COMMUNICATIONS

INVESTIGATION OF RETINOBLASTOMA WITH SPECIAL REFERENCE TO HISTOLOGY AND PROGNOSIS*

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THE results of the analysis of a series of 287 cases of retinoblastoma, studied and followed up, are here presented. Particular attention is given to those histopathological features thought to be related to malignancy.

General Considerations

The distribution of cases according to the age at which the tumour was diagnosed (Fig. 1) shows that the incidence of the disease reaches its peak between the ages of 1 and 4 years. It falls rapidly after the age of 4, to become exceedingly rare after the age of 7. This is in accordance with the accepted views (Dollfus and Auvert, 1953), and would be expected from a congenital tumour arising from immature neural retinal elements.

FIG. 1.—Analysis of cases according to age.

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The frequency of familial retinoblastoma in this study was found to be 1.07 per cent., namely, lower than that generally estimated (4 per cent., François, 1958). It should be noted, however, that since this aspect of the disease has not been the main concern of the present investigation, it is possible that a familial occurrence in some cases in this series may have escaped detection.

Features of hereditary retinoblastoma worthy of particular mention are the high incidence of congenital appearance of the tumour and the bilateral involvement. They were observed in this study, suggesting increase of penetrance of the defective gene through transmission.

Although the number of familial cases in this series is very small and the pathological gene has not been transmitted through more than three successive generations, as might be anticipated, no evidence was found to support the suggestion of Griffith and Sorsby (1944) that familial retinoblastoma presents a particular histological type.

The incidence of bilateral retinoblastoma ranges from 20 per cent. to 30 per cent. (Duke-Elder, 1940). Merriam (1950) and Reese (1951) give figures of 27.6 per cent. and 25 per cent. respectively. Dollfus and Auvert (1953), reviewing different statistics, found an average figure of 20 per cent. In this study (Table I), it was found to be considerably higher (39 per cent.), a fact which, although in part may be due to the relatively selected type of the material referred to Moorfields Eye Hospital (from which a great number of the cases included in this investigation has been provided), clearly suggests that bilateral involvement is more common than is generally believed. Table II illustrates the incidence of complications leading to

TABLE I
ANALYSIS OF CASES ACCORDING TO UNILATERAL
OR BILATERAL INVOLVEMENT AND AFFECTED
SIDE

Retinoblastoma			Total No. of Cases
Unilateral	Right eye	94	175
	Left eye	81	
Bilateral			112

TABLE II
INCIDENCE OF VARIOUS COMPLICATIONS IN
FATAL CASES

Total number of fatal cases	48
Optic nerve invasion	21
Invasion of choroid	30
Extra-ocular extension through sclera and optic nerve	20

fatal outcome. These findings, based on post-mortem data are, on the whole, in accordance with previous reports. The high incidence of involvement of the uveal tissue is evident and its significance obvious, although such a complication does not necessarily imply haematogenous dissemination, a fact shown by a long follow-up in several cases. It is well known that the mortality from retinoblastoma has considerably decreased in recent years. In the present series it was found to be only 16.07 per cent. In view of the long survival in most cases examined (Figs 2 and 3) the possibility of delayed complications from the growth may be excluded, and it is very unlikely that this figure would be altered by an even longer follow-up.

FIG. 2.—Showing the length of survival in the total number of cases. (This length also coincides with the length of follow-up period.)

FIG. 3.—Showing the length of survival in fatal cases. (Calculated from the time of enucleation in unilateral cases, and the time of enucleation of the first eye in bilateral cases. The length of survival is identical with the length of follow-up.)

The clinical and pathological features of the condition were observed in their usual frequency. Some of the latter, however, are worthy of particular mention.

Histology

While endophytic and exophytic growth were most frequently seen to occur together, diffuse infiltrating retinoblastoma (Ashton, 1958; Schofield, 1960) was found to be the only distinct type of growth. It was encountered on four occasions, and being peculiar both pathologically and clinically, deserves special comment, for it represents a generalized involvement of the neural retinal elements, further suggesting that the malignant change in retinoblastoma may concern retinal tissue as a whole. The genetic character of the condition supports this concept.

A chemical factor elaborated by retinoblastoma cells and stimulating neoplastic growth of mature retinal cells, was postulated by Teng and Katzin (1955). This would explain the characteristic histological picture of diffuse-infiltrating retinoblastoma and also the delayed appearance of the tumour. However, the presence of mitotic figures within the apparently unaffected retina, on which this hypothesis was based, has never been conclusively observed in the present study.

Attention was given recently to the presence of clusters of cells within the lumen of the rosettes in the form of projections from their wall, and it was thought that this might be an imitation of the process of invagination of the primitive vesicle, connoting a higher degree of differentiation (Wolter, 1961). Such appearances are not uncommon, and since they are not always observed in the rosettes of the most differentiated tumours they may be due to artefacts from oblique section. Indeed, rosettes should be evident, not as they are seen microscopically, but in their real stereoscopic form as they exist within the growth.

A comparison between Tables III and IV shows that although complete invasion of the optic nerve occurred in 21 cases, the follow-up revealed that death was induced by this complication only in 10 cases. The explanation of this probably lies in the gross invasion of the uvea, which was also present in the remaining 11 cases and which may have led to dissemination of the tumour before spread into the central nervous

TABLE III
INCIDENCE OF INVASION OF DIFFERENT OCULAR
STRUCTURES AS FOUND IN TOTAL NUMBER OF
CASES IN THIS SERIES

a. Choroidal invasion	57
b. Complete optic nerve invasion	21
c. Invasion of sclera and extension into orbit	26

Note.—b occurred independently or in association with a, while c was always associated with a.

TABLE IV
MODE OF DISSEMINATION IN 48 FATAL CASES,
ACCORDING TO POST-MORTEM DATA

Metastasis through the blood or lymphatic circulation (generalized or localized)	34
Extension of tumour into the central nervous system through invasion of the optic nerve	10
Dissemination through circulation of cerebrospinal fluid	3
Extension of tumour from the orbit by direct spread	1

system was effected through the optic nerve. These findings, the high incidence of invasion of the uveal tissue (Table III), and the preponderance of fatal complications thus induced (Table IV), point to the paramount importance of the involvement of the vascular structures of the eye, and strongly suggest that this complication now involves the highest risks for life. It is also clear that the mode of spread of retinoblastoma, contrary to popular belief, is more frequently by way of the blood circulation than through the optic nerve.

TABLE V
DEGREE OF DIFFERENTIATION AS SEEN IN TOTAL
NUMBER OF 239 TUMOURS (NON-FATAL CASES)

Entirely undifferentiated	9
Tumours showing slight tendency only of neoplastic cells to arrange themselves in rosette-like formations	103
Tumours in which degree of differentiation ranged from mere tendency to formation of incomplete or very occasional rosettes	51
Well differentiated	54
Number of tumours in which degree of differentiation could not be elicited	22

TABLE VI
DEGREE OF DIFFERENTIATION EXHIBITED BY
TUMOURS IN FATAL CASES

Entirely undifferentiated	6
Tumours showing slight tendency only of neoplastic cells to arrange themselves in rosette-like formations	27
Tumours in which degree of differentiation ranged from mere tendency to formation of incomplete or very occasional rosettes	10
Well differentiated	5
Total number of tumours examined	48

FIG. 4.—Retinoblastoma showing a slight tendency to differentiation. Note the rosette-like arrangement of cells. Haematoxylin and eosin. $\times 430$.

FIG. 5.—Tendency to rosette-like arrangement of the tumour cells within another slightly differentiated retinoblastoma. Haematoxylin and eosin. $\times 430$.

A fact emerging from the post-mortem examinations in this study is the existence of another possible route of intracranial extension of the growth which may not be so uncommon, namely, through the circulation of the cerebrospinal fluid (Table IV). This mode of spread is characterized by a superficial gravitational involvement of the central nervous system with no invasion of the optic nerve and optic chiasma. In view of the absence of haematogenous dissemination, this type of lesion can be explained only by assuming that malignant cells entering the subarachnoid space of the optic nerve in the vicinity of the intra-ocular tumour are transported and implanted in the distant parts of the central nervous system through the circulation of the cerebrospinal fluid.

It is evident from Tables V and VI that the vast majority of retinoblastomas show some degree of differentiation. Indeed, most tumours show at least a slight tendency of the neoplastic cells to arrange themselves in a way reminiscent of the pattern of rosettes (Figs 4 and 5), as can be easily ascertained, especially if immersion-oil magnification is used. This feature should be interpreted as the earliest sign of differentiation, implying that the concept in which the majority of these growths are undifferentiated is incorrect. The process of differentiation of a retinoblastoma usually gives rise to a mixed histological picture and varying degrees of differentiation may prevail in different parts of a tumour (Tables V and VI).

Prognosis

None of the proposed classifications of retinoblastoma is satisfactory from the histological point of view, or contributes to their better understanding, a fact that is also suggested by the irrelevance of histological features to prognosis. It has been thought that a classification according to degree of histological differentiation is of importance, for it relates to differences in malignancy. Thus more differentiated retinoblastomas were believed to have a better prognosis (Parkhill and Benedict, 1941; Carbajal, 1958; Tsukahara, 1960). Herm and Heath (1956) found a higher incidence of choroidal involvement and extra-ocular extension in less differentiated growths. They suggested that the longer a retinoblastoma is present in an eye the more undifferentiated it becomes, and considered that the undifferentiated character of the tumours seen in their fatal cases was due to longer existence of the tumour before enucleation, rather than to primary non-differentiation. These views are not supported by the findings of this investigation, since no significant relationship was found between the incidence of various complications leading to fatal outcome and the degree of differentiation (Fig. 6). Moreover, the degree of differentiation was unrelated to the size and therefore to the age of the tumours. Well differentiated as well as less differentiated retinoblastomas seem to arise as such, and not through de-differentiation or anaplasia, as Parkhill and Benedict (1941) suggested.

The relationship between the degree of differentiation and the length of survival in the fatal cases, as shown in Fig. 7, may lead to the deduction that a shorter period of survival should be expected from less differentiated tumours. It should be realized, however, that the preponderance seen in this figure is only apparent, since the growths included in the last two groups represent post-irradiation cases with

FIG. 6.—Showing incidence of complications leading to fatal outcome in relation to degree of differentiation in 33 cases.

FIG. 7.—Showing length of survival in relation to degree of differentiation in 37 fatal cases.

temporary regression. The longer survival, therefore, cannot be attributed to a relatively higher degree of differentiation. Analysis of the total number of tumours examined according to the degree of differentiation (Fig. 8), shows that although the relative distribution of fatal and non-fatal cases with regard to the prevailing histological features has been similar, fatal tumours exhibited a lower degree of differentiation. Whether this finding can be related to prognosis is very doubtful. Indeed, a long term follow-up (Fig. 8) has revealed that about half of the tumours in the non-fatal cases had an uncomplicated course, despite the low degree of their histological differentiation, while many of the fatal tumours were well differentiated. It is evident, therefore, that other factors affect prognosis more than the degree of differentiation. They constitute the only real difference between fatal and non-fatal cases in this series and are: (1) interval between appreciation of clinical signs of the disease and initial treatment; (2) delay in treatment; and (3) correctness of clinical diagnosis and effectiveness of treatment applied.

The decisive significance of the first factor is clearly demonstrated in Fig. 9, in which the distribution of a number of fatal cases is considered in relation both to the

FIG. 8.—Showing degree of differentiation in fatal and non-fatal cases.

FIG. 9.—Showing relationship between degree of differentiation and interval between appreciation of noticeable clinical signs and initial treatment (27 fatal cases).

above interval and the degree of differentiation. It is clear that the frequency of fatal complications increases in parallel with this interval, irrespective of the degree of differentiation of the tumours involved. The fact that the peak of this graph corresponds to 12 months and not to 36 as might be expected, is attributable to the high mortality from the disease in the first year of life.

These findings suggest that the growths which showed a higher malignancy did so not because of any particular histopathological feature, such as a stronger tendency to invade other tissues and to metastasize or to grow more rapidly, but because they

existed in the eye longer than their counterparts in non-fatal cases, which were accurately diagnosed and promptly treated. The impact of appropriate treatment on prognosis is obvious enough not to require comment.

Naturally, more than one of the above factors may often influence prognosis. The belief that the degree of differentiation of a retinoblastoma has no bearing on its malignancy by no means opposes any general principle of the biology of tumours, since it should be realized that in spite of slight histological variations, all these growths consist of poorly differentiated neoplastic cells, the behaviour of which would not be expected to differ in any substantial way.

Conclusions

The main conclusions to be drawn from this study are as follows:

(1) The general clinical and pathological features of the condition, as seen in this investigation, are in accordance with those classically described.

(2) The incidence of bilateral retinoblastoma was found to be 39 per cent., namely, higher than is generally believed. The condition may concern retinal tissue as a whole and this is also suggested by the genetic character of the disease.

(3) The analysis of the material has shown that metastasis through the blood or the lymphatic circulation is the most common route of dissemination of the tumour.

(4) The rate of mortality as found in this study (16.07 per cent.) is lower than in other previous series and suggests a real decline in the toll from the disease. It is attributed to improved methods of diagnosis and treatment.

(5) The survival from the disease has in the vast majority of cases (about 78 per cent.) exceeded three years and has almost equally been distributed between three and eleven years. Many patients were followed up for a period longer than eleven years. The length of survival in most cases with a fatal outcome (about 81 per cent.) has been shorter than two years. The rate of mortality is highest during the first year. According to this study, any patient treated for retinoblastoma, with an uncomplicated course over three years, can be regarded as having survived the disease.

(6) No significant relationship exists between malignancy of retinoblastomas and degree of their histological differentiation, which is unrelated to the mortality rate, the length of survival, and the incidence of fatal complications.

(7) Dissemination of the intra-ocular growth in the central nervous system through the circulation of the cerebrospinal fluid presents certain typical pathological features, and is not very uncommon.

(8) No classification of these tumours based on histological features is at present either justifiable or expedient.

(9) While prognosis is unrelated to any histopathological feature of the tumour itself, it is influenced by, and depends upon, other factors of paramount clinical importance, such as early diagnosis and prompt and appropriate treatment.

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