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PROGNOSIS IN UVEAL MELANOMA*†

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THE material recorded in this study represents the total number of cases of uveal melanoma seen at the Royal London Ophthalmic Hospital and at the Royal Eye Hospital, London, during 1925 to 1939, except for a few specimens that could not be traced. In some cases the ultimate outcome was known, but in most the end result had to be ascertained from the records of the Registrar General. This study, therefore, largely hinges on the reliability of such records. It is generally assumed that they are of a high degree of accuracy—an assumption borne out by the fact that a test group of 20 cases, equally divided between those known to

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have died and those known to have survived, checked up accurately against the findings of the Registrar General. In all cases (a total of 285) the type of cell and in all but two cases the amount of pigment contained could be assessed. The investigation of reticulin was restricted to 150 cases. The classification used is largely that employed by Callender and his associates, in which spindle cell A. is Grade 1, spindle cell B. Grade 2, mixed cells Grade 3, and epithelioid cell is Grade 4. A few cases showed spindle cell B. in a fascicular arrangement, and in a few others the cells were necrotic and did not allow of a clear differentiation. Pigment content was assessed as light, medium, or heavy, and reticulin graded as: trace, light, medium, and heavy. Figures 1 to 10 are illustrative.

1. STATISTICAL ANALYSIS

A Series of 250 Cases of Melanoma of the Choroid

A detailed analysis is given in the Tables in the Appendix. The following are the salient points:—

1. *Age distribution* (248 cases).—There were no cases in the age group 0—9; there were only 3 cases in the age group 10—19. The subsequent decades gave an increasing number, but 53 per cent. of the total of cases were concentrated in the two decades 50—69. The mean age at excision of the eye was 53.71 ± 0.90 . There was some slight difference in the age incidence as between men and women, but this was not statistically significant, as can be seen from Table I in the Appendix.

2. *Sex distribution* (250 cases).—No accurate assessment was possible as the relative male and female populations from which the cases were drawn was not known. Indirect computations (as seen in Table II of the Appendix) indicate that there is nothing to suggest that the incidence of melanoma is higher in one sex than in the other.

3. *Histological Components*.—As can be seen from Table III spindle cell B. was the commonest cell type with 59.6 per cent. of the total of cases. Tumours with mixed cells account for 17.6 per cent., and epithelioid cells for 8.8 per cent. Heavy pigment was uncommon accounting for 13.7 per cent., whilst light and medium pigment were fairly equally represented with 41.5 per cent. and 44.8 per cent. each. Heavy reticulin was likewise uncommon (8.3 per cent.); the other extreme—a trace of reticulin—was more common (19.5 per cent.) but light and medium distribution were the most frequent (39.1 per cent. and 33.1 per cent. respectively).

There was little evidence of any definite correlation between

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the different histological components, apart from a tendency for tumours with epithelioid cells to be heavily pigmented.

4. *Mortality generally* (250 cases).—The chance of escaping death from metastases in the first five years was 0.822 for males and 0.795 for females, with 0.807 for both sexes combined. The odds declined somewhat if taken for a period of the first ten years, being 0.733, 0.734, 0.734 for males, females and both sexes together respectively (Table IV). The highest mortality occurred in the second year (see graph). Statistically there was no significant sex difference in mortality.

Central death ratio (m). (Ratio of deaths from cancer to mean lives exposed during the year). The discontinuous line indicates the underlying trend. In view of the restricted data no attempt was made to fit a curve of a specific mathematical law but an approximation thereto was obtained by drawing a curve through the observed values by graphic graduation.

5. *Effect of age on prognosis* (248 cases).—When three broad age groups were taken—under 40, 40–59, and 60 and over—a statistically significant increase in mortality from metastases with advancing age was observed for the first five years. The odds against the fatal recurrence of cancer shortened from 9:1 to 7:1 between the youngest and oldest age groups (Table V).

6. *Mortality according to type of cell* (250 cases).—No statistical significance could be attributed to the variation in mortality with the different types of cell except for epithelioid cells, the mortality from which was distinctly higher (Table V).

7. *Mortality according to pigment* (248 cases).—A statistically significant lower mortality was found to be associated with a low pigment content (Table VII).

8. *Mortality according to reticulin* (133 cases).—There was a significant correlation between high mortality and low reticulin content (Table VIII).

9. *Mortality by cell and pigment* (248 cases).—Within each pigment group there was little variation with different types of cell apart from epithelioid cells. Within each cell grade low mortality was associated with light pigment content (Table IX).

10. *Cell, pigment and reticulin combinations* (133 cases).—It appears likely that each of the factors has an independent effect on prognosis, but that cell grade is less important than pigment or reticulin. The determination of the partial association of mortality with each of the three factors cannot be reliably made on the data of the present series (Table X).

A Series of 30 cases of Melanoma of the Ciliary Body

In this small series there was no significant difference in age or incidence between the two sexes. The average age of the whole series was 56.3 ± 3.1 . The chance of escaping death from metastases was rather lower than for melanoma of the choroid. The material was not sufficiently extensive to lend itself to detailed analysis.

Five cases of melanoma of the iris

The group consisted of three men and two women. There was one death from metastases in this group. Table XII shows the salient features observed in this small series.

2. COMPARATIVE STUDIES ON CHOROIDAL MELANOMA

The considerable literature on prognosis in uveal melanoma is unfortunately largely vitiated owing to the general lack of statistical assessment of the results obtained. Comparative studies of results obtained by different observers also present difficulties owing to the lack of uniformity in criteria used; the older literature is largely inapplicable, particularly since recent studies have shown the significance of reticulin in the assessment of prognosis. Only partial comparison with the variously recorded results is, therefore, possible.

1.—*Age distribution.* The following summary table shows the age distribution in our own series compared with those published by Callender, Wilder and Ash (1942) and Pahwa (1941). The first represents an extensive study covering 1,418 cases observed in the United States. The second deals with 100 cases seen at the Royal London Ophthalmic Hospital between 1930 and 1935—a group covered by our own series.

These three series give essentially the same data: melanoma of the choroid is concentrated in the age groups 40—70.

	Callender, Wilder & Ash. 1,418 cases. per cent.	Pahwa 100 cases. per cent.	Present series. 250 cases. per cent.
0-9	0'14	—	—
10-19	0'92	—	1'21
20-29	5'01	6'3	4'44
30-39	13'33	11'6	12'50
40-49	20'87	22'1	18'55
50-59	26'44	25'3	25'40
60-69	23'13	23'1	27'82
70-79	9'17	11'6	9'27
80-89	0'92	—	0'81
90 and over	0'07	—	—
	100'00	100'0	100'00
Mean age	52'76	53'7	53'71

2.—*Sex distribution.* In 1,550 cases noted by Callender, Wilder and Ash there were 799 men and 751 women. It would appear that their series is not consecutive, but a random selection. In their findings, as in ours, there is nothing to suggest that there is a significant sex difference.

3.—*Cell type.* The following summary table shows the distribution of cell type in the comparable series:—

	Callender, Wilder & Ash.	Pahwa	Terry & Johns	McKee	Present Series.
Spindle A. ...	35	22	6	14	11
Spindle B. ...	117	7	12	—	149
Mixed ...	276	29	31	2	44
Epithelioid ...	14	25	8	7	22
Fascicular ...	13	9	8	4	18
Necrotic ...	45	—	—	—	6
	500	92	65	27	250

The series given by Callender, Wilder and Ash and also that of Pahwa and of Terry and Johns contained a high proportion of mixed tumours reducing the proportionate incidence of other cell

types. Our series shows a high incidence of spindle B. types. The proportion of epithelioid cell tumours in our series is distinctly higher than in the American series, though lower than in the other small series.

4.—*Pigment*. The following summary table shows the comparative incidence of pigment in a series recorded by Callender, Wilder and Ash, and by ourselves:—

	Callender, Wilder & Ash.	Present Series.
<i>Pigment</i>		
Light	141	103
Medium	235	111
Marked	111	} 34
Heavy	13	
	500	248

It will be noted that there is a greater incidence of marked and heavy pigment in the first series.

5.—*Reticulin content*. The significant studies on reticulin are those that have come from Callender and his associates. The small series of 41 cases published by McGregor and Hill does not lend itself to statistical assessment; their general conclusion that a low reticulin content is disadvantageous is also brought out in the 61 cases recorded by Pahwa. The distribution of reticulin in the series by Callender, Wilder and Ash, and our own, are shown in the following summary table:—

Reticulin content	Callender, Wilder & Ash	Present Series.
Heavy	19	} 11
Marked	90	
Medium	143	44
Light	223	52
Absent	25	26*
	500	133

*Absent or trace.

Our series would appear to contain more cases with low reticulin content.

6.—*Prognosis in general.* As different series of cases appear to contain different proportions of the constituent histological elements it would seem that the assessment of prognosis is difficult unless one is sure that the various series are comparable and unselected. Moreover, the time at which the affected eye was removed may vary in different statistical computations. Our own series gives a distinctly good prognosis, the survival rate for a period of five years being 80·7 per cent., and 73·4 per cent. for ten years. Callender, Wilder and Ash (1942) give a survival rate of 52 per cent. for five years and 34 per cent. for ten years, but their findings are open to the statistical criticism that they have not dealt with the cancer mortality within a definite period. Martin-Jones, likewise, obtained a poorer prognosis than our series shows. His survival rate for a period of five years is 64·2 per cent., and for a period of ten years 44·5 per cent. Recalculating his data on the basis of chance of escaping death from cancer during X years following excision, his percentages are raised nearer to ours, being 67·2 and 53·0 respectively. Pahwa's total mortality from secondary growth (for material overlapping ours, but in which mortality was assessed by direct enquiry) approaches ours still more closely. Closer still is the mortality of about 26·5 recorded by Hippel (1930) in a collected series of 609 cases.

7.—*Prognosis in relation to histological components.* Callender, Wilder and Ash found that prognosis varies directly with cell type, pigment content and reticulin content. For a five-year period there was a mortality of 6 per cent. with spindle cell A., 25 per cent. with spindle cell B., 62 per cent. with mixed tumours and 71 per cent. with tumours composed of epithelioid cells; tumours with spindle cell B. in fascicular arrangement and those with necrotic cells gave a mortality of 38 per cent. and 49 per cent. respectively. The mortality from tumours containing light, medium, marked and heavy pigment was respectively 34, 51, 55 and 69 per cent. Mortality decreased with increase of reticulin content. It was 80 per cent. when reticulin was absent, and 55, 44, 36 and 10 per cent. when the reticulin content was light, medium, marked and heavy respectively. It is unfortunate that their assessment is not made by a statistical analysis which takes account of period of observation. Our own findings are distinctly more limited: a statistically significant increased mortality in relation to epithelioid cells, a lower mortality with light pigment content, a higher mortality with low reticulin content.

8.—*Age in relation to prognosis.* Callender, Wilder and Ash suggest that the worse prognosis is in the higher age group. Martin-Jones also finds a less favourable prognosis at older ages. Our statistical evaluation shows the same trend.

3. DISCUSSION

Judging by the older literature, prognosis in uveal melanoma has improved steadily during the last seventy years. Thus, Hirschberg gives the survival rate as 25 per cent. in 1882, 35 per cent. in 1895, and 56 per cent. in 1903. References to further data of this type are given by v. Hippel (1930) and Teraskeli (1928). Continental studies have been largely concerned with the stage of growth and its bearing on prognosis, stage I representing the phase when the tumour is confined to the uveal tract, stage II when it has penetrated into the ocular tunics, and stage III when it has perforated these. (In another classification stage I is the quiet eye, stage II the secondary glaucomatous process, stage III orbital invasion, stage IV dissemination.) Studies on these lines have led to rather sterile discussions as to the best time for removing the affected eye. The great merit of Callender's work at the American Registry of Ophthalmic Pathology is that in the first place he introduced an adequate classification (and possible grading) of cell type (Callender, 1931), and that secondly he established the significance of reticulin as a prognostic factor in uveal melanoma (Callender and Wilder, 1935). These excellent pathological studies, recorded in three successive papers, covered at first 111 cases (Callender, 1931), subsequently 253 cases (Wilder and Callender, 1939), and more recently 500 cases (Callender, Wilder and Ash, 1942). It is unfortunate that in rightly stressing the need for adequate histological detail, Callender and his associates have tended to overlook the grosser—but necessary—criteria implied in the classification by stages.

Our data do not suggest that there is any correlation between the three histological components, except that tumours with epithelioid cells tend to be heavily pigmented. Since heavy pigmentation is regarded as an unfavourable prognostic feature, the unfavourable effect of epithelioid cells is emphasized.

If choroidal melanomata are therefore to be regarded as consisting of three freely variable components, it is clear that prognosis must be assessed on the basis of each of the components. In addition, the behaviour of the tumour as a whole must also be taken into account. As long as a true measure of prognosis is not available it is impossible to indicate whether exenteration

Figs 1-4 to illustrate cell types

FIG. 1 Spindle cell A
(Magnification $\times 160$)

FIG. 2. Spindle cell B
(Magnification $\times 160$)

FIG. 2a. Spindle cell B, fascicular
arrangement (Magnification $\times 160$)

FIG. 3. Mixed cells
(Magnification $\times 160$)

FIG. 4. Epithelioid cells
(Magnification $\times 80$)

Figs. 5-7 to illustrate pigment content. Figs. 8-10 to illustrate reticulin content

FIG. 5. Light pigment content
(Magnification $\times 80$)

FIG. 6. Medium pigment content
(Magnification $\times 40$)

FIG. 7. Heavy pigment content
(Magnification $\times 40$)

FIG. 8. Light reticulin content
(Magnification $\times 40$)

FIG. 9. Medium reticulin content
(Magnification $\times 40$)

FIG. 10. Heavy reticulin content
(Magnification $\times 40$)

of the orbit rather than excision of the globe, or possibly radiotherapy, is the proper treatment. It would seem essential that in the further collection of pathological material uniform criteria should be employed. These criteria might well be:—

(i) Histological. The classification employed by Callender and his associates is eminently satisfactory for cell type. The grouping of pigment into four quantitative groups is probably an unnecessary refinement; in practice a classification into light, medium and heavy is easier and probably more reliable. Likewise with reticulin: the distinction between marked and heavy seems unnecessary and rather troublesome.

(ii) Gross features in the tumour. Vascularity, haemorrhage and necrosis all need to be noted.

(iii) Extension beyond the uvea. Extension into the ocular tunics, the emissary vessels and into the orbit also need to be recorded.

The classification into stages is now largely a matter of historical interest. Eyes with melanoma of the choroid are generally removed in what constituted stage I, so that as many distinctive components as possible in addition to histological features have to be isolated and studied. It should be redundant—but nevertheless it appears to be necessary—to add that proper statistical evaluation of the collected material is also essential.

Summary

(1) A series of 250 cases of melanoma of the choroid, 30 cases of melanoma of the ciliary body, and 5 cases of melanoma of the iris was studied histologically and correlated with mortality from metastases.

(2) Fifty-three per cent. of all cases of choroidal melanoma were concentrated in the two decades 50—69 years. The mean age at excision of the eye for the whole series was 53.71 ± 0.90 . There was no statistically significant sex difference in age distribution or incidence. Histologically spindle cell B. predominated, accounting for 59.6 per cent. of the total of cases. Spindle cell A. accounted for 4.4 per cent., mixed cells for 17.6 per cent., epithelioid cells for 8.8 per cent., spindle cell B. in fascicular arrangement for 7.2 per cent., and necrotic tumours for 2.4 per cent. Heavy pigment was present in 13.7 per cent., whilst light and medium pigment distribution gave 41.5 and 44.8 per cent. respectively. Reticulin, studied in 133 cases, was present in heavy amounts

in only 8.3 per cent. A trace of reticulin was present in 19.5 per cent., whilst light and medium reticulin distribution was observed in 39.1 per cent. and 33.1 per cent. respectively. Apart from a statistically significant association of heavy pigment with epithelioid cells, there was no evidence of any other correlation between the histological components. The chance of escaping death from metastases in the first five years was 0.807 for the series as a whole, declining to 0.734 for a period of ten years. The highest mortality occurred in the second year after excision. There was a statistically significant better prognosis in the younger age groups. No statistical significance could be attributed to variation in mortality with different types of cells, except that epithelioid cells carried a worse prognosis. A low mortality was found associated with a low pigment content, and a high mortality with low reticulin content. Each of the three histological components appears to have an independent, but not equally forcible, effect on prognosis, so that mortality is influenced to some extent by cell grade, but more by pigment and reticulin content. The main prognostic factors as they emerge from this study are: a favourable effect from light pigment content, and an unfavourable effect from epithelioid cells and from low reticulin content. These general conclusions support the findings of Callender and his associates, though they are not as emphatic as theirs.

(3) A study of the 30 cases of melanoma of the ciliary body suggests that mortality from this type of tumour is rather higher than for melanoma of the choroid.

(4) The importance of studying the stage of development of the tumour in addition to its histological features is stressed.

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APPENDIX—STATISTICAL ANALYSIS

1.—Melanoma of the choroid

1. *Age distribution.*—Table I shows the sex and age distribution of the series at excision, together with the mean ages and standard deviations.

TABLE I—*Sex and age distribution of cases of melanoma of the choroid.*

Age	Males	Females	Total	
			No.	Per cent.*
0 —	—	—	—	—
10 —	2	1	3	1'21
20 —	4	7	11	4'44
30 —	11	20	31	12'50
40 —	18	28	46	18'55
50 —	32	31	63	25'40
60 —	34	35	69	27'82
70 —	13	10	23	9'27
80 —	1	1	2	0'81
Not stated	1	1	2	—
Total	116	134	250	100'00
Mean age	55'26 ± 1'31	52'37 ± 1'22	53'71 ± 0'90	

* Based on 248 stated cases only.

In the actual samples the mean age at excision is less for females than for males, but this difference is not statistically significant and there is no evidence of association between sex and age.

The analysis of the variance of age is as follows:—

	Degrees of freedom	Sum of squares	Mean square
Between sexes	1	515'98	515'98
Residual	246	48,671'12	197'85
	247	49,187'10	

The probability that the difference in variance estimates is attributable to sampling fluctuation exceeds 0.10.

The mean age at excision may therefore be estimated at 53.71 ± 0.90 years.

2. *Sex distribution.*—The relative male and female populations from which the cases were drawn is not known and therefore the sampling error of the numbers for each sex cannot be accurately assessed, but it will be seen from Table II that the ratio of male to female cases in any age group is not inconsistent with that operating in the general population of England and Wales.

TABLE II—Sex incidence.

Age	Male cases	Ratio of females to males in England and Wales census 1931	Expected female cases on basis of census ratios	Actual female cases	Actual — expected	Approx. standard error of expected female cases*
10 —	2	0·995	1·99	1	— 0·99	1·40
20 —	4	1·059	4·23	7	+ 2·77	2·11
30 —	11	1·157	12·72	20	+ 7·28	3·84
40 —	18	1·160	20·87	28	+ 7·13	4·92
50 —	32	1·115	35·69	31	— 4·69	6·31
60 —	34	1·159	39·41	35	— 4·41	6·76
70 —	13	1·360	17·69	10	— 7·69	4·91
80 —	1	1·782	1·78	1	— 0·78	1·78
Not stated	1	—	1·09	1	— 0·09	1·09
Total	116	1·088	127·31	134	+ 6·69	11·72

* On assumption stated in text.

In the above table the variance in the expected female cases due to the application of the census ratios to the unknown portion of the population included in the sample is ignored, and account is taken only of the sampling error of the number of male cases in each group. The standard error in the estimate of the female cases arising from this is shown in the final column and is taken as approximately $r \times \sqrt{M}$ where r =census sex ratio, M =actual male cases. It will be seen that the excess or deficiency in the actual female cases in any age group is in no instance greater than twice this standard error. The systematic character of the differences in the penultimate column of the table (at first positive then negative) reflects the fact that the females are as a group younger than the males in this series, though this difference has been shown not to be statistically significant. It would appear that the incidence of melanoma cannot be regarded as any greater in one sex than the other.

TABLE III—Histological Components.

	Males	Females	Persons	Percentage
Cell type (250 cases)				
Spindle Cell A.	5	6	11	4·4
Spindle Cell B.	71	78	149	59·6
Mixed	17	27	44	17·6
Epithelioid Cell	10	12	22	8·8
Spindle Cell B. fascicular	12	6	18	7·2
Necrotic	1	5	6	2·4
				100·0
Pigment (248 cases)				
Light	49	54	103	41·5*
Medium	52	59	111	44·8*
Heavy	14	20	34	13·7*
				100·0
Reticulin (133 cases)				
Trace	11	15	26	19·5*
Light	26	26	52	39·1*
Medium	23	21	44	33·1*
Heavy	5	6	11	8·3*
				100·0

* Of stated cases.

3. *Histological components.*—The type of cell could be established in all cases, the degree of pigmentation in all but two cases, and reticulin content in 133 cases. The sub-joined table shows the findings obtained.

The possibility of association between the three components was investigated by independence tests of the chi square type. There appeared to be a significant association of heavy pigment content with epithelioid cells, but no other significant finding emerged.

TABLE IV—*Survivorship factors.*

Year of survival	Males			Females			Both sexes combined		
	Mean exposed	Deaths from metastases	Chance of escaping death from cancer	Mean exposed	Deaths from metastases	Chance of escaping death from cancer	Mean exposed	Deaths from metastasis	Chance of escaping death from cancer
x	E	θ	P_x	E	θ	P_x	E	θ	P_x
0 —	113	4	0·965	132	2	0·985	245	6	0·976
1 —	106·5	6	0·945	123·5	13	0·900	230	19	0·921
2 —	99	6	0·941	115·5	2	0·983	214·5	8	0·963
3 —	93·5	2	0·979	109·5	9	0·921	203	11	0·947
4 —	89	2	0·978	104·5	1	0·991	193·5	3	0·985

Chance of escaping death from cancer in the first five years :—

0·822

0·795

0·807

5 —	84·5	1	0·988	102·5	2	0·981	187	3	0·984
6 —	78	—	1·000	95·5	2	0·979	173·5	2	0·989
7 —	68·5	2	0·971	84·5	1	0·988	153	3	0·981
8 —	59·5	2	0·967	75	2	0·974	134·5	4	0·971
9 —	49·5	2	0·960	66·5	—	1·000	116	2	0·983

Chance of escaping death from cancer in the first ten years :—

0·733

0·734

0·734

The survivorship factor $P_x = \frac{2 - M}{2 + M}$ — where $M = \frac{\theta}{E}$, and the chance of escaping death from cancer during the first five or ten years is given by the product of the first five or ten of the series of values of P_x .

4. *Mortality generally.*—The cases have been analysed according to the number of years observed since excision. The deaths from metastases occurring between x and $x \pm 1$ years after excision have been related to the mean number of patients exposed to risk of death from cancer during that year leading to the calculation of the chance of escaping death from cancer in each of the consecutive years following excision. The principal details (up to 10 years) are shown in Table IV.

The difference between the five year factors for males and females is not significant, as will be seen from the following test.

	Mean exposed E	Deaths from metastases θ	Central death rate $M = \theta/E$	Expected deaths $\theta^1 = E \times M$	$\theta - \theta^1$	$\frac{(\theta - \theta^1)^2}{E \times M(I - M)} = \chi^2$
			(both sexes)			
Males	100·2	20	—	21·68	— 1·68	0·166
Females	117·0	27	—	25·32	+ 1·68	0·142
Total	217·2	47	0·2164	—	—	0·308
						$P = 0·58$

In calculating the exposed to risk for any particular year, deaths whether from metastases or from other causes were given six months' exposure.

The graph, in the text illustrates the variation of the risk of death from metastases according to duration after excision. The continuous curve connects the observed values of the ratio of deaths from metastases in each year to lives exposed during the year (M) (both sexes combined). The irregularity is, of course, inevitable in view of the small numbers involved. The general trend is indicated by the discontinuous line. In view of the restricted data no attempt was made to fit a specific mathematical law, but an approximation thereto was obtained by drawing a curve through the observed values by inspection. The risk of metastases rises to a peak in the second year and thereafter falls fairly rapidly.

5. *Effect of age on prognosis.*—The chance of escaping death from metastases during the first five years following excision was calculated separately for each of three broad age groups—under 40, 40-59, 60 and over. A statistically significant increase in mortality with advancing age takes place as indicated in the following table.

TABLE V—*Mortality in age groups—first five years.*

Age group	Mean lives exposed	Deaths from metastases	Expected deaths on the assumption of no association with age.	Actual — expected	Chance of escaping death from cancer.
Under 40 ...	42.5	4	9.16	— 5.16	0.910
40 — 59 ...	100.5	15	21.67	— 6.67	0.861
60 and over ...	75.0	28	16.17	+ 11.83	0.685

Using Yates' correction — $\chi^2 = 15.38$ $P < 0.0005$.

There were no significant differences between the two sexes in any age group. It will be seen that the odds against the recurrence of cancer in the first five years shorten from 9:1 to 7:1 between the youngest and the oldest age group.

6. *Mortality according to type of cell.*—In Table VI the mortality data for the first five years are analysed according to the cell type of the melanoma, and actual deaths from metastases in each group are compared with those expected on the assumption that mortality is not associated with cell.

TABLE VI—*Cancer mortality by cell grade — first five years (both sexes combined).*

Grade of cell	Mean lives exposed	Deaths from metastases	Expected deaths (assuming no association with cell grade)	Actual — Expected
1 (Spindle A) ...	10.5	1	2.24	— 1.24
2 (Spindle B) ...	131.5	25	28.09	— 3.09
3 (Mixed) ...	39.0	8	8.33	— 0.33
4 (Epithelioid) ...	17.5	8	3.74	+ 4.26
2 Fascicular ...	16.5	3	3.53	— 0.53
Necrotic... ..	5.0	2	1.07	+ 0.93
Total... ..	220.0*	47	47.00	—

*This differs from the average in Table IV because for the purpose of the above table the data are not analysed according to the individual years of the period.

Of the differences in the final column of this table that for Grade 4 alone can be regarded as statistically significant. Comparing the cancer mortality in this grade with that of the remainder, we find $P_{\chi^2} = 0.0096$.

7. *Mortality according to pigment.*—When the melanomata are classified by pigment the mortality experience in the first five years is as shown in Table VII.

TABLE VII—*Mortality by pigment—first five years (both sexes combined).*

Pigment	Mean lives Exposed	Actual deaths from metastases	Expected deaths (assuming no association with pigment)	Actual — Expected
Light	94.5	9	19.16	— 10.16
Medium	92.5	28	18.76	+ 9.24
Heavy	30.0	7	6.08	+ 0.92
Total	217.0	44	44.00	—

$$\chi^2 = 12.64$$

$$P = 0.002$$

It appears that lower mortality is associated with light pigment.

8. *Mortality according to reticulin content.*—The reticulin content was not stated in all cases and the mortality data are scanty, but the following analysis suggests that higher mortality is associated with low reticulin content. The

TABLE VIII—*Mortality by reticulin content first five years (both sexes).*

Reticulin	Mean lives exposed	Actual deaths from metastases	Expected deaths (assuming no association with reticulin content)	Actual — Expected
Trace or light	61.5	26	15.65	+ 10.35
Medium	41.0	2	10.43	— 8.43
Heavy	11.5	1	2.92	— 1.92
Total stated	114.0	29	29.00	—

differences between actual and expected deaths for the first two groups are greater than twice the standard errors involved, and the differences are significant.

9. *Mortality by cell and pigment.*—In Table IX the mortality experience in the first five years is subdivided according to cell grade and pigment and the ratios of deaths to lives exposed are given. The numbers involved are small and in only a few cases which have been underlined do the ratios differ significantly from that based on total deaths and total exposures.

In the "light pigment" group, the ratios for the different cell grades are very close to that for the "light pigment" group as a whole with the exception of grade 1 and the necrotic type where there were no deaths and grade 4 where the ratio was higher though not significantly. For medium pigment there is uniformity except for grades 4 and 2—fascicular where the ratios are higher than that for the medium pigment group as a whole (significant for grade 4). For heavy pigment, grade 4 alone shows a ratio higher (though not significantly so) than the group ratio. Within each pigment group therefore there is very

TABLE IX—*Mortality from metastases by cell and pigment first five years (both sexes combined).*

Pigment												
Cell grade	Light			Medium			Heavy			Total		
	E	θ	M	E	θ	M	E	θ	M	E	θ	M
1	6	—	—	3·5	1	0·29	1	—	—	10·5	1	0·10
2	62·5	6	0·10	53·0	14	0·26	14	2	0·14	129·5	22	0·17
3	11·5	1	0·09	20·5	6	0·29	6	1	0·17	38	8	0·21
4	3	1	0·33	8	4	0·50	6·5	3	0·46	17·5	8	0·46
2 Fascicular ...	10·5	1	0·10	4	2	0·50	2	—	—	16·5	3	0·18
Necrotic ...	1	—	—	3·5	1	0·29	0·5	1	2·0	5	2	0·40
Total	94·5	9	0·10	92·5	28	0·30	30	7	0·23	217	44	0·20

- (1) E = mean exposed. θ = deaths metastases. M = θ /E.
(2) Discrepancies with Table 6 are due to the exclusion of cases in which the pigment is not stated.

little variation of mortality with cell grade apart from grade 4. On the other hand when the effect of pigment within each cell grade is inspected it will be seen that low mortality is associated with light pigment in every instance.

This analysis suggests that while the observation of light pigment is by itself an indication of light mortality, no inference as to mortality may be drawn from cell grade alone (except perhaps for grade 4); it is necessary also to determine the pigment.

10. *Cell, pigment and reticulin combinations.*—The numbers were too small to bring reticulin into account in the above mortality analysis, but Table X shows the analysis of the whole series by cell, pigment and reticulin content excluding those in which all three factors were not recorded.

TABLE X—*Analysis of series according to cell, pigment, reticulin.*

Reticulin	Cell 1 Pigment			Cell 2 Pigment			Cell 3 Pigment			Cell 4 Pigment			Cell 2 Fascicular Pigment			Necrotic Pigment			Total Pigment		
	L	M	H	L	M	H	L	M	H	L	M	H	L	M	H	L	M	H	L	M	H
Trace or light	2	1	1	24	11	7	3	4	3	2	4	3	8	2	2	—	—	1	39	22	17
Medium	1	1	—	12	19	—	3	2	2	—	1	1	1	1	—	—	—	—	17	24	3
Heavy	2	—	—	4	3	1	—	—	—	—	—	—	1	—	—	—	—	—	7	3	1
Total	8			81			17			11			15			1			133		
Per cent. "Trace or light"	50			52			59			82			80			(100)			59		

If these figures are representative of the whole series, the following inferences may be drawn:—

(i) It might be suggested that the high mortality in epithelioid cell-type cases was due to light reticulin content. A rough test can be made from Table X,

assuming that these figures (which are only a fraction of the total exposed-to-risk in the series) are yet representative of the whole series.

Considering the distribution of Table X, viz.:—

Reticulin	Cells					
	1	2	3	4	F+N	Total
L	4	42	10	9	13	78
M	2	31	7	2	2	44
H	2	8	—	—	1	11
	8	81	17	11	16	133

If these numbers were exposed to the mortality of Table VIII, *i.e.*, if the reticulin content were the only factor and mortality was unaffected by cell-type, we should get the following expected deaths and death-rates:—

Expected deaths on reticulin mortality.

Reticulin	Cells				
	1	2	3	4	F + N
L	1·7	17·8	4·2	3·8	5·5
M	0·1	1·5	0·3	0·1	0·1
H	0·2	0·7	—	—	0·1
	2·0	20·0	4·5	3·9	5·7
Hypothetical mortality rates	0·25	0·25	0·26	0·35	0·36
Actual rates (Table 6)	0·10	0·19	0·21	0·46	0·23

There is a substantial difference between "hypothetical" and actual rates in cell grade 1 and in the fascicular-necrotic group, though it has to be borne in mind that the actual rates are here based on small numbers. On the whole the impression is gained that the cell grade may be an independent factor in prognosis but is not such an important one as reticulin or pigment. This is not a conclusive finding, however, and requires confirmation.

(ii) In the pigment groups the percentages with "trace or light reticulin" are as follows:—

Light pigment	...	...	62
Medium "	...	...	45
Heavy "	...	...	79

The mortality experience of the light pigment group is not, therefore, explicable on the hypothesis that the reticulin with which it is associated is the causative factor, as this would lead to the expectation of heavier mortality in the light pigment group than in the medium pigment group instead of the lighter mortality actually observed.

(iii) Conversely the heavy mortality associated with light reticulin does not arise from association between reticulin and pigment or cell. If the rates of Table IX are weighted with the proportions of Table X, the death-rates for the reticulin groups, if cell grade and pigment were the only operating factors, would be as shown below. The *actual* rates are quite different.

	Central death-rate (θ/E)	
	" Expected "	Actual
Trace or light reticulin...	0.20	0.42
Medium	0.21	0.06
Heavy	0.13	

(iv) It appears likely that each of the factors has an independent effect on prognosis but that cell grade is less important than pigment or reticulin content. The determination of the partial association of mortality with each of the three factors cannot be reliably made on the data of the present series.

2.—Melanoma of the ciliary body

1. *Age and sex distribution.*—There were only 30 cases in this series, the age and sex analysis being as follows:—

Age	Males	Females
20—	1	2
30—	2	1
40—	2	2
50—	3	2
60—	3	5
70—	3	3
80—	1	—
Total	15	15

There is no significant difference in age or incidence between the two sexes. The average age of the whole series is 56.3 ± 3.1 .

2. *Mortality.*—The chances of escaping death from metastases in the first five and ten years following excision, calculated in the same way as for melanoma of the choroid (except that individual years of the periods were not observed separately), are as set out below:—

Chance of escaping death from metastases in X years.

X	Males	Females	Both sexes
5	0.459	0.739	0.601
10	0.345	0.484	0.412

Differences in these factors between males and females arise in the first five years. The details are:—

Years	Males			Females			Difference between sexes
	Mean exposed $\frac{E}{\theta}$	Deaths from cancer $\frac{\theta}{\theta}$	$M = \theta/E$	Mean exposed $\frac{E}{\theta}$	Deaths from cancer $\frac{\theta}{\theta}$	$M = \theta/E$	
0 — 4	10.8	8	0.741	13.3	4	0.301	Significant
5 — 9	3.5	1	0.286	7.2	3	0.417	Not significant

It appears that metastases occurred later in females than in males.

In such a small series, the sampling errors arising in an analysis of mortality by cell grade or pigment or reticulin content were relatively large, and no statistically significant variations were found.

3. *Histological components.*—The following summary table gives the salient features observed:—

TABLE XI—*Ciliary Body: distribution of histological components.*

	Cell grade					Pigment			Reticulin				
	1	2	3	4	2 Fasc.	Light	Medium	Heavy	Trace	Light	Medium	Heavy	Not stated
M.	1	7	4	3	—	4	9	2	2	3	2	—	—
F.	1	7	2	2	3	6	3	6	4	3	2	—	—
P.	2	14	6	5	3	10	12	8	6	6	4	—	14

The distribution of these components is not substantially different from that observed in choroidal melanoma.

3.—Melanoma of the iris

The following summary table gives the available information on the five cases in this series:—

TABLE XII—*Findings in five cases of melanoma of the iris.*

	Age	Cell	Pigment	Reticulin	Outcome
Males	18	Spindle B.	Medium	Not stated	Alive 6 years later.
	51	" "	" "	" "	Alive 20 years later.
	71	" "	Heavy	Heavy	Alive 14 years later.
Females	52	Spindle B.	Light	Not stated	Died from metastases within 2 years.
	60	" "	Medium	" "	Died 12 years later from cerebral thrombosis.

The one case with death from metastases was vascular histologically.