The Inheritance of Retinoblastoma and Its Relationship to Practical Eugenics*

Carl V. Weller, M.D.

(From the Department of Pathology, University of Michigan, Ann Arbor, Michigan)

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In a brief review (51), published several years ago, the author called attention to the fact that it was no longer possible to discuss the inheritance of predisposition to the development of neoplasms if all neoplasms were considered in one group. Satisfactory evidence was available even then that the significance of intrinsic factors, the part played by genes and by extrachromosomal factors, and the extent to which mendelian laws might be applied must be investigated separately for each kind of neoplasm. In respect to the etiology of some relatively common malignant neoplasms hereditary factors seemed to play but a minor part. Squamous cell carcinoma of the lip was an example of this group. At the other extreme were found neoplasms, both benign and malignant, in connection with which the hereditary pattern was obviously of considerable importance in etiology. For instance, this had long been known to be true of neurofibromas, particularly those of the type characterized clinically as "molluscum fibrosum." Similar evidence has continued to accumulate.

The neoplasm under consideration has been designated by a variety of terms. In the older literature it was known as cancer of the eyeball, encephaloid of the eye, haematodes oculi, amaurotic cat's eye, and other variants of this group of names; in the early period of microscopy, as glioma retinae, sarcoma of the retina or gliosarcoma; later as glioblastoma, and still more recently as neuro-epithelioma retinae and retinoblastoma. This list is by no means complete but it will serve to illustrate the range of titles under which the case reports appear. For several reasons retinoblastoma seems to be the best term. It is now understood to designate a group of neoplasms having a common origin but not of identical histological structure; for, just as the neoplasms of the brain and cord differ among themselves in both direction and degree of differentiation, so also do the retinoblastomas (Favalaro, 12). Histological classification within the group has not as yet been utilized sufficiently to give subgroups for genetic study. We must, therefore, deal with retinoblastomas as a whole.

GENERAL CONSIDERATIONS

Retinoblastoma is a highly malignant neoplasm of the eyes of infants and young children which may be present at birth, is most frequently recognized during the first and second years of life, seldom appears after the sixth year and has never been known to originate in adult life. Unlike most carcinomas, therefore, it presents the distinct advantage to the geneticist of a fairly definite "end point." In evaluating the hereditary significance of carcinoma there is always a large group of individuals in regard to whom the intrinsic liability to the disease can never be known. Death at any time prior to the ultimate physiological life limit leaves unanswered the question of hereditary predisposition. This enigmatical group is very small.
indeed in respect to retinoblastoma, since it is made up only of the stillborn and of those dying in early childhood. Thus, it will be seen that retinoblastoma offers some of the advantages that pertain to the sharply limited unit characteristics employed in experimental genetics. Some exceptions to this concept, perhaps not very important because of their rarity, will be pointed out in the discussion to follow.

Course.—Retinoblastoma first grows from its area or origin in the retina into the vitreous chamber. The patient is usually too young to be aware of the resulting unilateral visual disturbance. As the mass becomes larger a parent or attendant commonly notices the peculiar opalescent light reflex from the affected eye, which was the basis for the older name of amaurotic cat's eye. If untreated, the growth, which advances both by expansion and infiltration, may rupture the eyeball anteriorly and grow out of the orbit as a fungoid hemorrhagic mass; or it may penetrate the sclera into the orbit and extend within, or along, the sheath of the optic nerve, to reach the meninges and substance of the brain. At the same time distant metastases may occur, particularly (53) to the cranial and facial bones, pia mater and brain, regional lymph nodes, parotid glands, general skeletal parts, and liver. Once extraorbital extensions or metastases have occurred, a fatal outcome is inevitable. If the growth is removed by enucleation or orbital evisceration while it is still intraocular, or if it is destroyed by roentgen ray irradiation or by radium (38), the life of the patient may be saved. Only in extremely early cases and those with the new growth located in an especially favorable position is it possible to destroy the neoplasm by irradiation without serious injury to the eye. Therefore, actual, or functional, loss of the eye is the alternative to death. The terminal stage in the disease is the second neoplasm of the second eye develops in the same proportion of cases regardless of how early the enucleation of the first has been performed. Usually there are no evidences of general metastatic spread at the time the second neoplasm is recognized. This is significant since various other structures, particularly the cranial and facial bones, provide a congenial situation for the growth of metastatic retinoblastoma. Moreover, when neglected unilateral retinoblastoma does metastasize, there is no predilection for the contralateral eye.

To the dictum that loss of the eye is the price for survival for those on whom an early diagnosis is made, there are occasional apparent exceptions. One group is made up of those who have received an incorrect diagnosis of retinoblastoma. They are examples of partial detachment of the retina, with or without retinal proliferation. This condition may occur at any age and has nothing to do with retinoblastoma, but the presence of the resulting mass in the vitreous chamber may lead to a false diagnosis. The subsequent clinical behavior will naturally appear to be highly unusual for retinoblastoma, until the error in diagnosis is recognized.

A second group of cases, which prove to be exceptions to the general rule that untreated retinoblastoma is a uniformly fatal condition, is made up of those in whom there is apparent spontaneous retrogression of the neoplasm. Naturally, the assumption of spontaneous retrogression seldom can be subjected to complete microscopical proof, since biopsy of an intraocular growth is not done. I have recently examined an otherwise untreated eye, enucleated for retinoblastoma, in which almost the entire neoplastic mass, which had filled the globe, was necrotic. Only in one very small area were there living cells, but these were sufficient to make identification of the neoplasm possible. Spontaneous retrogressive changes might have become complete in this eye. Wells (52) has commented very recently on this interesting possibility and has brought together several observations of apparent spontaneous loss of malignancy in retinoblastomas. Most of these concern the retrogression of a small growth in the second eye, after enucleation of one eye for a more advanced retinoblastoma. No further survey of the casuistical literature dealing with this phenomenon is appropriate here, but some examples of it appear in the family histories to be given later. To the extent (at present unknown) to which it may occur, it interferes with the accuracy of statistics as to the incidence of retinoblastoma by reducing the total number of cases. If spontaneous retrogression of this highly malignant neoplasm can occur, as now seems certain, it is of far greater significance as a contribution to the knowledge of the general biology of neoplasms than in its influence upon a restricted statistical analysis.

Bilateral occurrence.—Retinoblastoma is often a bilateral condition. As a rule both eyes are not involved simultaneously nor to the same degree, although both eyes frequently show neoplasm when the patient is first examined. The interval between recognition of a new growth in the first eye and in the second may vary from a few days to as much as 3 years. There are no reasons for considering the neoplasm of the second eye to be other than a new primary. Direct extension between the eyes cannot be demonstrated. So far as can be determined from many case histories, the neoplasm of the second eye develops in the same proportion of cases regardless of how early the enucleation of the first has been performed. Usually there are no evidences of general metastatic spread at the time the second neoplasm is recognized. This is significant since various other structures, particularly the cranial and facial bones, provide a congenial situation for the growth of metastatic retinoblastoma. Moreover, when neglected unilateral retinoblastoma does metastasize, there is no predilection for the contralateral eye.

The extent to which retinoblastoma has been found to be bilateral varies considerably in different series. Adam (1) found but 8.5 per cent of his cases bilateral, while Lange (22) reported 30 per cent. In his large monograph analyzing 497 collected cases, Winter-
The children with unilateral retinoblastoma who die before 6 or 7 years of age or who escape from medical supervision, introduce a negative error. This is probably more than balanced by the greater clinical interest attaining to bilateral involvement, which increases the probability that such cases will appear in medical literature. Institutional series, dealing with an abundant material and fortified by an adequate "follow-up" system, will give more accurate information than is now available on the proportion of cases of retinoblastoma which become bilateral.

\textbf{Incidence.}—Of prime importance in estimating the effect of the hereditary influence in the causation of a neoplasm is a knowledge of the incidence of that neoplasm. Multiple appearances in a particular family assume significance only when they far exceed those which might be expected under the free operation of the laws of chance. In other words, the more rare the neoplasm, the more significant does familial concentration become. Retinoblastoma is a very rare neoplasm, indeed. Berrisford (4) found that there had been 131 cases in 1,259,452 admissions to the Royal London Ophthalmological Hospital, a ratio of 1:9614 or 0.0104 per cent. Adam (1) reported the ratio in Berlin to be 1:5832 or 0.0170 per cent. Wintersteiner (53) considered the incidence of retinoblastoma to be 1:2500 patients with disease of the eye, or 0.400 per cent. While these figures demonstrate that retinoblastoma is a rare neoplasm, they give only its incidence among those with afflictions of the eyes of such a nature as to require medical attention. Naturally its incidence in the total population is much lower. The best information available on this point is from Hemmes (17) who found, by means of circular letters, that in the years 1927, 1928, and 1929 three-fourths of the Dutch ophthalmologists saw 12 new cases of retinoblastoma. Dividing three-fourths of the living births in Holland during the same period by 12 gave an approximate incidence of 1 case of retinoblastoma in each 34,000 births of living children. This ratio seems to be in agreement with the incidence in hospital patients as given above. These figures suffice to demonstrate the rarity of retinoblastoma, which is of such a degree that it would make little difference with the application of the ratio if subsequent studies should show that the denominator is either too large or too small by several thousands. For our present purposes we accept the rate of incidence as given by Hemmes—1 example of retinoblastoma in each 34,000 living births.

\textbf{Evidence for Hereditary Influence in the Etiology of Retinoblastoma}

In the preceding section basic information as to the nature, course, and incidence of retinoblastoma, necessary for understanding the discussion which follows, has been presented. Most of this material will not be new to the ophthalmologist or to the pathologist dealing with ophthalmological specimens. To those whose interests must cover the entire field of neoplasia and to the nonmedical geneticist, this summary of general considerations may prove to be essential.

The evidence for an hereditary influence in the etiology of retinoblastoma will be presented in three main divisions: (a) The Significance of Bilateral Retinoblastoma; (b) Retinoblastomatous Fraternities, and (c) Retinoblastoma in Successive Generations and in Collateral Lines.

\textbf{The Significance of Bilateral Retinoblastoma}

It has been stated previously that retinoblastoma is bilateral in about 20 per cent of those afflicted and that there is no adequate basis for opposing the opinion that the disease in the second eye is a new primary neoplasm. In view of the general incidence of retinoblastoma (one case in 34,000 living births) the probability that two primary retinoblastomas would be the fate of a given individual is extremely slight, provided the distribution is dependent upon chance alone. That this excessively rare event will occur in the lives of some 20 per cent of all those who have retinoblastoma is unthinkable unless some other factor than chance is operating.

This question lends itself readily to mathematical treatment. The accepted incidence of retinoblastoma of 1 in 34,000 living births, means also 1 patient with retinoblastoma for each 68,000 eyes. Since \( \frac{1}{4} \) of those with retinoblastoma are afflicted in both eyes, it may be considered that there are \( \frac{1}{4} \) retinoblastomatous eyes in each 68,000; or, disposing of the fraction, 6 in 340,000. Therefore, the probability that a given individual will have retinoblastoma in the right eye is \( \frac{6}{340,000} \), and similarly for the left eye. Thus the probability of having retinoblastoma in one eye only is \( \left( \frac{6}{340,000} \right)^2 = \frac{1}{28,333} \). This is simply a modification of the case incidence of \( \frac{1}{34,000} \) to include the factor of bilaterality by considering eyes rather than patients. However, the probability that one individual would have retinoblastoma in both eyes is \( \left( \frac{6}{340,000} \right)^2 = 3.114 \times 10^{-9} \) or approximately once in 3 million times, provided the distribution is determined by chance alone. The actual or observed incidence of bilateral retinoblastoma is approximately 1 case in 170,000 (5 \( \times \) 34,000) living births, or about 19,000 times greater than would be expected under random distribution.

If the incidence of bilateral retinoblastoma is such as to prove that this mode of appearance cannot be due to chance alone, it must be due either to \textit{extrinsic factors} (noninherent in the germ plasm) or \textit{intrinsic factors} (inherent in the germ plasm), or to both. These terms are not entirely synonymous with \textit{environmental} and \textit{hereditary}, but approximate them suf-
ciently closely that the latter may be substituted in the present discussion. There is no information at present which in any way indicates that an environmental factor plays a part in the causation of retinoblastoma. Such an influence may be discovered in the future but there is every indication that in the etiology of this neoplasm extrinsic factors must play an exceedingly small part, if operating at all. This point can be discussed more effectively after illustrating the familial distribution of retinoblastoma.

If both chance and extrinsic factors can be excluded we are left with the explanation that the development of primary retinoblastoma in both eyes is due to the fact that a common hereditary pattern has made them both vulnerable to this form of unlimited and imperfectly differentiated proliferation.

It is interesting that the percentage of bilateral involvement is much higher in familial retinoblastoma (Best, 5) than in collected series of solitary or sporadic cases. This seems to indicate that there may be quantitative differences in the intensity of the intrinsic factor or complex.

### Retinoblastomatous Fraternities

Familial retinoblastoma, limited to a single generation and involving several of a group of sibs, has long been recognized. This may be designated as a horizontal distribution in a family. The earlier literature of such observations was collected by Leber (23) whose table follows:

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of children in family</th>
<th>Number with retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newton</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Thompson and Knapp</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Calderini</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Leber</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Wilson</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Lerche</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>de Gouvea</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>von Graefe</td>
<td>6 or 7</td>
<td>2</td>
</tr>
<tr>
<td>Marshall, C. D</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>MacGregor</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Carline-Calderaro</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Schönenmann</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Valenti</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Fuchs</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Snell (1st case)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>von Hoffmann</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Snell (2nd case)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Steinhaus</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Owen</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>119</strong></td>
<td><strong>63</strong></td>
</tr>
</tbody>
</table>

The 19 families in Leber’s compilation included 119 children of whom 63 developed retinoblastoma. Obviously, in these families retinoblastoma was not distributed by chance alone, when the general incidence is 1 example in 34,000 living births.

No effort has been made to collect for this study the retinoblastomatous fraternities which have been reported since the publication by Leber. This manifestation of retinoblastoma is so generally recognized today that examples are unlikely to be recorded unless they present some unusual feature.

The family reported by Newton (31) in 1902 is such a remarkable example of fraternal retinoblastoma (also possibly collateral) that it should be reviewed here. It is shown diagrammatically on Fig. 1. There is good evidence that the father’s brother had retinoblastoma, although this was not definitely established. The disease appeared in 10 of 16 children and was bilateral in 7. There was no evidence of sex linkage since 5 of 9 boys and 5 of 7 girls were affected. Of the 6 children reported as normal, 2 died when less than 12 months old and while they were still potential candidates for retinoblastoma. The chief information in respect to the children follows:

1. Male. Died at 6 weeks of bronchitis.
3. Female. Alive, but described as “delicate” at 23 years.
4. Male. Retinoblastoma of right eye. Enucleation at 24 years, followed by local recurrence and death at 3 years.
5. Female. Retinoblastoma, bilateral. Died at about 3 years of age.
6. Female. Healthy at 19 years.
7. Female. Retinoblastoma of the left eye. Died at 2 years.
9. Male. Retinoblastoma of the right eye. Enucleation at 31 years, followed by recurrence and death at 5 years.
15. Female. Retinoblastoma, bilateral. Died at 3 years.

If the incidence of retinoblastoma is 1 in 34,000, the probability of 10 occurrences in a group of 16 individuals, as in the family reported by Newton is $3.874 \times 10^{-15}$, a fraction so small that a single example in all medical literature is sufficient demonstration that some factor other than chance must determine such a concentration.

**A hitherto unreported retinoblastomatous sibship.**—I have had the opportunity of examining several eyes from members of a family which has not been described previously. Six of the 10 children developed retinoblastoma and in 4 the disease was bilateral (Fig. 1). The paternal grandfather had died of carcinoma of the stomach. The chief data on the children follow:

2. Girl. Left eye removed for retinoblastoma when 3 years old. The remaining eye is apparently normal. Her present age is 18 years.

1 Most of the afflicted members of this family have been patients in the University of Michigan Hospital. I am indebted to the Social Service Department of the Hospital and to Dr. L. W. Switzer of Manistee, Michigan, for details of the family history.
3. Girl. Both eyes removed for retinoblastoma before the age of 2 years, when death occurred.

4. Boy. Now 16 years old. Has no neoplasm but is practically blind in one eye due to structural changes which have been diagnosed "deterioration of the retina."

5. Girl. Both eyes removed for retinoblastoma before the age of 27 months, when death occurred.


7. Boy. Right eye removed for retinoblastoma when 4 years old. Died 8 months later of diffuse cranial neoplasia—"head twice normal size."

8. Boy. Right eye removed for retinoblastoma when 16 months old. Left eye removed when 44 months old. Cranial metastases and death 3 months later.

9. Girl. Left eye enucleated at 20 months for retinoblastoma. Right eye normal at last report.


The probability that 6 examples of retinoblastoma would occur, by chance alone, in a fraternity of 10 members is $1.358 \times 10^{-25}$. It does not greatly assist in comprehending the infinitesimal degree of this probability if one states that it means less than one chance in a trillion trillion.

**Retinoblastoma in monochorial twins.**—The occurrence of retinoblastoma in monochorial twins is a special form of fraternal retinoblastoma which has been reported by Benedict (3). His observation met the requirements set forth by Militzer (30) in that the neoplasms were similar, simultaneous, and symmetrical. The development of such a rare neoplasm in the left eyes of both members of the pair would be difficult to explain on other than an intrinsic basis. A diagram of this family appears in Fig. 1 and brief notes on the cases follow here:

Benedict, 1929 (3). The mother of the affected twins had a twin sister, twin nieces, and 2 sets of female twin cousins. Thus, twinning, limited to females, was probably an hereditary trait in this family. The twin girls developed retinoblastomas in their left eyes at about the same time. One died 6 months after enucleation. The other survived, but developed a small growth in the right eye. This apparently retrogressed following the application of radium. Six years after the enucleation and at the time of the report, there was increasing cloudiness of the lens, but no sign of neoplasm.
Retinoblastoma in Successive Generations and in Collateral Lines

Knowledge that retinoblastoma may occur in successive generations of the same family, thus exhibiting a vertical inheritance in contrast to the horizontal type described in the preceding section, has been a relatively recent development. In 1908 von Hoffmann (49) gave what he believed to be the first report of glioma retinae in successive generations of the same family. He was in error in that belief since von Graefe (48) in 1868, Thomspon and Knapp (43) in 1874, de Gouvea (10) in 1886, Marshall (28) in 1897, Steinhaus (39) in 1900, and Taylor (41) in 1905 had preceded him with reports of the occurrence of retinoblastoma in successive generations of the same family, although these examples were not all equally well authenticated. Von Hoffmann's assertion of priority is a clear indication of how little knowledge there was among ophthalmologists that inheritance of this type could be demonstrated by retinoblastoma.

That there were not more examples of vertical inheritance observed during the earlier period was due to the fact that there were practically no survivors among those who developed retinoblastoma. With prompt diagnosis and early enucleation, or evisceration of the orbit, an increasing number of those who had had retinoblastoma survived to marry and to procreate. This group has been largely responsible for the many examples now available of retinoblastoma in successive generations of the same family.

In addition to the many examples of direct inheritance there have been reported other families showing transmission through an unafflicted parent or the appearance of the disease in collateral lines rather than in lineal descendants. For earlier collections of families with retinoblastoma in more than one generation, reference may be made to the monographs of Clausen (9) and of Julia Bell (2) which are important sources of data in this field. To the families which they reported have been added all of the examples of familial retinoblastoma, other than those confined to sibships, which I have been able to find. Abstracts of these follow, giving such data as are available. The arrangement of this material is not chronological, but in groups of examples which have some genetic characteristic in common.

Apparent inheritance of retinoblastoma through an affected male parent.—Fourteen families have been found in which the father of one or more affected children had had retinoblastoma. These are shown diagrammatically in Figs. 2 and 3.

de Gouvea, 1886, 1910 (10). This family includes retinoblastoma in a father and in 2 daughters among 7 children. The right eye of the father was removed in 1872 when he was 2 years of age. He married at 34 years. The first child was normal; the second, a girl, developed bilateral retinoblastoma and died at 2 years; the third, also a girl, had bilateral retinoblastoma and died at 5 months. The sex of the 5 normal children is not given. (de Gouvea stated that this family was reported by him in the Bull. Sociedade de Medicina e Cirurgiao do Rio de Janeiro, August 25, 1886; and subsequently in the Annals of the Academia de Medicina of that city. Through these reports, not known to other early writers on familial retinoblastoma, he claimed priority in this field.)

van der Hoeve, 1926 (47). The father lost one eye (side not stated) when he was 3 years old. Of his 12 children, the sixth and the eleventh developed bilateral retinoblastomas. The sex of these children was not given in the report.

Syr, 1928 (40). The father was operated upon for glioma of the left eye at the age of 9 months. He recovered, married, and had 4 children. At 27 he died of multiple intracranial new growths, the nature of which was not given. His first child was a stillborn fetus of which the sex was not stated. The second child was a girl who died at about 4 years of age. She had bilateral retinoblastomas, and the father refused to permit operation. The third child, a boy, also had bilateral retinoblastoma and died when about 4 years old. Again the father refused operation. The fourth child, a girl, was apparently normal at 3 years. The author comments that, racially speaking, the father may have been wiser than he himself knew in declining to have the 2 affected children operated upon.

Maher, 1902 (27); Pockley, 1919 (34). Maher reported this family because of multiple examples of "glioma" in one generation. In 1902, the oldest child, a boy, was apparently normal at 8 years of age. The second child, also a boy, had had one eye removed at 18 months and the other when 2 years old. He was surviving at the age of 7 years. A daughter had had both eyes removed at 2 years and was living at 5 years. The fourth child, a girl, was living at 5 years, after removal of the left eye when 1 year old. Pockley reported that the father of his patient had had both eyes removed by Maher and that 2 of the father's sisters had had both eyes removed in infancy. Thus these two reports must refer to the same family. The affected boy survived to marry a woman who was blind in one eye as was also her mother, but there is no evidence that their blindness was due to retinoblastoma. The sex of the child from this union is not stated, nor is information available as to whether one or both eyes were involved. At least one eye was removed since the diagnosis of retinoblastoma was confirmed by microscopical sections. Our diagram utilizes information from both reports.

de Haas, 1916 (11). In 1913 de Haas enucleated the right eye of a child (sex not stated) who had bilateral gliomas. The mother would not consent to the removal of the left eye. The father of de Haas had enucleated the right eye of the father of this child in 1882 for glioma retinae.

Hemmes; Waardenburg, 1932 (50). Waardenburg credits Hemmes with the observation of bilateral retinoblastoma in a girl whose father had survived enucleation for unilateral retinoblastoma. No other data are provided.

Stallard, 1936 (38). From the father in this family the left eye was removed for glioma retinae at the age of 14 months. The nature of the process was confirmed by microscopical examination. The right eye appeared to be similarly affected, but the parents had refused to allow enucleation. At the age of 4 years, he had had a very severe attack of scarlet fever, during which the right eye gradually "cleared." In 1934, when 34 years old, there were irregular pale areas in the eyeground and some additional pigmented disturbances. There was no other evidence of an intraocular neoplasm and no defect in visual acuity. His older son suffered enucleation of the left eye for glioma retinae when 21 years old. The right eye was found at that time to contain a white mass which was diagnosed clinically as glioma retinae. The parents refused enucleation of this remaining eye.
Two sons were born to them, both of whom developed bilateral retinoblastoma when 2 years and 3 months old. Of his children 1 died at birth and 1 was living and well at the time of report. The sex and sequence of these 2 children were not given. Leonard, born in 1919, developed bilateral retinoblastomas which caused his death. Walter, born in 1921, had his right eye enucleated for retinoblastoma at the age of 3 months. He was otherwise well when 7 years old. Ernest, born in 1928, developed retinoblastoma of the right eye which was removed when he was but 2 months old. He was living when the family was reported.

Lange, 1938 (22). (First family.) In 1911 the left eye of a boy, 4 years of age, was removed for tumor when he was 6 months old. His first child was stillborn. The second, George, had his right eye removed in 1914. The age of 6 months; and the left eye was removed in 1917. He died with generalized metastases in 1918. The third child, Mary, developed retinoblastoma of the left eye. Operation was refused and death was attributed to bronchopneumonia. (The child's names were obtained from Fiotta (13).)

Lange described a family which had been reported by Arthur Griffith in 1933. The grandfather and grandmother on the paternal side were free from neoplastic disease of the eyes. A son, born in 1895, suffered enucleation of the left eye when 2 years old. He was thought to have a healed lesion of the right eye. This boy survived, married, and had 5 sons. The first was prematurely born and died at the age of 6 months. The second, 19 years old, at the time of report, showed areas of choroidal and retinal atrophy which Hine believed were sufficiently characteristic to justify an opinion that they represented bilateral healed gliomas. The third son had retinoblastomas of both eyes and died at 21 months. Bilateral enucleations had been done. The fourth son was living at 11 years of age. The left eye was normal. The right had been removed for retinoblastoma, first noted at 3 months. The fifth son died when 4 years old. He had developed bilateral retinoblastoma. One eye was enucleated and the other treated with radon.

Lange, 1938 (22). (Second family.) In 1911 the left eye of a boy, 4 years of age, was removed for retinal glioma. No other disease of the eyes was known in his family. He married a woman whose eyes were normal as were those of her 11 siblings. Two sons were born to them, both of whom developed bilateral retinal glioma, one at 13 years, followed by death, and the other at 4 years. This later child appears to have been living at the time of the report.

Meyer-Riemslagh, 1929 (29). The first-born son developed a neoplasm of the left eye when 6 months old. The eye was removed and the diagnosis of retinal glioma was confirmed by microscopical examination. The father had lost his right eye in 1901, when 3 years of age, because of a glioma.

Lange, 1938 (22). (Second family.) A boy whose parents, grandparents, and 6 siblings were without disease of the eyes, developed retinal glioma of the left eye when 21 months old. The eye was enucleated and he survived to become a parent. Of his 4 children, one boy developed bilateral retinal glioma at 21 months and died. The left eye was enucleated and the right was treated by irradiation. Lange emphasized the fact that in the first generation known to be affected there was every indication that only a "sporadic" example of retinoblastoma was under observation.

Sleight (Weller), 1940. Through the cooperation of Dr. R. D. Sleight of Battle Creek, Michigan, I am able to include an additional example, hitherto unreported, of familial retinoblastoma with the diagnosis verified in two generations and family tradition indicating presence of the disease in two additional preceding generations. If these unproved occurrences can be accepted, this record exceeds by one generation any other as yet published.

Alexander, M., of Austrian extraction but born in Michigan, was seen by Dr. Sleight in 1917 when he was 23 years old and glioma of the left eye was diagnosed. Enucleation was advised but could not be done by Dr. Sleight as he was leaving immediately for military service. About 6 weeks later this eye was removed in the University Hospital at Ann Arbor and microscopical examination confirmed the diagnosis of retinoblastoma. The patient survived and became the father of 2 daughters. The older girl, Jacqueline, had her left eye enucleated for retinoblastoma in 1937, when 10 months old, by Dr. J. O. Wetzel of Lansing. She had been seen at the University Hospital where the diagnosis had been confirmed and operation advised. In July, 1938, the mother wrote the Social Service Department of the Hospital as follows: "Jacqueline had her right eye removed. Now her left eye is affected—she's blind. Youngest daughter, Sherson, 12 months old, also has glioma in her left eye—must be removed immediately." Dr. Sleight subsequently removed the left eye of the second daughter and also saw the first child in the final stage of the disease, enucleation of her second eye having been refused by the parents. Upon medical advice (Dr. Sleight) the mother's third pregnancy was interrupted and the father was sterilized. While the history was being reviewed with the family, Dr. Sleight was told that the father of Alexander (grandfather of the girls) had had one eye removed when he was 3 years old and that his father also had had one eye removed in childhood. No practicable method of verifying this information could be discovered.

**Apparent inheritance of retinoblastoma through an affected female parent.**—Seven families have been found in which the mother of one or more affected children had had retinoblastoma. These are shown diagrammatically in Fig. 4.

Taylor, 1915 (41). Information in respect to this family is extremely meager. In discussing a paper by S. Snell (37), Taylor said that some years before he had removed a child's eye for glioma. The second eye was subsequently involved and he died. The mother of that child had had an eye removed in early life, and he believed that also had been for glioma.

Caspar, 1912 (7). The maternal grandmother in this family had a congenital angiomata of the left upper lid and forehead. Her daughter's left eye was enucleated for retinoblastoma in 1892, when she was 2 years old. She survived and married. From the grandchild the right eye was enucleated in 1911, at 16 months, and found to be filled with retinoblastoma.

Reiser, 1937 (36). The affected mother in this family had her right eye removed at the age of 1 year. Neither among her antecedents and collateral relatives, nor among those of her husband, was another example of ocular neoplasm known. Her son developed retinoblastoma of the left eye, which was removed, but he died later of metastases. A daughter was unaffected at the time of report.

Griffith, 1917 (16). The Smith family. From the mother, who was 22 years old when her first son was found to have retinoblastoma, the right eye had been removed for a growth.
Fig. 2.—Eight families showing apparent inheritance of retinoblastoma through an affected male parent.
Fig. 3.—Six additional families showing apparent inheritance of retinoblastoma through an affected male parent.
at the age of 9 months. The grandmother stated that the mother's eye had been exactly like that of a grandchild and "flushed fire." The children were:

1. John. Seen January 3, 1903, when 5 months old. The left eye was removed for glioma a few days later. In September of the same year the mother found the right eye affected and it was removed shortly thereafter. This child was well until the age of 7 years, when a tumor developed in the right upper jaw and palate. He died 3 weeks later and both kidneys were found to be involved. There was no growth within the skull. (From this it is far from clear that the original neoplasms of the eyes were the cause of death.)

2. Ethel. Twelve years of age at the time of report, with both eyes normal.

3. Lucy. Growth in left eye at 6 months and in right eye at 9 months. Both eyes were removed. She died about 1 year later from measles.

4. William. Both eyes were removed for glioma and he died of this disease at the age of 2 years and 11 months.

5. This child was born dead. The sex was not stated.

6. Mary Elizabeth. Left eye was removed for glioma at 5 months. The right eye was affected shortly thereafter but was not removed. Death from bronchopneumonia at 13 months.

7. Baby, 10 weeks old at time of report. Sex not stated.

Griffith, 1917 (16). The Jones family. From the mother of this family the right eye was removed in 1879, when she was 23 years old. Her first child was stillborn. The second, Doris, had a right-sided enucleation in 1906, when she was 3 years old. She was well at 13 years, with the left eye normal. The third child, George, also required enucleation of the right eye when 3 years old and was well at 12 years of age. In the fourth child, Florence, the disease was bilateral. The right eye was removed when 7 months old and the left at 22 months. This child was surviving at the time of the report, approximately 2 years after the second operation.

Fietta, 1925 (13). Retinoblastoma appeared in the right eyes of a mother and her daughter. From the mother, the right eye was removed at the age of 19 months. She was 36 years old at the time of report. The right eye of the daughter was removed at 22 months for the same condition.

von Hoffmann, 1908 (49); Leber, 1916 (23). When von Hoffmann reported this family he erroneously believed it to be the first account of the occurrence of glioma retinae in successive generations. His father had enucleated the right eye of the mother of his patient about 28 years before, when she was 2 years old. Her son developed bilateral retinoblastoma at 1 year. The author stated that another baby was expected and would be kept under observation. In 1916, Leber provided additional information. "Through the kind cooperation of Dr. von Hoffmann, I have received the following account: Only the right eye of the first child was enucleated and he died at the age of 4 years of cranial metastases. In the second child, also a boy, bilateral glioma retinae was recognized at the age of 4 months. Only one eye was operated upon, and this was only for palliation of pain. Death occurred in 2 years, with cranial metastases. A third child was without evidence of the disease at the age of 7 months." (Translation.)

Apparent inheritance of retinoblastoma through an affected parent, sex not stated.—There is one family which could not be placed in either of the preceding groups since the sex of the affected parent was not stated in the report. This is shown in Fig. 5.

Best, 1934 (5). Details as to sex and sequence of births are lacking. Retinoblastoma was unilateral in a patient who had 6 normal siblings. Therefore this appeared to be a sporadic case, but this individual survived and became the parent of 3 children, 2 of whom had bilateral retinoblastoma.

Apparent inheritance of retinoblastoma through a nondemonstrating male parent.—Four families have been found with retinoblastoma in more than one generation, or in collateral lines, in which the tendency to develop this neoplasm appears to have been transmitted through nondemonstrating male parents. These are shown in diagrams in Fig. 5.

Thom[ps]on and Knapp, 1874 (43); Thompson, 1898 (42). These two reports clearly refer to the same family. Our diagram utilizes information from each account. Definite information is given of a family of 14 children, 7 boys and 7 girls, of whom 2 boys and 3 girls were affected by retinoblastoma. In 1874, only 2 of these 5 had been born. The order of births is not known, except for the order of the affected sex in relation to one another. In 1874 it was stated that a cousin (on the father's side) of the 2 children then affected, had shown a similar condition in the left eye when 2 years old and had died a few months later; and further, that 2 children of the father's aunt had presented similar findings and had died between the ages of 2 and 4 years. By 1898, not only had 3 more children in the original family developed the disease, but further information about one of the collateral lines is given. The mother is quoted: "I did not know my husband's people, but an old lady, who did, told me that a great-aunt died of cancer of the breast, and that she had 3 children [who] had died of cancer of the eyes." This is rather slender hearsay evidence. If the father's great-aunt was meant, it does not accord with the earlier report. If the mother was thinking of her children's great-aunt, the only discrepancy lies in reporting 3 instead of 2 affected individuals in that collateral line.

Steinhaus, 1900 (39). In a sibship of 10 members, the third child, a son, had one eye removed for retinoblastoma when 2 years old (1875). After some months there was recurrence and death. The fifth child, a daughter, also had one eye removed (1877) for retinoblastoma. She survived in good health with the other eye uninvolved, at 25 years of age at the time of report. The sixth child, also a girl, was in a late stage of unilateral retinoblastoma when operated upon at 7 years of age. There was recurrence and death soon after. Of 6 of the sibs, who did not have retinoblastoma, the sex is not stated. The first-born was a son, who did not have retinoblastoma, but his daughter had her left eye enucleated for retinoblastoma (1894) at 4 years of age. At the time of report there had been no recurrence and the right eye was normal. Her brother, when 8 months old (1898), was found to have a small subretinal retinoblastoma of the left eye, which was enucleated. There had been no recurrence at the time of report. It is not stated whether there were other children in this generation.

Hemmès, Waardenburg, 1932 (56). Waardenburg refers to Hemmès for this family but it was not mentioned in the extensive paper on hereditary diseases of the eye which Hemmès published in the preceding year. Data are meager. Four of the 7 siblings of the father were affected. Although a non-demonstrator himself, 4 of his 5 children developed retinoblastoma. Sex and sequence of birth were not given for either generation.

Lukens, 1908 (26). From the patient the left eye was enucleated at the age of 9 months and the right eye at 3 years and 4 months, both for glioma retinae. He was apparently well 1 year later. A cousin on his father's side had died 13 years before and the uncle and aunt recognized the appearance of the eye of the patient as being like that of their own child.
Fig. 4.—Seven families showing apparent inheritance of retinoblastoma through an affected female parent.
Fig. 5.—One family showing apparent inheritance of retinoblastoma through a parent, sex not stated; and 4 families showing apparent inheritance of the tendency to develop retinoblastoma through a nondemonstrating male parent.
Apparent inheritance of retinoblastoma through a nondemonstrating female parent.—Four families have been found with retinoblastoma in more than one generation, or in collateral lines, in which the tendency to develop this neoplasm appears to have been transmitted through nondemonstrating female parents. These are shown in diagrams in Fig. 6.

von Graefe, 1868 (48). Notwithstanding the meager data available, this observation should be included. After mentioning other authors who had seen several examples of glioma in one family and referring to a patient of his own with 2 siblings thus afflicted, von Graefe continued: “Several siblings of the mother of another child [with glioma] had died in the first year of life of eye-cancer.” (Translation.) We know no intraocular neoplasm other than retinoblastoma which could destroy several children in the same family. This case was accepted by Bell. It is judged to be admissible to the group showing transmission through a nondemonstrating female.

Owen, 1905 (32); Berrisford, 1916 (4). The same family was described by Owen and by Berrisford. Although already a very interesting example of familial retinoblastoma on the occasion of the first report, two additional examples of the disease appeared during the following 11 years. Thomas G., the grandfather, developed a neoplasm of the left eye which was removed in 1899 when he was 5 months old. He survived and from his son, Frank, the right eye was removed for retinoblastoma in 1898, at the age of 3 years. Frank’s death resulted from neuritis when he was 15 years old. The daughter of Thomas, Beatrice, had normal vision herself, but of her 8 children, 4 developed retinoblastoma, as follows:

Nellie: bilateral retinoblastoma; both eyes removed; died at 4 years.
Charles: bilateral retinoblastoma; both eyes removed; died at 4 years.
Julia: retinoblastoma of the right eye which was removed; died at 4 years.
Three normal daughters and 1 normal son were next in order of birth.

Gordon: bilateral retinoblastoma; died at age of 34 years.
There are two versions of this family in the reports utilized. The diagram in Fig. 6 and these notes follow the description of this family as given by Berrisford, but in the diagram in his article and the description of the family by Owen differ in that they make Thomas G. a brother, rather than the father of Beatrice; and Frank a nephew of Beatrice, rather than her brother. With either version this family includes 7 cases of retinoblastoma and shows transmission of the trait through a demonstrating male and through a nondemonstrating female. The latter feature, as being of greater interest and possibly of greater genetic significance, determined our grouping of this family.

Townsend, 1939 (44). From the genetic standpoint this is one of the most significant reports in the literature of familial retinoblastoma. In this Negro family, through a nondemonstrating mother, the disease was transmitted, apparently, to 3 daughters by 2 marriages. The first daughter had an enucleation of the right eye for retinoblastoma at 18 months. This was done in 1933 and there was no evidence of recurrence in 1938. The second daughter, by another father, also had a retinoblastoma of the right eye when 18 months old. Enucleation was not done and multiple metastases developed in the skull, brain, facial bones, and right ovary, with death about 18 months later. The third daughter, the second by the second husband, developed retinoblastoma of the right eye in 1938, when 2 years old. Enucleation was done and this child was living at the time of reporting. The author does not state whether there were other children in addition to the 3 girls who were affected.

Purtscher, 1915 (35). This family tree of three generations includes 3 examples of retinoblastoma of the usual type and 2 other individuals with abnormal eye grounds of such a character as to be diagnosed spontaneous retrogression of retinoblastomas. The grandfather died of sarcoma of the upper arm, recurrent in the thoracic wall following amputation. There were 11 children and 5 grandchildren, as follows (the sequence of the children is uncertain in some respects):

Ludmilla: 33 years of age at the time of reporting and married; vision normal. In this branch of the family there were 3 grandchildren, all without evidence of ocular neoplasm. The 2 boys were hypermetropic.
Karl: 32 years of age; eyes normal.
Josefa: 30 years old; unmarried; abnormalities of the eye grounds of both eyes, but more marked in the left eye which was nearly blind. The original diagnosis was choroiditis or neoplasm, but repeated study led to the opinion of spontaneous retrogression of retinoblastomas.
Josef: 29 years old; good vision.
Thomas: traumatic death when 1 year old.
Johanna: 25 years old; unmarried; vision not good.
Ella: 24 years old; married; mother of 2 sons. The first of these, Karl, aged 5 years, had abnormalities of both eye grounds, but more marked in the left eye with which he could count fingers only with difficulty. It was believed that these changes could best be interpreted as due to the spontaneous retrogression of retinoblastomas. Wältier, the second son, developed a retinoblastoma of the left eye when 2½ years old. This caused his death about 9 months later.
Hubert: 23 years old; good vision.
Theresa: 23 years old; unmarried; very good vision.
Engelbert: developed bilateral retinoblastomas when 8 years old, which caused his death at the age of 9½ years.
Ferdinand: found to have bilateral retinoblastomas when 10 months old. These caused his death at the age of 2 years and 8 months.

Summary of families with retinoblastoma in more than one generation or in collateral lines.—In the preceding sections there have been presented, in five categories, 30 families in which retinoblastoma has appeared as a "familial" disease, but in a pattern other than the familiar involvement of siblings alone. In the 30 families there were 102 reasonably well established examples of retinoblastoma and 6 additional doubtful cases. Before discussing the possible genetic significance of this group, attention should be turned to other evidence opposing the view that the observed incidence of retinoblastoma is indicative of an hereditary influence.

Evidence Against an Hereditary Influence in the Etiology of Retinoblastoma

There is a general clinical impression that retinoblastoma is not a familial disease. Except in large clinics, an ophthalmological surgeon will see in a lifetime but few examples of this neoplasm, and most of these will appear as isolated phenomena. Even with careful inquiry into case histories many such cases must be listed as sporadic examples. Thus, among 47 pa-
Fig. 6.—Four families showing apparent inheritance of the tendency to develop retinoblastoma through a nondemonstrating female parent.
tients with retinoblastoma, Adam (1) found no reference to the disease in ancestral or collateral line. There were, however, three pairs of affected siblings.

In the 16 families from which came the 16 cases of retinoblastoma seen in Reiser's (36) clinic in Bonn, there were 64 children, but even in large families of 7, 9, and 16 children there was but the single case. The ancestors of the 16 patients were investigated and in only one instance (Fig. 4) was a second case in the same family found. From such experiences, Reiser was led to oppose the use of retinoblastoma as an example of an inheritable neoplasm. On the average, in his opinion, about 50 per cent of those operated upon survived; and he estimated that more than 1,000 patients, the world over, had had enucleation done for this disease. Many survivors must have married and had children by this time. Yet there are but few examples of familial retinoblastoma.

In a similar manner Keller (21) failed to find the slightest evidence of hereditary transmission in his study of 13 patients with retinoblastoma. There were many children in most of the families from which these afflicted children came. Neither among the siblings nor among the ancestors was another case of retinoblastoma found.

Hemmes (17) gathered as complete information as possible upon the families of 48 patients with retinoblastoma. Not one of the parents had had an eye enucleated. Nine cured cases of unilateral retinoblastoma were older than 25 years at the time of Hemmes' study. Two had become fathers and 2, mothers. There were 9 children in these 4 families, ranging in age from 15 months to 22 years. Not one of the 9 had shown disease of the eyes, but not all of them had passed the retinoblastoma age. The 48 glioma patients had 253 brothers and sisters, born alive. Of these, 31 died before reaching the sixth year of life and 11 were not yet 6 years old at the time of investigation. Eliminating these two groups, the 48 glioma patients had 211 sibs older than 5 years. Not one of these had had an eye removed, and not one of them had died of disease of the eye. Thirty-four of these patients came from families with more than 4 children and altogether this group had 190 sibs older than 5 years.

Further, Hemmes found that 76 sibs of 24 glioma patients had 281 children. Of these, 36 died before reaching the sixth year of life, and 26 died before reaching the sixth year of life and 51 were under 6 years of age at the time of investigation. None had lost an eye, and there was no evidence that any one of them was glomatus.

The parents of 45 of Hemmes' patients were unrelated. Twice they were cousins and one of his patients was born as the result of incest between father and daughter. From these data Hemmes concluded, seemingly with good reason, that as a rule retinoblastoma appears as an isolated example and only occasionally in blood relatives, and that when retinoblastoma appears as an isolated case, it is not justifiable to forbid the later marriage of the patient.

POTENTIAL RECONCILIATION OF EVIDENCE FAVORING AND OPPOSING AN INTRINSIC BASIS FOR RETINOBLASTOMA

It has been shown in the preceding sections that entirely different conclusions as to a possible hereditary basis for retinoblastoma are reached, depending upon the material studied and the methods of analysis which are used. It even appears that there may be two distinct disease entities, familial retinoblastoma and sporadic retinoblastoma. However, it is apparent that these conflicting views are even now subject to partial reconciliation and it is probable that with fuller understanding of the disease they will be unified. No one can say that the victim of apparently sporadic retinoblastoma may not become the originator of familial retinoblastoma if he survives and marries. The first case to be observed in each retinoblastomatous family is of necessity considered sporadic until others appear.

Lenz (24) has shown that in view of the limited number of offspring in each human family apparent "sporadic" occurrence is precisely that which should be expected in recessive inheritance. Assuming families of 4 children each, in every 256 families in which both parents are heterozygous there are to be expected 108 families in which only one child will show the recessive trait. All of these would appear to be sporadic cases. The families in which 2, 3, or 4 children were affected would total 67. Hence the "sporadic" cases would exceed in number the "familial" group. When the number of children per family is less than 4 the number of "sporadic" cases will be relatively greater.

Not only do we need detailed and long-continued observation of the direct and collateral descendants of the apparently sporadic case, but also a record of the ancestors of the first-recognized retinoblastomatous individual in each familial group. Such a study has been made by Lange (22) in reference to the two families charted above his name in Fig. 3. In one of these, the father of 2 children who developed bilateral retinoblastoma had lost his own left eye because of that disease when 4 years old. At that time and until his children were affected, he would have been considered an example of sporadic retinoblastoma, for no eye trouble was known in the family and 11 siblings remained normal. In the second family the father, whose left eye was removed at the age of 21 months for retinoblastoma, would have been placed in the sporadic group, for his grandparents, parents, and 6 siblings were free from this disease. Yet one of his 4 children developed bilateral retinoblastoma. Upon such evidence Lange opposed the opinion that sterilization of the surviving retinoblastomatous child is justified only if there is a family history of retinoblastoma.
In such family histories is found proof that any patient whose retinoblastoma is apparently sporadic may, with survival, become the founder of a family line containing multiple examples of this disease. It may be that only "intensity" of inheritance differentiates familial from sporadic retinoblastoma.

**THE MODE OF INHERITANCE OF RETINOBLASTOMA**

The collected data on familial retinoblastoma give a confused picture when the attempt is made to evaluate mendelian implications. The large proportion of affected children in the familial group (63 of 119 in Leber's (23) series) and the numerous examples of apparent direct transmission of the condition from parent to child speak for dominance and the possibility that a single hereditary factor may be concerned. On the other hand, among the families in which retinoblastoma has appeared in more than one generation and of which the charts are reproduced in this review, 15 instances appeared in which both parents were free of retinoblastoma. This suggests a recessive factor, but the evidence is far from satisfactory since consanguinity appears in but few retinoblastomatous families. Nor does it seem possible that such a recessive factor can be as widespread in the general population as would be required to give both the family reported by Lukens (26) (Fig. 5), in which the mating of a unaffected brothers with unrelated and unaffected women produced retinoblastomatous cousins, and that of Townsend (44) (Fig. 6), in which the mating of an unaffected female with 2 unrelated and unaffected males gave retinoblastomatous children in both instances.

It must be concluded that neither dominance nor recessiveness has been demonstrated for retinoblastoma itself. Such contradictory evidence points to some mechanism which admits of degrees of inheritance. That is, there must be inherited a basic character, probably a somatic variation, which makes retinoblastoma possible but not inevitable. Such a mechanism will provide the intrinsic potential candidates for retinoblastoma who are not demonstrators of the condition.

Others have encountered the same difficulty in attempting to formulate the mode of inheritance. Clausen, (9) in 1924, stated that he considered it very doubtful that two different hereditary mechanisms, perchance one dominant and the other recessive, are operating together in the transmission of retinoblastoma. It is more probable, he wrote, that for the development of this neoplasm some promoting or releasing factor, in addition to other elements, is essential. Actually all that he could state definitely was that in a part of the cases retinoblastoma appears to be hereditary and certainly by both direct and indirect transmission. Hemmes (17), 1931, concluded that if the basis for retinoblastoma is hereditarily dominant, not all of the parents, children, and siblings of his patients would have remained free from the disease; and that it is also improbable that it is always recessive, for in that case the required number of intermarriages between cousins and other close relatives would have been much higher than was actually the case in the population studied. Waardenburg (50), in 1932, concluded that there was evidence for both dominant and recessive inheritance in the production of retinoblastoma and that the unilateral cases suggest the mediation of some disturbing influence in the hereditary mechanism. The numerical proportion between diseased and normal children in the familial examples spoke for dominance but occasional evidences of the influence of consanguinity suggested recessiveness, although the number of such cases was much lower than the theoretical expectation. Best (5), 1934, stated that for glioma and to some extent, for other severe malformations of the eye, Mendel's laws do not apply. One must assume the concomitance of some unknown but hereditarily established derangement which can thwart normal development. Passow (35), in 1916, reproduced the conclusions of Waardenburg and stated that a final decision as to the mode of inheritance could not be given at that time but one could anticipate such information by the certainty that in part of the cases retinoblastoma was determined by heredity and by both direct and indirect transmission.

There is no evidence of sex linkage in the inheritance of the predisposition to retinoblastoma. No significant differences appear in the sex incidence among the demonstrators of the condition or among the non-demonstrating transmitters. The failure to discover definite mendelian implications on the part of all who have investigated the inheritance of retinoblastoma is understandable if a predisposing somatic variation, itself hereditarily determined, capable of varying degrees of intensity and of continuing throughout life without developing malignancy, is assumed. Naturally, it will be very difficult to accumulate morphological evidence that such a variation exists. As early as 1897, Wintersteiner (53) stated that the occasional coincidence of glioma retinæ with coloboma of the iris gave ground for the impression that congenital malformation had something to do with this neoplasm. Fuchs (14) subscribed to this view as the following quotation shows:

> "The primordium for glioma is congenital in all probability. Not infrequently one finds small malformations of various sorts, indeed even very small tumors, which may be looked upon as points of origin for glioma as one studies the territory of the retina in the wider sense in the eyes of children and fetuses."

Clausen (9) summarized the earlier literature on the inheritance of various structural disturbances in the retina, including the occurrence of medullated nerve fibers, familial separation, alleged familial retinal changes associated with arthropathy, amaurotic idiocy, and angiomatosis retinæ.

Inheritable retinal defects are known to occur in laboratory animals. Keeler (20) has found in the house mouse a retinal defect characterized by the absence of the visual cells (rods), absence of the external molecular layer, and reduction of the external nuclear layer to a single layer of nuclei. This defect is inherited as a simple mendelian recessive, without
influence upon viability or upon the sex ratio. All results indicated free segregation between "rodless retina" and a number of other characters which were tested. Bourne, Campbell, and Tansley (6) have described a retinal defect in rats which also is inherited as a mendelian recessive. This defect involves a marked distortion of retinal histology. The authors thought that it might have some bearing on retinitis pigmentosa.

Examples of presumptive preblastomatoid lesions, and of early retinoblastoma, in human eyes have accumulated slowly. Hirschberg (19) described multiple early gliomas as circumscribed masses of round cells in the inner nuclear layer, resembling miliary tubercles. Similar observations have been made by others but origin at other levels has likewise been described. This literature has been reviewed by Ch'in (8) who observed in the left eye of a child, whose death had been caused by retinoblastoma of the right eye, 3 small opaque nodules which could not be considered metastases. He recognized that in the early lesions of retinoblastoma "there is a certain amount of overlapping between 'malformation' and 'neoplasm.'"

Even more significant as suggesting a preblastomatoid structural deviation are the changes in the contralateral eye which, if neoplastic at all, fail to progress and are interpreted as retinitis, choroiditis, or as healed retinoblastoma. In the family reported by Purscher (35) (Fig. 6) there was one individual (Engelbert) who had several small nodules in the partially detached retina of the left eye, with advanced retinoblastoma of the right eye. Structural changes may be found in one or both eyes of nondemonstrating members of retinoblastomatous families. This was true of 2 members of Purscher's family (Josefa and Karl) who each had abnormalities of the eyeballs of both eyes. The original diagnosis was choroiditis or neoplasm but further study led to the opinion that these changes were due to the spontaneous retrogression of retinoblastomas. The fourth child in a family which I have reported in this paper (Fig. 1) belongs in this group. Six of his siblings have developed retinoblastoma. He has no neoplasm but is practically blind in one eye due to structural changes which have been diagnosed "deterioration of the retina."

As a special type of glioblastoma, in the broad sense of the term, retinoblastoma should be found to be related to that group of developmental disturbances and neoplasms of the nervous system which have long been recognized as having some degree of hereditary linkage. In this group are to be found tuberous sclerosis, the glioblastomas and neuroepitheliomas proper, neurofibromatosis, 'molluscum fibrosum,' solitary neurofibromas, meningiomas, and cutaneous neurofibromatous nevi. Some of these, such as the nevi and tuberous sclerosis, have the property of remaining indefinitely in a quiescent state and then suddenly acquiring enhanced proliferative activity and rapidly becoming malignant. van der Hoeve (47) found retinal tumors in several patients with tuberous sclerosis. Some of these contained large cells resembling neurocytes, probably derived from the primitive retinal anlage. The multiple small nodular growths in the retina gave the impression of being developmental lesions rather than true neoplasms. His description of multiple round grayish white nodules in the retina is in full accord with that of the nodules seen in the contralateral eye of some patients with retinoblastoma. van der Hoeve has seen 2 patients with neurofibromatosis (Recklinghausen) who had retinal lesions like those seen with tuberous sclerosis.

Leber (23) credited Elschnig with having brought to his attention a girl of 13 years whose death was caused by an infiltrating cerebral glioma. Ten years previously her 2-year-old sister had undergone enucleation of one eye for retinoblastoma.

In reviewing the reported examples of familial retinoblastoma no reference by name to neurofibromatosis or to related conditions has been found. There are, however, rather frequent references to neoplastic conditions which might belong to this general group.

The grandmother in Caspar's (7) family (Fig. 4) had a congenital "angioma" of the left upper lid and forehead. It is possible that this was a neumatosus nevus. In the Smith family, reported by Griffith (16) (Fig. 4), a child, from whom both eyes had been removed for retinoblastoma by the end of its first year of life, died at 7 years of a tumor thought to have developed in the right upper jaw and palate. There was no growth within the skull. The right eye of Frank G., a member of the family reported by Owen (32) and Berrisford (4) (Fig. 6), was enucleated at 3 years for retinoblastoma. He died of "paralysis" at 15 years of age. The time interval is much too great to suggest metastasis from the eye. This may well have been a manifestation of a glioblastoma. In Purscher's (35) family (Fig. 6), the father's death was caused by a recurrent sarcoma of the upper arm. One can only surmise that this may have arisen in a neurofibroma. The father in Sym's (40) family (Fig. 2), had multiple intracranial new growths when he died at the age of 27 years. His left eye had been removed for retinoblastoma when he was 8 months old. While the evidence now available does not permit statistical proof, it seems probable that such observations are of some significance as indicating a greater prevalence of such neoplasms in retinoblastomatous families than would be expected from chance distribution.

**RELATIONSHIP TO PRACTICAL EUGENICS**

If it is accepted that the predisposition to retinoblastoma is determined to a considerable degree by heredity, certain practical eugenic measures would seem to be indicated:

1. Parents of a child with retinoblastoma should not have additional children.

2. Exenteration, or irradiation, if used as a life-saving procedure in a child with retinoblastoma,
should be accompanied by sterilization. Since any apparently sporadic case may be the founder of a retinoblastomatous family, this principle should be applied to the isolated example as well as to the familial case. Need for sterilization of surviving retinoblastomatous children is much greater now than it was a generation ago when few were operated upon early enough to effect a cure. Reiser (36) opposed sterilization for the sporadic case but this opinion seems not to be based on sound biological considerations.

3. The nondemonstrating members of retinoblastomatous fraternities should be advised of the possibility, by no means remote, that their children may develop retinoblastoma. Parenthood should be discouraged in this group.

Since most cases of retinoblastoma appear to be isolated examples, it may seem that the three principles stated above constitute too harsh a code; or that more evidence should be awaited before fallible human judgment should be invoked in such a manner. Those who have seen the distressing state of a child in the terminal stage of a neglected retinoblastoma, or the dismay of the parent who sees a second child similarly afflicted, will realize that a trial of such methods is indicated. Much less important considerations, offering little or nothing in the way of race betterment or the reduction of human suffering, are today frequently urged and accepted as reasons for avoiding the responsibilities of parenthood.

**SUMMARY**

The extent to which heredity is important must be investigated separately for each neoplastic entity. The multiple occurrences of retinoblastoma in certain families make it a peculiarly suitable neoplasm for such a study. Although actually a very rare neoplasm (1 case in 34,000 living births), retinoblastoma is bilateral in one-fifth of those afflicted and in such patients the involvement of the second eye is to be considered an independent primary neoplasm. In many families retinoblastoma has appeared in more than one-half of the children. Such retinoblastomatous fraternities have long been known, but only recently has it been appreciated that this disease may exhibit also a vertical familial distribution, appearing in successive generations or in collateral lines. Thirty families giving evidence of this type of hereditary influence have been collected. Among these families transmission of the predisposition to retinoblastoma through both male and female, demonstrating and nondemonstrating, parents can be noted. On the other hand, a large majority of the examples of retinoblastoma, observed clinically, appear to be sporadic cases. Evidence is advanced to show the probable relationship between the sporadic and the familial group. The first case to be observed in any family appears to be sporadic.

The available data give no clear-cut evidence that the factor or factors determining predisposition to retinoblastoma behave as do either a simple mendelian dominant or recessive. This clouded picture, together with various other considerations, leads to the belief that a somatic variation, probably a structural anomaly of the retina, is inherited, and that upon this basis retinoblastoma may, or may not, develop. Hereditary retinal anomalies are known for rats and mice and have been observed in the opposite eye in patients with retinoblastoma. They have been seen also in the eyes of patients with tuberous sclerosis and with neurofibromatosis. Retinoblastoma apparently belongs in the same group with these last-mentioned diseases. That such conditions have some hereditary basis and take origin in lesions intermediate between developmental disturbances and true neoplasms is generally accepted.

Having in mind the possibility of racial betterment and the prevention of human suffering, sterilization of any child who survives enucleation or irradiation for retinoblastoma and the interdiction of further progeny to the parents of a child with retinoblastoma appear to be justifiable measures.

**REFERENCES**

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Carl V. Weller

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