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DIFFUSE INFILTRATING RETINOBLASTOMA*†

BY

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NEARLY two centuries ago Hayes (1767) published a description of a neuro-epiblastic tumour of the retina and in the years since then the volume of literature on retinoblastoma has become immense, describing, one would have thought, every form of the neoplasm. There is, however, a type not widely known or described which has several unusual features and often presents in a manner allowing a definite pre-operative diagnosis to be made.

The differential diagnosis of a hypopyon should include retinoblastoma, and on the four occasions, at the Institute of Ophthalmology, that the fluid has been aspirated and examined, malignant cells were found and a definite cytological diagnosis made before removal of the eye. Although these four tumours were identical they differed greatly from the more usual form. The four cases were under the care of Mr. A. G. Cross, Mr. E. F. King, Mr. Maxwell Shafto, and Mr. K. C. Wybar, who have kindly given permission for the clinical details and post-operative follow-up to be summarized.

Material

The four children, three boys and one girl, were aged 9, 6, 4, and 1 years respectively. All presented with the clinical appearance of a hypopyon of not more than 4 months' duration, although in one there was a history of trauma 15 months beforehand and an irritable eye ever since. In three cases the ocular tension was raised, a retinoblastoma was suspected, and aspiration of the fluid for examination and culture was immediately carried out. In the fourth case, numerous investigations for a suspected iritis or choroiditis were undertaken, but because of their negative results and the lack of response to treatment, aspiration was finally performed.

Pathological Investigations

When examining the fluid, the main features to be looked for are clusters of darkly-staining polyhedral cells with small nuclei and scanty cytoplasm,

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occasional rosette arrangements, and complete absence of polymorphonuclear leucocytes and organisms (Fig. 1). Karyorrhexis and pyknosis of the cells are likely to cause confusion with leucocytes, but this must be guarded against

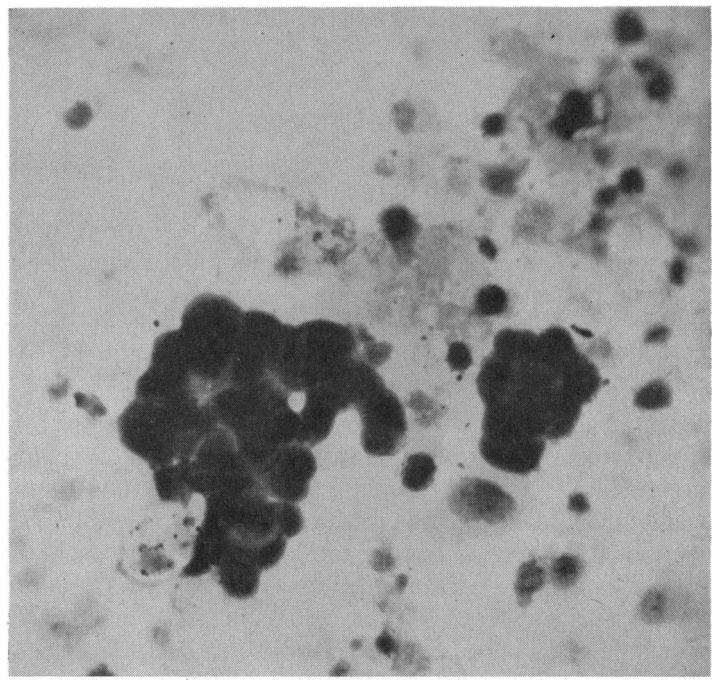

FIG. 1.—Smear of fluid aspirated from anterior chamber showing typical aggregation of malignant cells. Giemsa. × 573.

and a Gram-stain and bacteriological culture are of value in excluding an infective element.

Although all four cases were diagnosed with considerable certainty pre-operatively, the macroscopical appearances of the enucleated eyes showed surprisingly little to account for the hypopyon. In three, there was no apparent neoplasm except for a few small and benign-looking haemorrhages within the retina.

The only divergence from the above description was seen in Mr. Wybar's case, which showed, macroscopically, a ring replacement of the epithelium of the pars plana and ciliary body by a white layer. Histologically, however, the pattern in this case was identical with that in the others. In all examples much of the peripheral retina was replaced, but not thickened except in a few small areas, by closely-packed round or carrot-shaped cells with little cytoplasm and hyperchromatic nuclei (Fig. 2, opposite). Only isolated attempts at rosette formation were found and mitotic activity was moderate. Necrosis was not a marked feature although nuclear karyorrhexis and pyknosis were evident.

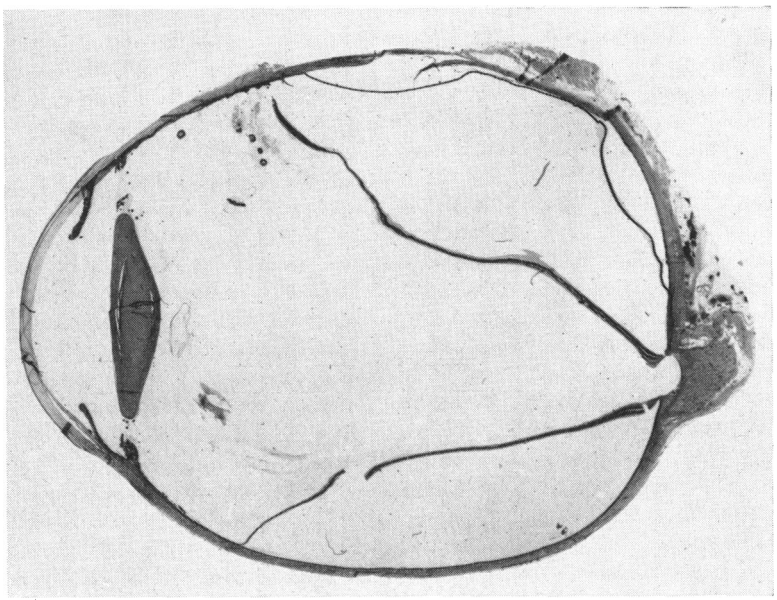

FIG. 2.—Low-power view of whole eye. Haematoxylin and eosin. × 2·3.

Malignant cells in many areas formed a relatively thick shell between the retina and pigmented epithelium and there was often a shallow albuminous exudate in association. In one eye the retinal replacement was almost complete around the globe but in the others this did not extend beyond the equator. In none was the optic nerve invaded. Anteriorly, without exception, the epithelium of the pars plana and ciliary processes was covered or replaced by malignant cells which also lay free amongst the processes and zonular fibres. Although no evidence of choroidal invasion was found, the ciliary body on at least one side of each section was infiltrated by retinoblastoma cells from whence they extended into the uveo-scleral meshwork and stroma of the iris (Figs 3 and 4, overleaf). Like the retina, the replacement, although diffuse, caused no structural thickening. As expected, malignant cells were present within the anterior chamber both as free aggregations or adherent to the iris and corneal endothelium (Figs 5 and 6, overleaf).

Prognosis

The post-operative progress in these four children has been good. To date they are all well and in none is there evidence of neoplastic activity either within the socket or in the other eye. The first patient has now survived for 5 years and, although it is only 10 months since the most recent case was operated upon, one is encouraged to feel optimistic about the survival of all four patients.

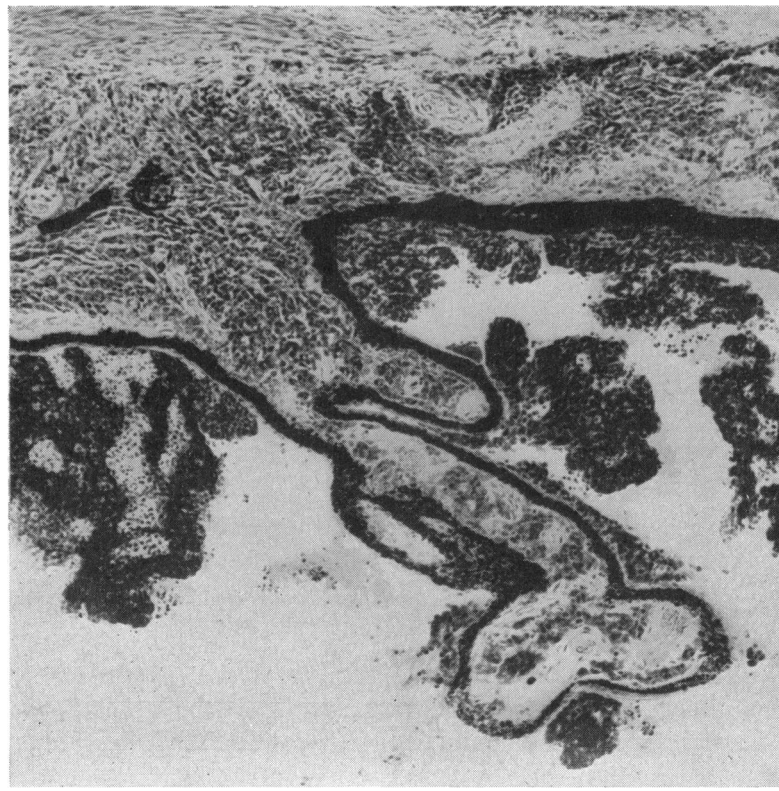

FIG. 3.—Diffuse infiltration of ciliary body, processes, and base of iris by malignant cells, which also cover the ciliary epithelium and lie free within the posterior chamber. Haematoxylin and eosin. × 110.

Discussion

The interesting feature of these cases is the unusual nature of the neoplasm for which the title "diffuse infiltrating retinoblastoma" suggested by Ashton (1958) would seem to be most suitable. A study of the literature has revealed only two similar examples, but it is unlikely that the condition is as rare as might be expected, since four cases have been seen at the Institute of Ophthalmology out of a total of 161 cases of typical retinoblastoma in the last 5 years.

In a short paper, Manschot (1956), the Dutch ophthalmologist, described a case of an 8-year-old boy who had a 3-months' history of severe inflammation with small tumours of the iris. The anterior chamber contained a fibrinous exudate with clusters of cells and the vitreous was hazy. The condition was thought to be tuberculous and eventually severe pain necessitated enucleation. It was not until the eye was examined histologically by Manschot that the true nature of the lesion was recognized. The clinical description and the one photomicrograph showing the iris only so closely resembled the cases already described that a request was made to examine the

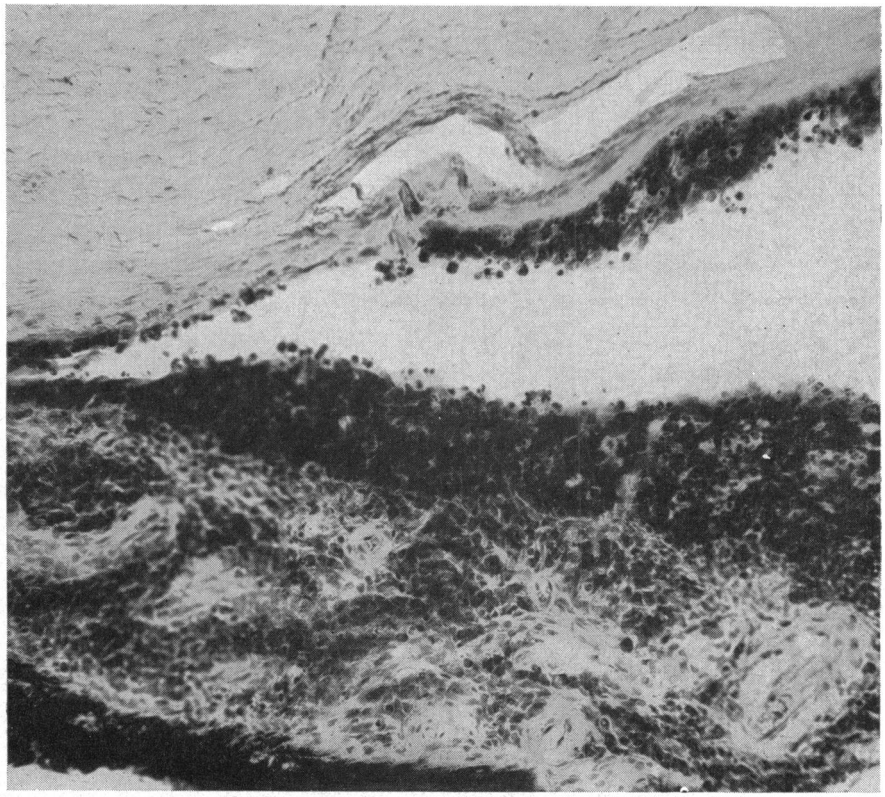

FIG. 4.—High-power view showing retinoblastoma cells within the iris stroma and lining the occluded filtration angle. Haematoxylin and eosin. × 170.

section of the whole eye. This was kindly supplied and examination showed that the lesion was indeed of the diffuse infiltrating form.

More recently Weizenblatt (1957) has described another example. This too occurred in a boy aged 8 years, who gave a history of impaired vision in the left eye for one year and inflammation for a few months. When he was first seen ciliary injection, vitreous opacities, and a grey focus at the fundus were observed, and the visual acuity was reduced to counting fingers. A diagnosis of uveitis was made and treatment consisted of atropine and cortisone. At subsequent examinations in the following 16 months before the eye was eventually enucleated, the optic disc and inferior retina became grey and opaque and large whitish slow-moving opacities were noted in the anterior chamber. The boy was examined for tuberculosis, syphilis, brucellosis, and tularaemia with negative results. However, the Sabin-Feldman dye test for toxoplasmosis was positive to a titre of 1 : 1024, later rising to 1 : 4096, and not unnaturally this was assumed to be the aetiology of the endophthalmitis, although a sensitivity to staphylococcal toxin was also noticed and considered. In the later stages the pupil became oval, grey opacities were noted on the

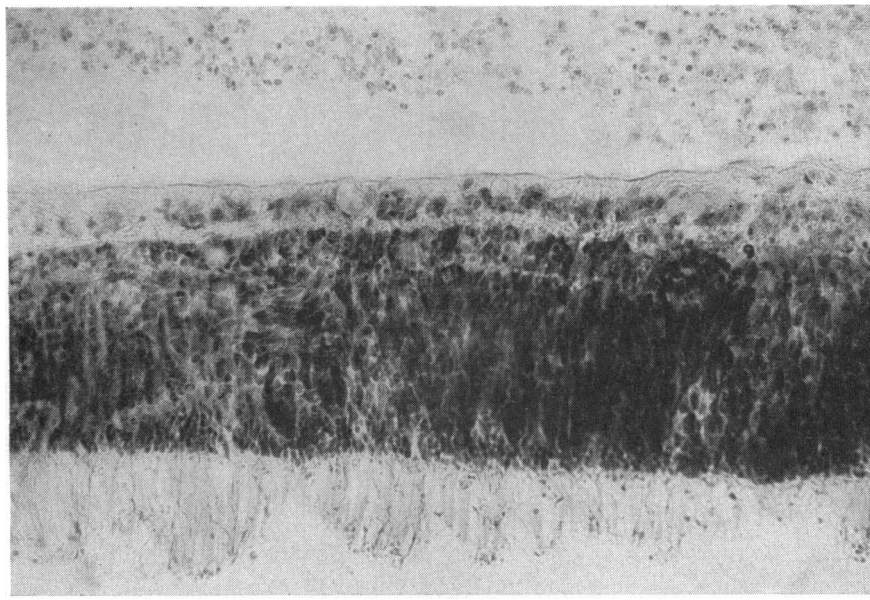

FIG. 5.—Extensive replacement of retinal layers by the neoplasm. Haematoxylin and eosin. × 170.

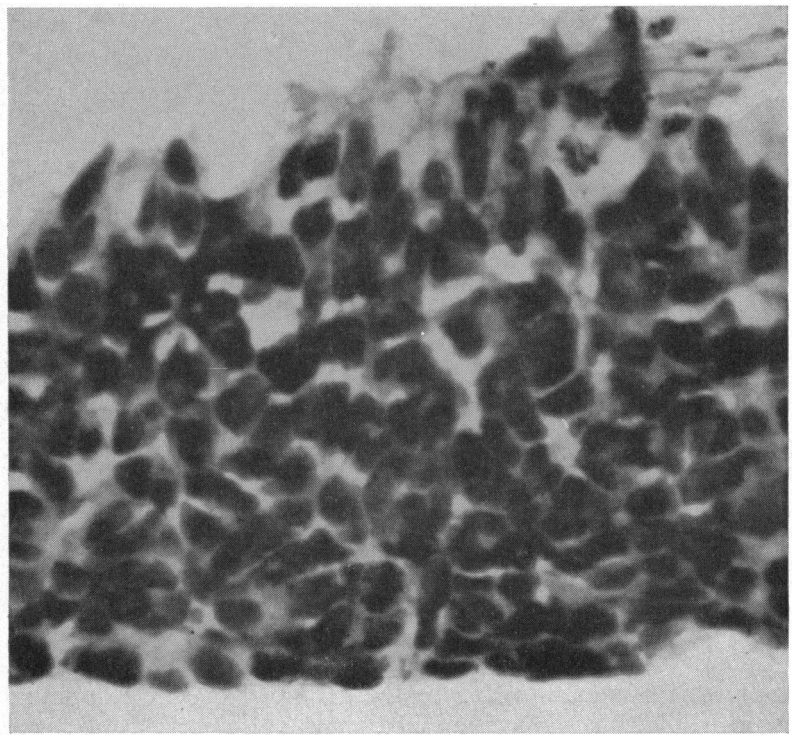

FIG. 6.—High-power view of malignant cells within the retina. Haematoxylin and eosin. × 720.

corneal endothelium, and floating opacities still existed in the anterior chamber. Eventually permission was granted for enucleation, but by then the child had signs of cerebral pathology and he died shortly afterwards. Histological examination of the enucleated eye showed features identical with those already described except for widespread invasion of the optic nerve by malignant cells. *Post-mortem* examination of the brain showed cerebral and cerebellar involvement by the neoplasm.

In retrospect, the positive dye test and sensitivity to staphylococcal toxin were undoubtedly misleading, and one wonders whether cytological examination of the aqueous in this case, as well as in that described by Manschot, might not have been rewarding.

Although many surgeons are opposed to anterior chamber puncture as a routine diagnostic procedure, Amsler and Verry (1943) and Verrey (1954) have found it safe and useful. Perhaps more use should be made of it, particularly in obscure cases of juvenile "endophthalmitis."

Another point of interest is that the majority of these cases belong to an older age group than is normal in retinoblastoma. Of the six described, only one was within the usual age of apprehension and three were of such an age that the surgeons might well have overlooked the condition.

Because of this feature and the atypical nature of the neoplasm, it is tempting to wonder whether the lesion might not have a different histogenesis from the usual form, but this seems unlikely since the cell type and growth from the nuclear layers are so typical. As Willis (1948) has said, retinoblastoma, in common with other tumours, has a considerable range of structure and behaviour and no histogenetic sub-division is warranted. Nevertheless, on clinical and morphological grounds, "diffuse infiltrating retinoblastoma" merits a separate sub-classification.

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REFERENCES

AMSLER, M. and VERREY, F. (1943). *Ophthalmologica (Basel)*, **105**, 144.
ASHTON, N. (1958). Personal communication.
HAYES (1767). "Medical Observations and Inquiries", 1st ed., vol. 3, p. 120. By a Society of Physicians in London.
MANSCHOT, W. A. (1956). *Ophthalmologica (Basel)*, **132**, 160.
VERREY, F. (1954). "Clinique de l'humeur aqueuse pathologique". Delachaux and Niestlé, Paris.
WEIZENBLATT, S. (1957). *A.M.A. Arch. Ophthal.*, **58**, 699.
WILLIS, R. A. (1948). "Pathology of Tumours". Butterworth, London.

ADDENDUM

Since going to press a further example of a diffuse infiltrating retinoblastoma has been received in this department. The eye was removed from an 11-year-old boy because of hypopyon following trauma one month before.