread, cell type, or site of tumour origin.

The incidence of the overall findings is compared with that of other series and the pathogenesis of rubeosis is discussed.

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References

- ANDERSON, D. M., and MORIN, J. D. (1971) *Canad. J. Ophthalmol.*, **6**, 196
- , ———, and HUNTER, W. S. (1971) *Ibid.*, **6**, 183
- ALEXANDER, R. L., and SHEA, M. (1964) *Arch. Ophthalmol. (Chicago)*, **72**, 498
- ARCHILA, E. A. (1970) *Rev. Soc. colomb. Oftal.*, **1**, 45
- ARMITAGE, P. (1971) "Statistical Methods in Medical Research", p. 371. Blackwell, Oxford
- ASHTON, N. (1958) "Malignant Tumours of the Eye and Adnexa" in "Cancer", ed. R. W. Raven, vol. 2, p. 599. Butterworth, London
- (1961) *Trans. ophthalm. Soc. U.K.*, **81**, 145
- (1972) Personal communication
- BAGHDASSARIAN, S. A., and SPENCER, W. H. (1969) *Arch. Ophthalmol. (Chicago)*, **82**, 69
- CALLENDER, G. R. (1931) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **36**, 131
- COATS, G. (1906) *Roy. Lond. ophthalm. Hosp. Rep.*, **16**, 516

- COCHRAN, W. G. (1954) *Biometrics*, **10**, 417
- DUKE, J. R., and DUNN, S. N. (1958) *A.M.A. Arch. Ophthalm.*, **59**, 204
- DUKE-ELDER, S. (1966) "System of Ophthalmology", vol. 9, p. 891. Kimpton, London
- ELLETT, E. C. (1944) *Amer. J. Ophthalm.*, **27**, 726
- FLOCKS, M., GERENDE, J. H., and ZIMMERMAN, L. E. (1955) *Trans. Amer. Acad. Ophthalm. Otolaryng.*, **59**, 740
- FONT, R. L., SPAULDING, A. G., and ZIMMERMAN, L. E. (1968) *Ibid.*, **72**, 877
- GOODMAN, R. (1957) "Teach Yourself Statistics", p. 224. English University Press, London
- HAMBURG, A. (1969) *Arch. Ophthalm. (Chicago)*, **82**, 72
- HOGAN, M. J. (1964) In "Boniuk's Ocular and Adnexal Tumours", p. 222. Mosby, St. Louis
- HOWSAM, G. (1963) *Orient. Arch. Ophthalm.*, **1**, 301
- INOUE, T. (1910) *Roy. Lond. ophthalm. Hosp. Rep.*, **18**, 24
- JENSEN, O. A. (1963) *Acta ophthalm. (Kbh.)*, Suppl. 75
- JONES, R. F. (1958) *Brit. J. Ophthalm.*, **42**, 636
- KURZ, G. H., and ZIMMERMAN, L. E. (1963) *Arch. Ophthalm. (Chicago)*, **69**, 581
- MARTIN-JONES, J. D. (1946) *Brit. J. Ophthalm.*, Suppl. XI, "Uveal Sarcomata". Pulman, London
- PASINO, L. (1958) *Studi sassaresi*, **36**, 104
- REESE, A. B. (1951) "Tumours of the Eye". Hoeber, New York
- and HOWARD, G. M. (1967) *Amer. J. Ophthalm.*, **64**, 1021
- RONES, B., and ZIMMERMAN, L. E. (1958) *A.M.A. Arch. Ophthalm.*, **60**, 193
- RUTKOWSKI, P. C., and THOMPSON, H. S. (1972) *Arch. Ophthalm. (Chicago)*, **87**, 25
- SAMUELS, B. (1933) *Trans. ophthalm. Soc. U.K.*, **53**, 520
- (1934) *Arch. Ophthalm. (Chicago)*, **11**, 998
- SCHULZE, R. R. (1967) *Amer. J. Ophthalm.*, **63**, 487
- SMITH, R. J. H. (1954) "Acta XVII Int. Congr. Ophthalm., Montreal—New York", p. 1164
- (1955) *Trans. ophthalm. Soc. U.K.*, **75**, 265
- (1961) *Ibid.*, **81**, 121
- TERRY, T. L., and JOHNS, J. P. (1935) *Amer. J. Ophthalm.*, **18**, 903
- WALTON, D. S., and GRANT, W. M. (1968) *Ibid.*, **65**, 598
- WILDER, H. C., and PAUL, E. V. (1951) *Milit. Surg.*, **109**, 370
- YANOFF, M. (1970) *Amer. J. Ophthalm.*, **70**, 898