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UNILATERAL AND BILATERAL RETINOBLASTOMA :*

A Possible Histological Difference

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ELSEWHERE in this journal (Vol. XXVIII, p. 279) Griffith and Sorsby drew attention to the great frequency with which both eyes are affected in the recorded instances of hereditary retinoblastoma, and the question was raised whether genetic retinoblastoma is histologically different from the sporadic variety of this affection. In an attempt to answer this question the specimens of unilateral, bilateral and hereditary tumours available at the Royal Eye Hospital were studied. In all 21 specimens were examined, but 2 were excluded from this study as they were examples of an unusual tumour formation, and these will be reported upon later. The remaining 19 cases consisted of 8 unilateral, 8 bilateral and 3 hereditary retinoblastomata. The specimens were in varying stages of preservation, but allowed sections to be cut in paraffin or celloidin. The following staining methods were employed—haematoxylin and eosin, Masson's trichrome method, Mallory's phosphotungstic acid haematoxylin and Gordon and Sweet's method for reticulin.

The clinical data of the cases are recorded in Table I.

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1. *The histological features seen in the unilateral retinoblastoma.*

The unilateral tumours all showed a fairly solid arrangement of cells except for one which tended to grow in a papillomatous manner. Little fibrous tissue stroma was to be seen, but blood vessels were fairly prominent. Necrosis was common with polymorphonuclear infiltration, which in some cases tended to obscure the histological picture. The cells composing the tumour were on the whole small, fairly deeply staining and with the nucleus almost filling the cell. Mitoses were not very common. The cells were slightly larger in two cases, the increase in size being due to a more abundant cytoplasm. There was a tendency for the cells to be arranged around blood vessels, giving a characteristic peritheliomatous arrangement.

Studying numerous sections it was possible in each case to make out the passage from normal retina to tumour. This change took place gradually in most cases, and it was possible to see the tumour apparently arising from the outer nuclear layer with portions of the inner nuclear layer covering a small part of the tumour. The inner nuclear layer became gradually thinned until it disappeared entirely. Fig. 1 shows this feature. Three of the cases had multiple tumour nodules; Fig. 2 shows one of these small nodules, and it can be seen that it is situated in the outer nuclear layer only and that the inner nuclear layer is not involved in the tumour process.

Rosettes or stephanocytes were found in one case, but the general character of the remainder of the tumour was identical with the other tumours in this group, and it did not seem possible to classify this tumour separately because of the presence of some rosette formation.

2. *The histological features seen in bilateral retinoblastoma.*

The general arrangement of the cells in the 8 bilateral tumours was not grossly dissimilar from those in the unilateral group. Some of the tumours were necrotic with polymorphonuclear infiltration. There was in some tumours less peritheliomatous arrangement and there was no tendency to a papillomatous condition.

The cells composing the tumour tended to be somewhat larger and to contain more cytoplasm than did those in the unilateral group, and this was to be seen more especially in the less necrotic tumours. Rosettes were found in four cases, but these four tumours did not differ in any other respect from the others in the group. Mitoses were no more common than in the unilateral tumours.

The site of origin of the tumours was of interest. Some of these tumours seemed to be multiple as in the unilateral group, but in contrast to the unilateral cases all the bilateral tumours appeared to arise from either the inner nuclear layer only, or from both nuclear layers, but not in any instance from the outer nuclear layer only. Figs. 3

and 4 show the picture seen and in these it appears that both layers are involved in the tumour process. In a few sections there are areas where the inner nuclear layer appears enlarged and thickened, and this is due to an increase of slightly larger, less deeply stained cells which resemble those seen in the main part of the tumour. This appearance has not been seen in the unilateral cases, and it has not been found possible in any section of a bilateral tumour to find a nodule of growth composed of small, deeply staining round cells in the outer nuclear layer similar in appearance to that seen in unilateral tumours. It was also impossible to find any area where the inner nuclear layer covered part of the tumour before becoming thinned out as occurred in the unilateral group.

3. *Familial tumours.*

No differences were found microscopically between tumours in the bilateral group and the familial tumours.

Discussion

All the cases reviewed are examples of tumours of the retinal epithelium but neuroglial fibres could not be found in any. In only one case (case E.C.S., a familial one) was reticulin demonstrated, and here it appeared to be derived from the wall of the orbit. No attempt has been made to determine the nature or type of cell from which the tumours have originated, and the staining methods

TABLE I.—*Summary of the Clinical and Histological Data on 17 Cases of Glioma*

Unilateral Cases

Name	Sex	Age When First Seen	Eye Affected	Date of Excision of Eye	Out-patient No. in Royal Eye Hospital Records	Histological Site of Origin
Henry H. D. ...	M.	2 years 7 months	Left	1/11/28	—	Outer nuclear layer
Christopher H.	M.	4 years	Right	19/1/28	—	Outer nuclear layer
Enid C. ...	F.	10 months	Left	9/10/30	0/1050	Outer nuclear layer
Kathleen M. ...	F.	7 years 6 months	—	31/5/35	35/6583	Outer nuclear layer (but difficult to determine)
Ronald M. ...	M.	2 years 3 months	Right	21/4/36	36/4082	Outer nuclear layer
Donoghue A. S.	M.	11 months	Left	25/9/38	38/9790	Outer nuclear layer
Derek L. ...	M.	2 years 1 month	Right	19/8/42	42/6733	Outer nuclear layer
Mary T. ...	F.	5 years	Left	-/2/42	Mr. Whittington's Case	Outer nuclear layer

TABLE I—continued. *Bilateral Cases*

Name	Sex	Age When First Seen	Eye First Affected	Date of Excision of First Eye	Date of Excision of Second Eye	Out-patient No.	Histological Site of Origin
Violet M. ...	F.	1 year 4 months	Right	28/1/24	9/8/27	—	No retina
Sidney B. ...	M.	3 months	Left	16/10/24	2/11/25	—	Both nuclear layers
William C. * ...	M.	2 years 7 months	Left	14/7/32	5/7/33 (at post mortem)	32/5070	Impossible to determine
Vera W. ...	F.	1 year 8 months	Right	3/1/44	Having radium treatment	43/11880	Both nuclear layers
James H. ...	M.	2 years 5 months	Right	-/11/42	-/5/44	Mr. Savin's Case	Both nuclear layers
Jean H. ...	F.	16 months	Both advanced when first seen	17/9/43	20/10/43	Mr. Whittington's Case	Inner nuclear layer
Georgina B. ...	F.	11 months	Both advanced when first seen	13/7/44	13/7/44	Mr. Nutt's Case	Inner nuclear layer
Michael L. ...	M.	1 year 6 months	Left	18/7/44	Having radon treatment	Case of Miss Strang and Mr. Archer Hall. By courtesy of Dr. Assinder	Probably both layers

* An account of this case by A. F. MacCallan, S. Cade and E. F. King appears in *Trans. Ophthal. Soc. U.K.*, Vol. LIV, p. 201, 1934.

Familial Cases

Name	Sex	Age When First Seen	Eye Affected	Date of Excision	Date of Excision of Second Eye	Ref. in Griffith and Sorsby, 1944	Histological Site of Origin
Leonard S. ...	M.	2 years	Right	6/8/21	14/1/23	Fii 3	Impossible to determine because of size of tumour
Ernest C S. ...	M.	9 weeks	Right	7/5/28	Unsuccessful radium treatment	Fii 5	Possibly inner nuclear layer
Helen S. * ...	F.	9 weeks	Left	-/9/43	-/2/44	Fiii 2	Impossible to determine because of size of tumour

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The inner nuclear layer is in the upper part of each Fig.

FIG. 1.

Showing origin of a unilateral retinoblastoma from outer nuclear layer and the thinning out of the inner nuclear layer over the tumour.

FIG. 2.

Showing isolated nodule situated in the outer nuclear layer in a case of unilateral retinoblastoma.

FIG. 3.

FIG. 4.

Figs. 3 and 4 showing origin of tumour from both nuclear layers in cases of bilateral retinoblastoma.

employed did not suggest any obvious differences in the tumour cells in the three groups.

Judging from the limited material studied here the unilateral tumours appear to develop in the outer nuclear layer from small deeply staining cells. It has been possible to show the junction of the tumour with normal retina, and although it might be reasonable to suggest that the tumour is invading the outer nuclear layer, yet it is unlikely that a tumour would invade only one layer. This view is strengthened by the finding of a small tumour originating in the outer nuclear layer and with no extension in the inner nuclear layer nor any connection with the main tumour mass. Origin from the outer nuclear layer was observed in every case of unilateral tumour, but only in three cases was it possible to find separate minute growths in this layer.

On the material at our disposal the site of origin of the tumour in bilateral cases was more difficult to determine as it was not always possible to find sections showing the junction of tumour and retina; in some cases the tumours were relatively large and had completely disorganised the normal structures. In the 6 cases where it was possible to trace the origin of the tumour, it appeared to start from both layers in 4 cases, from the inner layer in two cases, and in no case from the outer nuclear layer only.

Summary

The histological nature of unilateral and bilateral retinoblastoma has been studied, and it is suggested that the former originates in the outer nuclear layer, while the bilateral tumours are derived from both nuclear layers, or (possibly less frequently) from the inner nuclear layer. The three hereditary tumours were bilateral and did not appear to differ from the sporadic bilateral retinoblastoma.

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