The American Journal of Human Genetics

Vol. 12 No. 1 *March 1960*

A Study of Retinoblastoma in Ohio

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INTRODUCTION

IN OCTOBER 1955, an investigation into the frequency of retinoblastoma in Ohio was started. The purpose was fourfold: to find the frequency of the disease; to determine, as closely as possible, the mutation rate; to test the existing estimates of the degree of penetrance; and to express some sort of risk figure for subsequent children in families in which a so-called sporadic case had occurred.

PLAN OF THE STUDY

Methods of securing patients' names. Several methods of attack were used to secure the names of children with the disease. First, the files of the Ohio Department of Vital Statistics for the years beginning January 1, 1940 and ending with December 31, 1955 were searched for *deaths caused* by retinoblastoma. Children born between Jan. 1, 1940 and Dec. 31, 1953 were chosen to derive an estimate of the mutation rate. Since a large percentage of children who develop the disease, do so within the first two years, those who died of it would be found by carrying the search for two years past the 1953 period. Those who did not die of it within that period, or did not die of it at all, would be found through the other methods of ascertainment.

Second, letters were sent to all the *hospitals* in Ohio that were not tuberculosis or mental institutions, requesting the names of all children who had been operated upon for retinoblastoma in the hospital from January 1, 1940 on, together with the names and addresses of the parents. Only those for whom the diagnosis had been based on pathological section were accepted.

Third, similar letters were sent to all the *physicians* in Ohio listed in the American Medical Directory as Ophthalmologists or Eye, Ear and Throat specialists, requesting the names and addresses of their patients who had been treated for the disease.

Fourth, *The State School for the Blind* in Columbus was asked for the names of the pupils who were there or had been there after 1940 and whose blindness was caused by bilateral retinoblastoma.

Finally, the *Ohio Services for the Blind* kindly let us have their records, and in this way we obtained those families who had applied for financial assistance for the treatment of retinoblastoma.

No one method would furnish all the names of the children with the disease

Received June 3, 1959.

who had been born in Ohio during the 14 year period under study. Those who had only unilateral disease would attend a regular school and so not occur on the lists of the School for the Blind. Those who had survived the disease would not be found in the search of the death certificates. Those who had been treated by physicians now deceased or moved from Ohio, or who had been sent to hospitals outside the state would not be found. Those who had not applied for financial assistance would not be obtained from the records of the Ohio Services for the Blind. From each source, therefore, names were obtained that had not been secured from other sources, but in many instances the same family was ascertained in several ways.

There were 152 letters sent to hospitals, and 75 were answered. The majority of those answering were the larger hospitals from which such cases would be expected to be drawn. Fifty-five of the hospitals responding to the questionnaire had no record of retinoblastoma cases for the years under study; 20 had one or more cases whose names and addresses were furnished. There were 357 letters sent to physicians. To both physicians and hospitals a personal and typed letter rather than a mimeographed one was sent, to insure the greatest possible individual attention from the recipient. Of these 357 physicians 191 had either died and their records had been destroyed, or they limited their practice entirely to Otology. Of the remaining 166 physicians, only 60 answered. Of these 29 had never had a case of retinoblastoma, and 31 forwarded the names and addresses of the parents of their patients.

This 36 per cent of those who might have had cases seemed a small return. It was felt, however, that many who did not answer neglected to do so because they had no cases to report, and did not realize that their failure to state this fact minimized the value of the study. This idea was supported, when in 1958, a second set of letters was sent to hospitals and to those who practiced Ophthalmology only, asking for all cases they had ever had if they had not responded to the first appeal, and for all those cases which they had treated before 1940, and after 1955 if they had answered the first letter. Many of the physicians and hospitals who had failed to respond the first time did so the second, either giving new names, or explaining that their lack of response to the first letter had been caused by the fact that they had never had a case of retinoblastoma in their practice. This brought the response of the physicians to about 80 per cent of those to whom the appeal was sent.

Ascertainment. It is certain that not all of the cases occurring in Ohio in those years were found. Nevertheless, the frequency with which a given case was obtained by more than one of the methods of ascertainment listed above gave some assurance that the list of patients secured was comprehensive. Table 1 shows the frequency of ascertainment of those cases which appeared to be sporadic, also of those which gave evidence of other members of the family being similarly affected. An attempt was made to determine how often any one proband *could* have been expected to be recorded in such a survey, and how often they actually were. In the hereditary cases, 9 of a total of 26, or 34.6 per cent were ascertained

TABLE 1. FREQUENCY OF ASCERTAINMENT OF HEREDITARY AND SPORADIC CASES OF RETINOBLASTOMA

	Hereditary Cases				Sporadic Cases				
Observed	1	2	3	4-8	1	2	3	4	5
Expected									
1	3								
2	5	10	2	1	56	15	6	2	
3	1	3	1		16	13	10		1

but once, while in the sporadic cases, 72 of 119 were ascertained but once, a percentage of 60.5. A test for similarity of the two groups from the standpoint of ascertainment gives a χ^2 value of 5.75, $P < .05$.

Although it was assumed that each proband could have been reported by at least one hospital and one physician, some probands were reported by several physicians, and in some instances by several hospitals, because the parents went from one to another in the hope of a better prognosis, or because the child had been operated upon for the condition in one eye in one hospital and for the other eye in another hospital. This makes for a greater number of ascertainments in the case of bilateral disease. In the case of one family, a proband was reported by four physicians, and by four hospitals, thus making 8 ascertainments when two would be expected. For example, a living child with unilateral disease, not applying for financial aid, would have two as the expected number of ascertainments. Death records, school records and Ohio Services for the Blind records would not be applicable. But the same child could have been seen by many physicians and in many hospitals all of which reported the case, thus making the actual number of ascertainments far exceed two. Since bilateral disease is more frequent among the hereditary cases, this helped to increase the number of ascertainments of hereditary retinoblastoma.

After the names and addresses of the parents of the probands were secured, a personal letter was written to each family, asking them to give (1) the names and birthdates of all the children born before and after the proband, (2) any of these children who had any eye trouble, (3) any relationship between the parents, (4) the eye which the tumor had affected if it were unilateral, and any other information that they desired to give. The birthplace of the child was also asked for, since those children born outside of Ohio could be used for some aspects of the study, but not for estimation of the mutation rate of the gene in Ohio. Later a field worker was sent to visit the family to obtain the extensive family history which could be got only by interview. The probands were in almost all instances small children so that the histories were obtained from their parents. Most of these parents were young, and many of their parents in turn were living, hence it was frequently possible to obtain accurate information on the great-grandparents of the probands and on all of their descendants. Because the dis-

ease occurs in the very young as a rule, (although there was one man whose onset was at about 61 years of age), the inquiry into the family history was carried until the last generation was reached. This sometimes involved going down at least two generations beyond the proband until information was forthcoming on all offspring of descendants of the great-grandparents.

All death records of deceased relatives were searched for whether the death occurred in Ohio or in other states, and all living relatives who had reached adulthood were written to for information on themselves, their brothers and sisters, their own children, grandchildren, etc. This involved a great deal of duplication, but it also insured against any relatives having retinoblastoma, and not being recorded. Although this method seemed to snowball into a family history without end, the insistence that the name of every relative, the age, the address, the names of their children and their grandchildren etc. be recorded, paid off in the end. It prevented inaccurate guesses on the part of the relatives, and it linked several families in which the retinoblastoma would have been regarded as sporadic had the usual method of asking merely for other affected relatives been adopted. These cases will be referred to later in the discussion of the individual families.

SPORADIC AND HEREDITARY CASES

The findings in this study were comparable to those in other studies of this disease, in that most of the retinoblastoma cases had no history of parents, sibs or collateral relatives being affected, even after an intensive investigation. Among the cases traced there were 26 probands who were hereditary cases, if by hereditary one designates all those instances in which one or more relatives were affected. There were 119 sporadic cases.

Among the names of probands sent in by physicians or hospitals, there were 19 who for one reason or another were not traced for complete family history. The record had stated in each instance that no family history of the condition was known. There were four cases in which the parents refused to co-operate. Three others were not located, because they had moved, and left no forwarding address. Twelve others were cases where the child had not been born in Ohio, but had come to a hospital in the state for treatment. Of these twelve, eight sent in partial reports, but their homes were too far removed for the field worker to call. The information given on these eight families was as follows.

1. Third of five children, died at 2½ years. Not known if uni- or bilateral.
2. First of two children, died at age 2.
3. First of three children, living. Second died at 2 months, no eye cancer.
4. Third of three children living at age 8 years: bilateral.
5. First of three children, living. Left eye at 4 years.
6. Sixth of seven children, living; unilateral. Last child is now aged 10.
7. First of two children, living, age 20 years; right eye.
8. Seventh of seven children, living at 6 years; left eye.
   The first child in this family has 2 normal children.
   The fourth child died at 1 year of pneumonia.

TABLE 2. LATERALITY OF RETINOBLASTOMA IN HEREDITARY AND SPORADIC CASES

Hereditary					Sporadic				
R	L	Bil.	Uni.	Unk.	R	L	Bil.	Uni.	Unk.
5	6	20*	3	3	35	39	37#	6	2

* 58.8 per cent of known cases bilateral. # 31.6% of known cases bilateral. $\chi^2_{(1)} = 8.38$ $P < .01$.

LATERALITY OF RETINOBLASTOMA

Of the 34 hereditary cases, including probands and their relatives, for whom it was known whether they were uni- or bilateral, 20 or 58.8 per cent were bilateral. Of the 117 sporadic cases, 37, or 31.6 per cent were bilateral. $\chi^2 = 8.38$, $P < .01$ (Table 2). All other workers have found that bilateral disease is much more common among the hereditary than among the sporadic cases. This has led to the belief that at least some of the sporadic cases are caused not by germinal but by somatic mutations, or that they are phenocopies. Of course, some of the unilateral cases may have died from the disease before they had a chance to exhibit their potentiality for developing the disease in the other eye. Or they may have been reported while still unilateral cases, and have become bilateral at some subsequent time. Thus the probands shown in Figures 7, 10 and 14, (V 7) were all unilateral cases at the time their names were reported, but had become bilateral by the time the interview was held, or shortly thereafter. Three of the unilateral cases which were hereditary, (Figures 4 and 5), died sufficiently soon following the operation on the first eye, that the subsequent fate of the second eye remains unknown. The longest time noted in this study between the ages of onset in the two eyes was 51 months. None of these three unilateral cases (Figures 4 and 5) survived this long. One such case, the proband, has lived over four years still unaffected in the second eye. Another unilateral hereditary case (Fig. 15, III-4) has lived for 43 years without the second eye being involved, although his brother and child were both bilateral cases.

In the unilateral cases in which the affected side was known, there were five right and six left in the hereditary series, and 35 right and 39 left in the sporadic group (Table 2).

Survival of Unilateral Versus Bilateral Cases

Although one bilateral case has lived about 51 years after his operation at the age of 2 years, and another has survived about 25 years past his operation at the age of 2, the percentage of bilaterally affected patients who succumb early to the disease is significantly greater than that among those who have but one eye involved. All probands and their affected relatives were listed as to whether they were sporadic or hereditary cases, whether they were uni- or bi-lateral cases, and whether they were dead or alive. Table 3 shows the results. When only one eye was involved about 20 per cent of the people were dead, whether they were sporadic or hereditary cases. When both eyes were affected, 37.8 per cent of the sporadic cases and 50 per cent of the hereditary cases had died. Bilateral cases, therefore, have a much diminished chance of survival, $\chi^2_{(1)} = 8.42$,

TABLE 3. PROBABILITY OF SURVIVAL IN UNILATERAL AND BILATERAL RETINOBLASTOMA

Sporadic				Hereditary			
Unilateral		Bilateral		Unilateral		Bilateral	
Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive
16	64	14	23	3	11	10	10
20.0%		37.8%		21.4%		50.0%	

$P < .01$. Although it would appear that the hereditary bilateral cases have a greater risk of dying than the sporadic bilateral cases, the difference between them is not significant. $\chi^2_{(1)} = .81$, $P > .30$.

PARENTAL AGE

Although one would not expect that parental age would influence the appearance of retinoblastoma of the hereditary type, since the mutation causing these cases always had to occur in a generation before that of the parents of the affected children, it might be thought that parental age could influence the development of unilateral sporadic cases which might be caused by somatic or germinal mutations or which might be phenocopies. The bilateral sporadic cases, which are apparently caused by germinal mutation or are phenocopies, might likewise be affected by parental age. It is conceivable that bilateral cases might be caused by somatic mutations, but it is highly improbable that two identical mutations occur in the two eyes of the child. If the mutation is conceived of as having occurred past the zygote stage but before the embryo has had its bilaterality laid down, the period of occurrence would be very limited. It seems more credible to assume that bilateral cases are not somatic mutations. The cases of retinoblastoma were divided, therefore, into three categories, unilateral sporadic, bilateral sporadic, and hereditary cases, whether uni- or bilateral. The ages of the parents at the birth of their normal and affected children were computed in years and months. The difference in the average ages of mothers at the birth of their normal children and unilaterally or bilaterally affected sporadic cases was much less than the standard error of the difference. There was no significant difference in the average ages when mothers of unilateral and bilateral sporadic cases were compared, or when either of these were compared with the average age of mothers of children with the hereditary type, although the latter was higher than the average age of mothers of the sporadic cases.

When the father's ages were compared, however, some difference did occur. There was no significant difference in the average age of the fathers of unilateral as compared with bilateral sporadic cases, or with the average age of these fathers when they had their normal children but the age of fathers of hereditary cases was much higher than that of fathers of sporadic cases ($t = 3.7$, $P < .001$). This significant difference arose entirely because of one family, in which there were six sibs affected bilaterally, and in which the father was 18 years and 5 months older than the mother. This large difference was entered for each of the six affected sibs as well as for the normal sibs, thus accounting for all of

the excess in the average age of the fathers of hereditary cases as contrasted with the average age of the fathers of sporadic cases. It seems reasonable to conclude that in this series there is no association between parental age and the appearance of the disease.

Falls and Neel (1951) found no significant difference between the parental ages of sporadic and hereditary cases, although the former tended to be higher than the latter. The reverse of this was found in this study.

Place in Family

If parental age shows no effect, it is reasonable to conclude that place in family probably will show no effect. This proved to be the case when the Greenwood-Yule method of determining expected place in the family was used. This agrees with the findings of Falls and Neel.

Consanguinity of Parents

Two of the 145 matings (1.4 per cent) were between related parents. Both instances occurred in the same pedigree (Figures 4 and 5); both resulted in children with retinoblastoma. Many marriages between close relatives occurred in this family, which lived in a small, isolated section of Kentucky. Most of these consanguineous matings did not produce children with retinoblastoma. It is believed, therefore, that the association between the occurrence of the disease and the consanguinity in the parents is fortuitous. One of the marriages producing an affected child was not between related parents. The wife came from a different part of the country. The wife might have also carried the gene, and the whole pedigree could then be explained on the basis of the disease being caused by a recessive gene in this family. The infrequent occurrence of consanguineous matings in other series of cases reported in the literature would lead one to reject that explanation in this family, and to interpret the pedigree as exhibiting a dominant gene with low penetrance.

FREQUENCY IN THE POPULATION

All children who were not born in Ohio in the 17 years under study were excluded in making this estimate. There were 126 children found in this study who were born in Ohio between January 1, 1940 and December 31, 1956, who developed retinoblastoma. Excluding those dying under one year, there were 2,934,247 children born in Ohio during those 17 years. Thus one in every 23,287 children developed the disease. In round figures, it might be stated that 1 in every 25,000 children who survive to the age of one will be likely to develop retinoblastoma in Ohio, if this figure prevails over the coming years.

EMPIRIC RISK FOR FUTURE CHILDREN

This is a matter of some disagreement among workers. Reese (1946) formerly stated that if an adult is affected he advises the patient not to have children because the risk of producing affected children is too great, but that if normal parents have a child with retinoblastoma, he has no hesitancy in advising them

to have more children. In a conversation with Dr. Reese in 1958, he stated that he had materially changed that attitude because he had seen several cases in which normal parents with one affected child had produced other affected offspring.

The question of risk of future affected children has several aspects. One is the question asked by the normal parents who have produced one child with retinoblastoma as to the probability of their future children being affected. The second is the question asked by the affected persons themselves when the matter of their producing children arises. For many, the second question does not arise; the patient has died before the age of reproduction has been reached.

After the first group of cases born between January 1940 and the end of 1953 was investigated, a second set of letters requesting cases before and after those dates was mailed. This was to find persons, from those born before 1940, who had the disease and who had lived and had had children, to determine the number of affected offspring. The response for the names of patients occurring before 1940 was meagre, and of the names furnished, it was almost impossible to trace many of the families from the addresses obtained at that time. Fifteen families whose affected children were born between 1932 and 1940 were traced, however. Only three sporadic cases had married and had children. Two were cooperative and gave their history. They had one normal child each. The third patient may have been cooperative had we been able to obtain her married name and address, but her father, a physician, was adamant in refusing to give us any information about her, her whereabouts, or her children.

Two other families in which parents were affected were traced. This makes a total of four families with two having affected children. Before one can say that the two parents whose offspring are normal are sporadic cases caused by somatic mutations or are phenocopies, one must wait until their families have been completed, and until the children have had a reasonable length of time to develop the disease. If any of their offspring do become affected, one knows that they were hereditary cases. If none become affected, the matter still is unanswered since the parents might belong to families in which the penetrance was low.

Another family in which the person was reported as having unilateral retinoblastoma was so unusual that it was not included. The patient was a man, whose eye was removed at the age of 67 for the disease. Most of his relatives were in Europe, but his four sibs and their children were normal, as were his own four grown children, grandchildren and small great grandchildren.

Several studies have been made on the problem of the frequency of the disease in the offspring of persons who appear to be sporadic cases of the disease. Tucker, Steinberg and Cogan (1957) have recently reviewed the work done on this, and have reported 8 additional families in which a unilaterally affected sporadic case has had children. Two parents had two affected out of three children, the other six had twelve unaffected children past the age of 3, and three others under that age. These authors conclude that on the basis of the scanty data available approximately 25 per cent of the sporadic cases are likely to

transmit the disease to their children, and that when they do, 40 to 50 per cent of their offspring may be affected. They quote Vogel as stating that only 25 per cent of sporadic cases represent mutations, (this author presumes that germinal mutations are meant), and their findings are in agreement.

These authors quote Hemmes as having found four instances in which a person with unilateral involvement had married and produced nine children of whom seven were past the age at which the disease might be expected to develop. All nine were normal. They cite the pedigree of Lange in which a unilaterally affected parent had one of four children affected. These cases indicate the relatively low rate of transmission by sporadic cases.

The request made by Tucker and his co-workers that many centers collect data and publish them in detail is well made. However, unless some identification of the families is possible, the same unusual families may be replicated thus distorting the picture. Although Family 115 of this study is not an instance in which a parent is a sporadic case, it is unusual in that three of five children were affected. This family is being reported for the first time. The children were seen by physicians in Ohio and Michigan who might well choose to report it. A collection of cases from the literature in the future would show three families each with three children affected when there was but one.

It may be that from an accurate compilation of data some more comprehensive understanding of the inheritance of retinoblastoma will emerge, and that a more intelligent answer will be forthcoming to questions of normal parents who have had one child affected, and of affected persons who appear to be sporadic cases, as to future risk. It should be pointed out that, if the degree of penetrance may fall as low as 20 to 30 per cent as seems to have occurred in some of the families in this study, the estimate of Vogel's that only 25 per cent of sporadic cases are mutations will have to be revised. The low degree of penetrance may be responsible for transmission by only 25 per cent of the sporadic cases, who might after all, be largely or entirely caused by mutations.

With respect to the problem of future risk when normal parents have produced one affected child, some information can be gained from the present study. There are 145 sibships in these families in which the parents were normal. In 57 of them, the affected offspring was either the only child or was the last in the family. The fact that some normal children have preceded the affected child gives some assurance that the parents may not have been carrying the gene nonpenetrant. If the family is large, this assurance has more validity; if the family is small, it may mean little. Family 14 (Fig. 7) is a case in point. The mother had had 16 normal children by two husbands before her third marriage. If the gene is a dominant, this meant that there was only one chance in 65,536 that she had the gene and had failed to pass it on. Hence, even with a low degree of penetrance, it was unlikely that she was carrying the gene without the disease showing in some of her children.

There are 88 sibships remaining whose parents were normal. In 6, or 6.8 per cent, the first affected child had been followed by other affected children. If one considers the number of children born after the first affected child in all

the families listed here in which the parents were normal, there were 208 children of whom 14 developed retinoblastoma, or 6.7 per cent. In this series whether one counts sibships or children in whom this disease will be repeated, when the parents are normal, the probabilities are the same, namely, that about one in 15 will develop retinoblastoma after one child has shown the condition.

DESCRIPTION OF PEDIGREES

Penetrance and the mutation rate will be considered after the discussion of the pedigrees. The extent to which the investigation was carried in each of the families is indicated in Table 4. No one was included in this table unless accurate information had been obtained from the person himself, or from his parents, his children or his sibs. If the number of relatives were known, but they could not be traced, they are included with a question mark after them to show that although they were said not to be blind by the proband's family, no verification of this had been possible through direct contact. The anonymity of the families has been preserved, but future investigators of retinoblastoma in Ohio can determine whether their patients have come from one of these probands or his sibs. In Table 4, where the families are listed, an indication of the family surname is furnished by giving the total number of letters in the name followed by the first two letters. The sex, initial, and birthdate of each sib is shown, and the proband is indicated by italic type. For example, if the surname is Black, the family is designated as 5 Bl. If John is the proband and survives, his children, if any, can be studied 25 years hence, and the family history will be known as it exists now. If he has a sister Sheila, who marries a man named Jones, and if they have a child with retinoblastoma, inquiry into her maiden name, her birthdate and names of her sibs, will reveal that she belongs to this family whose history is already known.

The families with more than one affected person are shown in Figures 1–15. They are drawn in skeleton outline only, to reveal the relationships between the affected persons, which are often obscured when all relatives investigated are filled in. When it is obvious through which parent the mutant gene is transmitted, the other parent and all relatives may be omitted. Thus the number of sibs of grandparents, and their descendants shown in the pedigrees may not correspond with the number given in Table 4. In Figure 6, for example (Families 55 and 62) the pedigree shows only two sibs (III-1 & 3), sibs of the grandparents of V-3, but Table 4 lists five. This is because the wife of III-2 and her sibs are not shown. Sometimes the first generation given in the pedigree is not listed in Table 4, but is the last generation in which the mutation could have arisen to have it present in the two or more collateral lines exhibiting the trait.

Family 77 (Figure 1) shows two of three children affected. The father (II-1) was an adopted child who knew nothing of his family. The first child had both eyes removed and died at the age of 19 months. The parents had been assured by the surgeon performing the operation that there was no risk of a second child developing the condition since they were normal. Unfortunately this opti-

mistic attitude was not justified because the second child developed bilateral retinoblastoma also. The left eye was enucleated, but the second received diathermy and TEM treatment.

Family 115 is shown in Figure 2. The entire family tree is presented since it is not known through which parent the gene is transmitted. The disease was bilateral in the brother, unilateral at present in the next child, and unilateral in the third child, born in February 1959, at the age of 3 months.

Family 12 (Figure 3) is the same family as that reported by Sowik (1952). Much more information was secured on the family than is listed in Fig. 3. All six children were probands, ascertained independently, and through several channels. All were bilateral, three have died of the disease. The mother had a small, undeveloped eye in childhood with little vision on that side. According to the view expressed by some ophthalmologists, this might have been a rare example of spontaneously regressing retinoblastoma. The mother refuses to have this eye examined. Sowik stated that the father met any strangers at the door with a shotgun, so the family history was obtained from a brother of the father, and a sister of the mother. Later, the field worker secured an interview with the father.

Family 60 combines the features of sibs as well as collateral relatives being affected. The first contact with the family came through the proband V-5, in Figure 4. The interview revealed that three older sisters had died with the disease. This family came from Kentucky. The death certificates of the three sisters were obtained, and all gave retinoblastoma as the cause of death. The father and mother were related, but they were not sure how, and this was not known until the family was reinvestigated following the finding that a new proband (VI-1) belonged to this family also. IV-2 had been raised by his maternal grandfather after his mother had died in childbirth. He used his grandfather's name rather than his own. He knew that two brothers and a sister of his mother had died at the age of 2 years with the same eye cancer that had afflicted four of his children. He knew of no other instances in the family. The death certificates of his aunt and uncles (III-3, 4 and 5) were found and the cause of death was given as "glioma of the retina", the name formerly applied to retinoblastoma.

While the field worker was in the area in Kentucky in which this family had originated, information was secured on a child that had died with bilateral retinoblastoma, and the maiden name of the mother was the same as the real surname of the father of the four affected children who had been first investigated. The mother denied any relationship to the group of persons shown on the left side of Figure 4. The death certificate of her child was found and the cause of death was given as retinoblastoma.

Later, another proband was found in northern Ohio (Family 63), and many of the names present in his paternal line were also found in the relatives in Family 60. A return trip to Kentucky clarified the situation. Since many persons in this family marry very young, it was possible to interview some of the sisters of II-3, and to establish the relationships between IV-5, VI-1 and the other seven affected persons in Figure 4. This more intensive investigation revealed

TABLE 4. SUMMARY OF INVESTIGATED RELATIVES OF PROBANDS WITH RETINOBLASTOMA*

Fam. No.	Family Name		G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des. P. S. C.	Sibship	Sibs'C
1	5 AD	P	4	2	10	19, 37, 11, 2	+	5	5	9	♂ H. 3/3/41. ♂ *R.* 4/41/45. Rt. at 20	
		M	4	2	1	1, 2	+	3	5		mos. ♂ L. 11/21/53	
2	8 AN	P	4	2	13	48, 20	+	1			♂ R. 7/3/51. ½ bro. by mo. ♂ *D.*	
		M	4	2	15	82, 101, 5	+	5	4		6/15/55. Onset 3 mos. Bilateral at 16 mos.	
3	7 Ba	P	4	2	10	27, 43, 29	+	3	5	5	♂ *L.* 12/18/52; d. 3/12/55. Rt. at 9	
		M	4	2	13	44, 67, 3	+	6	4		mos. ♀ R. 12/21/55	
4	7 Ba	P	4	2	4	16?	+	5	17	5	♀ *Mrs. A.B.* 8/10/37. Le. at 12 mos.	
		M	4	2	12	34, 39, 24, 6	+	5	11	3	Has one son L. 5/1/56. ♂ S.J. 5/ 9/1/41. ♂ R.J. 8/3/43. . . B.J. 6/ 1/45. ♂ T.J. 7/20/49. ♀ C.J. 4/ 11/52	
5	6 Ba	P	4	2	2	4, 2	+	5	5	1	♀ D. 3/15/40. ♂ P. 12/19/46. ♂ *C.*	
		M	4	2	13	35, 61, 16	+	3	6		3/31/52. Bilateral. Rt. at 25 mos. Le. at 46 mos.	
6	7 Ba	P	4	2	20	70, 46	+	7	14	2	♀ V. 8/27/53. ♀ *K.* 9/14/56. Rt. at	
		M	4	2	10	12, 23	+	6	12	4	17 most. ♀ K. 6/14/58	
7	9 Be	P	4	2	1	2, 5	+	1	2		♀ *G.* 3/8/43. Le. at 3 yrs.	
		M	4	2	9	19, 24, 1	+	1				
8	6 Bi	P	4	2	9	17, 15	+	3	2		♂ M. 2/12/48. ♀ *D.* 5/2/50. Le. at 9	
		M	4	2	18	37, 14	+	6	4		mos. Rt. at 5 yrs. ♂ R. 2/5/53	
9	7 Br	P	4	2	10	24, 49, 63, 3	+	4	8	7	♂ *T.* 7/14/47. Le. at 2 yrs. d. at 4	
		M	4	2	8 3?	22, 18	+	10	20		yrs. ♂ J.A. 9/18/49. ♀ P. 7/1/50. ♀ J. 3/20/55	

10	6 Br	P	No information				+	1	2	8	♂ *S.* 7/23/37. Le. at 2 yrs.	
		M	4	2	7	5, 1	+	6	9			
11	5 Bu	P	4	2	12?	?	+	6	13	1	♂ R. 4/27/39. ♂ *D.* 7/?/41, d. 1/44. Rt. at 18 mos. ♀ M.A. 7/25/54.	
		M	4	2	8	28, 93, 43	+	3	18			
12	5 Ca	P	4	2	12	17 (1?), 35 (9?), 26	+	4	6		See Fig. 3 only skeleton pedigree in figure.	
		M	4	2	8 (4?)	12 (8?), 6	+	9	21		♂ *S.* 9/22/29. d. at 39 mos. Bilateral. ♂ *G.* 9/30/31. Bilateral. ♂ C. 7/16/33. ♀ B. 9/28/35. ♀ *G.* 10/19/37. d. 53 mos. Bilateral. ♂ *R.* 6/2/40. d. at 35 mos. Bilateral. ♀ M. 8/6/43. ♂ *E.* 11/8/46. Bilateral. ♂ *J.* 10/24/48. Bilateral. ♀ L. 3/27/49	
13	7 Ca	P	4	2	?		+	3	8		♂ *D.* 8/12/41. Rt. at 18 mos.	
		M	4	2	?		+	7	11			
14	9 Ca	P	4	2	12	37, 85, 23	+	9	20		See Fig. 7.	
		M	4	2	6	14, 33	+	7	21		♂ W. ½ bro. by mo. 6/21/30. d. at 16 mos. ½ sibs by mo.'s 2nd m. ♀ Mrs. D.M. 5/11/32. ♀ A.W. 11/19/33. ♂ J.W. 9/10/35. ♀ E.J.W. 7/13/37. ♂ C.W. 4/9/40. J.W. and G.W. Id. ♂ twins. 5/29/41. d. at 11 mos. ♂ ♀ twins K.W. and K.W. 6/3/42. ♂ d. at 11 yrs. ♀ E.W. 11/9/44. ♀ A.W. 1/17/45. ♂ J.W. 8/13/46. ♀ L.W. 1/13/48. ♀ K.W. 2/5/49. ♀ S.W. 3/11/50. Full sib. by 3rd. m. of mo. ♂ R.C. 12/4/52. ♂ *D.C.* 1/?/54. Eyes removed at 10 and 20 mos.	2

* See page 29 for explanations of abbreviations.

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
15	12 Co P	?	2	8?		+	6	5	3	♂ B. 6/16/47. ♀ *L.* 5/29/49. d. 34 mos. Rt. eye at birth, Le. at 1 yr. ♂ M. 9/21/51. ♂ T. 8/12/55	
	M	4	2	7 (2?)	13, 14	+	3	9			
16	3 Co P	4	2	7	13, 19, 5	+	3	3		♀ M. 10/6/45. ♂ W. 6/26/47. ♀ J. 7/31/48. ♂ *R.* 4/20/51. Rt. at 43 mos.	
	M	4	2	10	28, 46	+	2	6	1		
17	6 Co P	4	2	12	30, 42 (4?)	+	11	9		♂ *T.* 7/20/47. Bilateral at 19 mos. Noted at 2 mos. ♂ D. 12/27/48. 2 st. b.	
	M	4	2	4	8, 9	+	1	2			
18	7 Co P	4	2	12	28, 51, 24	+				♂ N. 3/17/20. ♀ Mrs. M.G. 5/20/16. ♀ Mrs. D.W. 10/15/18. ♀ Mrs. T.W. 9/1/21. ♂ *G.* 1/7/34. Le. at 2 yrs. d. 25 mos.	11
	M	4	2	7	23, 2	+	8	27	38		
19	5 Cr P	4	2	14	65, 13	+	5	3		♂ J. 11/28/53. ♀ V. 2/27/55. ♂ *M.* 1/10/57. d. at 20 mos. Bilateral, at 1 mo.	
	M	4	2	9	15, 4	+	10	5			
20	5 Cr P Negro	No information				+	No information			♀ L. 6/9/45. of ♂ J. 6/4/47. By mo. 1st m. Full sibs by mo. 2nd. m. ♀ *C.* 5/18/50. Le. at 5 yrs. ♀ ♀ G. and G. 7/19/54. ♀ L. 9/13/55. ♀ P. 9/6/56. ♂ J. 12/2/57	
	M	4	2	15 (7?)	19?, 11, 9	+	4	17			
21	6 Cu P	4	2	13	40, 98, 75	+	12	50	6	♂ *J.* 5/18/47. Rt. at 9 mos. ♀ C. 12/29/56	
	M	4	2	9	4, 10	+	6	7			

22	7 Da	P	4	2	1	4, 5	+	3	10		♀ *S.* 11/?/47. Unil. at 2 yrs. d. 42 mos. ♀ E. 1/30/55
		M	4	2	13	35, 54, 9	+	6	8	3	
23	4 De	P	4	2	10	16, 43, 15	+	5	8	2	♀ M. 1/27/47. ♂ *C.* 2/7/50. Rt. at 27 mos.
	See Fig. 13										
		M	4	2	3	12, 22	+	2	2		
24	9 De	P	4	2	6	7, 8	+	1	2		♀ P. 1943. ♀ *K.* 1946. d. at 5 yrs. Le. at 2 yrs. ♂ R. 1953
		M	2	2	?		+	7	13	10	
25	3 Dy	P	4	2	5	8, 6	+	4	3		♀ S. 2/19/47. ♀ *C.J.* 1/27/48. Le. at 6 yrs. ♂ T. 7/25/49. ♀ J. 7/16/50. ♀ E. 9/27/51
		M	4	2	9	25, 19	+	3	6		
26	8 Eb	P	4	2	13	44, 62, 9	+	5	11		½ sib ♂ C. 4/14/41. ♂ *W.* 10/11/51. Le. at 2 mos.
		M	4	2	9	30, 31	+	4	14		
27	10 Ec	P	4	2	14	33, 65	+	7	26	2	♀ C. 9/29/46. ♀ M. 1/4/48. ♂ W. 7/26/54. ♂ *J.* 7/26/55. Le. at 19 mos.
		M	4	2	8	13, 18	+	4	7		
28	5 El	P	4	2	9	36, 80, 34	+	3	9		♀ D. 4/20/41. ♂ K. 3/25/42. ♂ R. 11/22/43. ♀ *J.* 11/7/46. Rt. at 56 mos. ♂ S. 1/13/51
		M	4	2	10	12, 18	+				
29	5 Ev	P	4	2	10	14, 26, 8	+	1	2		♂ J. 4/28/41. ♀ *P.* 6/2/44. Bilateral at 3 yrs. d. 6 yrs. 8 mos.
		M	4	2	8	9, 7, 3	+	3	3	1	
30	5 Ev	P	4	2	12	25, 56, 17	+	6	5		♂ M. 2/14/44. ♂ *T.* 9/18/46. Le. at 51 mos.
		M	4	2	14	27, 31, 2	+	3	3		
31	8 Fe	P	4	2	11 (10?)	4, 8	+	5	10		♀ *A.* 10/30/52. Le. at 26 mos. ♂ *D.* 1/11/54
	Negro										
		M	4	2	9	?	+	3	2		

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
32	8 Fe P	4	2	14	19, 2	+	7	8	1	♀ M. 8/17/37 ♂ M. 8/17/39. ½ sibs by father. Full sibs. ♀ C. 7/29/55. ♂ *R.* 12/21/56. Rt. at 4 wks.	
	M	4	2	10	17, 4	+	6	10			
33	6 Fi P Negro	4	2	12	13, 25	+	5	14		♂ W. 9/22/33. ♂ R. 8/3/38. ♀ J. 9/22/42. ♂ *C.* 11/19/44. Rt. at 4 ½ yrs.	1
	M	4*	2	13 (10?)	12, ?	+	16	?			
34	8 Fo P	4	2	5	1, 3	+	4			♀ R. 1/9/48. ♂ J. 12/26/48. ♂ M. 11/6/50. ♂ M. 11/26/52. ♂ C. 5/16/54. ♂ *R.* 5/26/55. Le. at 23 mos. ♂ T. 11/7/57	
	M	4	2	4	6	+	5	3			
35	8 Fr P	4	2	11	8, 12, more?	+	1	2		♂ *T.* 12/2/41. Bilateral at 5 mos. ♂ R. 2/9/45. ♂ R. 5/9/47	
	M	?	2	14	29?	+	4	10			
36	3 Ga P	No information				+	No information			♂ *A.* 1/13/48. d. 3 yrs. 11 mos. Bilateral	
	M	No information				+	No information				
37	3 Ge P	4	2	6†	24, 51, 39	+	9	11		♂ A. 4/5/33. ♂ G. 12/7/34. ♂ B. 7/29/36. ♂ G. 7/26/39. ♂ D. 3/11/45. ♂ *B.* 2/4/51. Rt. at 18 mos.	3
	M	4	2	11	39 (18?), 44, 10	+	9	16	3, 3		
38	6 Ge P	?	2	7 (2?)	48, 10	+	8	18		♀ S. 12/14/38. ♂ J. 7/25/40. ♀ *M.* 12/22/41. Rt. at 18 mos.	
	M	?	2	?	?	+					
39	5 Ge P	4	2	5	5, 2	+	3	3		♂ *D.* 8/16/41. d. 7 yrs. Bilateral at 5 yrs. ♂ A. 6/?/44. ♂ L. 1/?/48	
	M	4	2	?	1, 1, 5, 2	+	4	6	2		
40	5 Go P See Fig. 11	4	2	16‡	19, 40, 45	+	1	1		♀ C. d. at 4 days. ♀ Mrs. M.H. 11/28/30. ♀ *J.* 11/17/36. d. 4 yrs. Le. at 21 mos. Rt. at 33 mos.	3
	M	4	2	7	39, 50, 90, 42	+	2	3	13§		

41	6 Go See Fig. 15	P	4	2	15	41‖, 74, 25	+	5	4		♂♂ J. and A. 9/7/50. ♂ *D.* 4/8/52. One eye at 8 mos. 2nd. at 3 yrs.	
		M	4	2	11	24, 47, 14	+	8	23	14		
42	8 Gr	P	4	2	13	27, 66, 55	+	2			♂ D. 1/21/47. ♀ *L.* 8/10/49. Le. 13 mos. Rt. X-ray. ♀ D. 7/27/56	
		M	4	2	11	22, 24, 6	+	4	7			
43	5 Gr	P	4	2	9	16, 16	+				♀ D. 9/7/49. ♂ *G.* 4/30/53. Le. at 3 yrs. 8 mos.	
		M	4	2	3	7, 12	+	1	2			
44	6 Ha	P	4	2	8 (3?)	3	+				½ sibs by father. ♂ J. 5/28/47. ♂ J. 12/27/49. ♀ D. 9/28/51. Full sibs. ♂ *E.* 10/7/52. Rt. at 9 mos. ♂ J. 5/28/54. ♀ N. 10/4/55	
		M	4 (2?)	2	1	1	+	1				
45	6 He	P	4	2	8	20, 33, 51, 6	+	2	3	9, 6	½ sib by father. ♂ J. 2/10/21. Full sibs. ♂ G. 5/27/34. ♂ *J.* 3/1/49. Onset 4 mos. Unil.	
		M	4	2	6	8, 6, 6¶	+	4	6	3		
46	6 Ho	P	4	2	7	17, 31, 41	+	4	12	17	♀ Mrs. J.B. 9131. No. ch. ♂ J. 1932. (1 ch.). ♂ G. 1934. ♂ D. 1935. ♀ R. 1936. ♀ M. 8/20/41. ♀ C. 12/25/42. ♂ R. 4/20/44. ♂ J. 6/28/45. ♀ L. 6/18/47. ♀ *A.* 12/1/48. Le. at 9 mos. ♂ K. 3/31/50. Drowned at 17 mos. ♀ K. 3/31/51	1
		M	4	2	7	5, 10	+	6	18	2		

* One had eye removed, age and cause unknown.
† One born with undeveloped eye; same condition present in his children and grandchildren.
‡ ♂ T. d. at 3 yrs. 10 mos. ca. of eye, metastases to skull.
§ One d. of Wilm's tumor.
‖ One said to have died of retinoblastoma at 2 yrs.
¶ 2 in a sibship of 3 have primary optic atrophy and mental retardation.

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
47	7 Jo P See Fig. 14	4 (2?)	2	12 (3?)	16 (8?), 6	+ Rt. 3* at 2 yrs.		6	?	♂ D. 10/7/38. (1 ch.). ♀ C. 10/17/43. ♀ J. 9/23/46. ♀ *J.* 10/14/50.	1♀
	M	4	2	5	8	+	4	14		Rt. at 8 mos. Le. at 6 yrs.	
48	5 Jo P Negro	?	2	15?	?	+	2	2		♀ *L.* 5/13/52. Le. at 18 mos. ♀ A. 12/22/53. ♂ L. 3/55	
	M	?	2	2?	?	+	6	14			
49	6 Jo P	4	2	11	16	+	9	19	7	♂ *R.* 9/3/47. Le. 16 mos. ♀ L. 8/11/54	
	M	4	2	4	8	+	1	2			
50	8 Ju P	4	2	7	9, 11, 5	+	1	2		♂ *D.* Le. at 1 yr. ♂ R. 4/16/57	
	M	4	2	12	17, 32, 6	+	2	4			
51	6 Ka P	4	2	7	7, 10	+	2	4		♀ *A.* 3/5/55. Rt. at 18 mos.	
	M	4	2	11	41 (12?), 12	+	2	3			
52	5 Ke P See Fig. 9	4	2	11	30, 41†	+	6	11		♂ *P.* 2/20/48. Eye rem. age 2. ♂ P. 5/2/51	
	M	4	2	4	7	+	1	3			
53	9 Kl P	?	?	1 (others?)	4	+	4	6		♀ S. 6/29/44. ♀ S. 8/6/47. ♂ *J.* 8/13/49. Le. at 15 mos. of J. 8/16/50. ♂ F. 12/5/52. ♂ R. 12/4/55	
	M	4	2	5	8, 16	+	4	9			
54	4 Ko P	4	2	9	11, 7	+	1			♀ K. 1/2/43. ♂ R. 12/1/44. ♀ *M.* 6/3/48. d age 6 yrs 10 mos. Rt. at 6 yrs. ♂ H. 5/22/51. ♂ T. 10/25/52. ♂ D. 2/27/56	
	M	4	2	2	7, 8, 1	+	10	12			

55	4 Ko See Fig. 6	P	4	2	11	18, 19, 1	+	10	26	3+	♂T. 3/19/42. ♂ *D.* 3/3/47. Le. at 5 ½ yrs. ♂ G. 10/12/48. ♀ D. 12/?/52
		M	4	2	6	6, 3	+	3	3		
56	6 Ko	P	4	2	6	6	+	3	4		♂ *D.* 10/29/55. Bilateral. Rt. at birth, Le. at 9 mos. ♀ K. 5/2/57
		M	4	2	17	62, 43	+	2	1		
57	6 Kr	P	?	2 (1?)	?		+	8	15	6	♂ *R.* 3/14/45. Rt at 5 mos. ♀ S. 7/4/48
		M	?	2	1	2?	+	1	1		
58	8 LaC	P	4	2	7	25, 45	+	7	14	4	♂ D. 6/17/49. ♀ *D.* 1/18/56. Bilateral at 19 mos.
		M	4	2	5	13, 10	+	1			
59	7 Le	P	4	2	6	9, 14, 4	+	4	6	1	♀ *J.* 6/10/39. d at 5 ½ yrs. Le. onset ? ♀ B. st. b. ♂ G. 8/27/47
		M	4	2	4	10, 12, 2	+	4	9	6	
60	6 Lu See Figs. 4 and 5	P	4	2	15‡	50, 88	+				♀ *R.* 10/21/37. d. 2 yrs. Bilateral onset at 15 mos. ♀ D. 7/19/40 d. at 2 yrs. ♀ *H.* 11/12/42. d. 2 ½ yrs. Le. eye. ♂ *K.* 3/29/46. d. 22 mos. Rt. eye. ♀ K. 6/4/47. ♂ F. 5/15/49. ♂ C. 11/8/50. ♂ *G.* 2/10/53. Rt. at 18 mos. ♂ ? /12/?/54
		M	4	2	18	126, 374, 13	+	5	27		
	Over 4,000 relatives of this family have been traced. Only a skeleton pedigree is shown in Figs. 4 and 5.										
61	6 Ly	P	4	2	8	20, 1	+	4	9		♂ J. 2/6/36. ♂ R. 7/27/42. ♂ J. 3/3/48. ♂ *T.* 10/2/52. Rt. at 2 mos. Le. at 22 mos.
		M	4	2	7	20, 16	+	14§	2		

* Bro. of father bilateral, d. age 4 yrs.
† One had unil. retinoblastoma.
‡ 3 died with glioma retinae at 2 yrs.
§ Children of 12 lost track of.

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
62	6 Ma P See Fig. 6 V3	4 (2?)	2	5	19 (7?), 27, 45*, 3	+	9	7	8	♂ H. 6/1/35. ♀ Mrs. F.L. 8/15/36. ♂ L. st. b. ♀ E. 4/10/40. ♂ R. 4/1/41. ♂ A. d. 25 days. ♂ *L.* 7/27/	
	M	4	2	21	46 (4?), 42 some ?	+	6 full 2 half 5?	25		44. d. at 8 yrs. Bilateral at 2 yrs. ♀ I. 12/20/49. ♂ T. 12/29/51	
63	7 Ma P See Figs. 4 and 5	4	2	21	78, 10	+	7	4		♂ *S.* 3/8/55. d. 26 mos. Le. at 2 yrs. ♂ R. 3/7/56	
	M	4	2	15	31, 17, 1	+	4	5			
64	6 Ma P	4	2	7	23, 13	+	8	20	23	♀ M. 1914, d. 1928. ♀ R. 6/12/17 d.	
	M	4	2	19	30, 43, 4	+	6	11	1	1943. ♀ H. 10/3/18. d. 5 mos. of 2/17/21. ♂ C. 11/17/23. ♂ G. 1/30/26. ♀ Mrs. M.S. 2/17/31. ♀ *L.* Mrs. V.G. 1928. ♂ H. 7/12/31. ♀ *L.* 7/16/36. d. 39 mos. Unil. at 29 mos. ♀ Mrs. D.S. 2/21/37	2 4, 4 2
65	7 Me P See Fig. 12	4	2	22	8, 10, 2	+	3	10		♂ R. 4/11/37. ♂ *T.* 8/10/40. Rt. at 2 yrs. ♂ J. 4/15/43. ♀ J. 6/9/44. ♂	
	M	4	2	21	56, 112, 126	+	8	11	2	J. 6/25/46. ♂ T. 6/20/48. ♂ C. 4/12/52	
66	5 Mi P See Fig. 10 10	4	2	9	13, 7	+	1	1		♀ *S.* 3/6/55. Le. at 30 mos.	
	M	4	2	5	12, 3	+	6	4†			
67	5 Mi P	?	2	?	?	+	8	24		♂ *J.* 8/22/45. ♂ E. 10/31/48. ♂ *T.*	
	M	4	2	20	40, 6	+	4	8		8/15/52. Rt. at 27 mos.	

* See Family 55.

† A 1st cousin of the proband also had retinoblastoma.

68	5 Mi	P	4 (2?)	2	3 (some?)	10, 9	+	4	11		♂ R. 9/27/46. ♀ J. 10/30/47. ♂ T. 8/29/50. ♀ A. 6/23/53. ♀ J. 7/9/55 ♂ *W.* 9/23/56. Bilateral at 15 mos.	
		M	?	2	6	14, 11, 4	+	8	4			
69	7 My	P	4	2	7	9, 13	+	3	4	12	♀ Mrs. J.H. 11/30/29. ♂ W. 4/6/31. ♀ Mrs. E.G. 6/27/32. ♀ M. 8/18/34. ♀ *D.* 5/3/38. Le. at 2 mos. ♂ R. 2/14/43. ♂ L. 9/30/49	3
		M	4	2	14	44, 78, 32	+	2	3	2		4, 0
70	6 Mc Negro	P	?	?	?	?	+	?	?		♂ *M.* 7/5/50. d. at 29 mos. Rt. at 2 yrs.	
		M	4	2	4	1	+	6	4			
71	7 Mc	P	4	2	14	23, 7	+	1			½ sis. by father. ♀ B. 7/29/37. ½ sis. by mother. ♀ J. 10/24/41. ♀ M. 5/12/43. ♀ P. 3/3/45. Full sibs. ♂ *D.* 12/18/51. Bilateral at 18 mos.	
		M	4	2	10	15	+	6	9			
72	8 Na	P	?	2	?	?	+	9	8	6	♂ *N.* 2/13/42. Le. at 2 yrs. d. 2 yrs. 7 mos. ♂ R. 7/4/43. ♂ J. 5/29/48. ♂ A. 10/6/50	
		M	?	2	1 (Others?)	3, 4, 1	+	5	7	1		
73	9 Ni	P	4	2	10	22, 14	+	3	6		♂ *R.* 1/31/56. Rt. at 3 mos. ♀ M. 12/7/57	
		M	4	2	5	14	+	4 (half)				
74	5 Og	P	4	2	14	28, 45 (8?), 7	+	3	9	3	♀ *Mrs. M.B.O.* 6/13/37. Unil. at 10 mos. has 1. ch. 5/5/56. ½ bro. by father. ♂ M.B. 6/8/49	
		M	?	2	10 (7?)*	10 (6?)*	+	2	7	1		
75	5 O'N	P	4	2	12	10	+	1			♀ M. 8/17/49. ♀ M. 10/11/51. ♀ M. 10/7/52. ♀ M. 3/20/54. ♂ *K.* 11/28/56. Bilateral at 11 mos.	
		M	4	2	8	29, 54, 3	+	7	19			

* Although not traced, said to have no eye cancer.

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
76	3 Ot P	4	2	8	23, 24	+	5	7		♂ *G.* 1/2/54. Le. at 9 mos. ♂ A. 5/7/55	
	M	4	2	8	14, 5	+	1	2			
77	8 Ov P See Fig. 1.	?	?	?	?	+	?	?		♀ *M.* 8/6/48. Rt. at 13 mos. Le. at 19 mos. d. 26 mos. ♀ *P.* 2/11/51. Bilateral at 11 mos. ♂ W. 8/3/52	
	M	4	2	9	12 (?)*	+	1				
78	8 Ov P	4	2	9	6, 9	+	4	6		♂ G. 7/27/52. ♂ *S.* 9/12/55. Le. at 24 mos.	
	M	4	2	5	10, 6	+	3	6			
79	5 Pe P	4	2	18	51, 63, 1	+	1	2		♀ P. 10/22/40. ♂ *R.* 7/17/46. Bilateral at 7 mos. ♀ 3/21/57	
	M	2	2†	4	4, 2	+	1				
80	5 Pe P	4	2	16 (9?)		+	5	8	7	♀ Mrs. B.H. 3/6/26. ♀ Mrs. D.R. 3/25/27. ♀ J. 7/26/28. ♀ Mrs. J. C. 12/21/31. ♀ *S.* 7/2/32. d. 17 mos. Bilateral. ♂ R. 4/21/33. ♂ R. 6/1/35	3, 6 8 1
	M	4	2	12	49, 94, 104, 5	+	5	15	17		
81	5 Pe P Negro	?	?	?	?	+	?	?	?	♂ J. 8/1/34. ♀ Mrs. E.C. 2/23/36. ♂ B. 8/26/37. ♀ ♀ Mrs. G.S. and *Mrs. M.F.* 8/9/40. Le. at 1 yr. Twins said to be identical. No conf. ♂ V. 9/29/44. ♀ J. 3/7/48	1, 2 2 1, 1
	M	4 (2?)	2	4	29	+					
82	7 Pr P	4	2	7	21, 19	+	1	3		♀ C. 1/31/50. ♀ *L.* 6/12/51. Bilateral at 18 mos. ♀ S. 4/20/53. ♀ C. 10/30/54	
	M	4	2	12	16, 7	+	5				
83	5 Pr P	4	2	13	28 (2?), 32, 16	+	5	4		♀ A. 11/23/45. d. at 3 days. ♂ M. 12/30/46. ♀ *K.* 6/13/49. Le. at 22 mos.	
	M	4	2	6	18, 39, 1	+	2	2			

84	6 Qu	P	4	2	6	46, 3	+	4	2		♀ Mrs. M.R. 8/9/27. ♀ *A.* 10/13/32. Rt. at 8 mos. ♀ J. 9/15/35. ♂ R. 7/9/44
		M	4	2	8	15, 25, 7	+				
85	6 Ra	P	?	2	?	?	+	1	2		½ sibs by mother. ♀ S. 9/5/43. ♀ T. 9/6/46. ♂ M. 10/22/48. ½ sibs by father. ♂ L. 5/10/46. Full sib. ♂ *L.* 11/8/51. d at 25 mos. Bilateral at 20 mos.
		M	4	2	6	6, 4	+	3	2		
86	5 Ra	P	4	2	1	2	+	10			♂ T. 1/48. ♂ D. 4/49. ♂ R. 5/8/50. ♂ D. 1/17/52. ♂ *K.* 8/4/53. Le. 1 mo. ½ sis. by mother. ♀ R. 6/25/56
		M	4	2	4	17, 24	+	2 (half)			
87	7 Ra	P	4	2	20	28, 51, 5	+	7	23		♂ F. 11/24/33. ♀ B. 10/25/36. ♂ C. 2/7/39. ♀ *M.* 6/2/42. d. 3 yrs. Bilateral at 2 yrs. ♂ W. 3/19/45. ♀ E. 10/12/47. d. at 3 yrs. no eye ca. ♂ J. 11/4/48. ♂ R. 3/4/49
		M	4	2	6	9	+	5			
88	6 Re	P	?	2	?	?	+	5	12		♀ *C.* 2/26/47. d 4½ yrs. Bilateral at 20 mos. ♂ F. 12/14/50. ♂ D. 2/20/53
		M	4	2	10	22, 32	+	4	1		
89	6 Rh	P	4	2	8	19, 2	+	8	9	1	♀ *B.* 5/28/38. d 27. mos. Rt. at 17 mos. ♀ S. 3/20/41. ♀ H. 3/13/43. ♂ P. 10/11/54. ♀ M. 7/15/56
		M	?	2	3 (others?)	?	+	6	13		

* Not traced but said not to be blind.

† One an adopted child, no family history.

TABLE 4—*continued*

Fam. No.	Family Name	G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des, P. S. C.	Sibship	Sibs'C
90	4 Ro P	?	2	12?	19?	+	7	22 (2‡)	7 (3‡)	♂ J. 6/19/28. ♂ J. 11/25/30. ♀ Mrs. G.W. 11/19/33. ♀ P. 10/31/38. ♀	
	M	4	2	8	24 (11?), 16	+	8	17 (2‡)	13 (3‡)	V. 2/2/47. ♂ *D.* 11/11/50. Le. at 5 yrs.	
91	5 Ro P	4	2	17	49, 76, 2	+	10	11		♀ M. 1/25/46. ♂ *H.* 3/2/47. Rt. at 3	
	M	4	2	5	1	+	4	6		yrs. 10 mos. ♀ R. 9/16/52	
92	7 Ro P	4	2	7	4	+	1	1		♂ *S.* 6/51. Le. at 39 mos. ♂ J. 6/54.	
	M	4	2	6	18, 27	+	5	11		♀ ♀ J. and J. 1/9/57	
93	4 Ro P	4	2	15	16	+	3	7		♀ C. 6/14/46. ♀ J. 6/25/47. ♂ *R.*	
	M	4 (2?)	2	2	2	+	1	3		10/12/53. Rt. at 2 wks.	
94	5 Ru P Negro	?	2	4 (others?)	2	+	1	?		♀ R. 3/24/43. ♀ M. 12/2/44. ♂ *R.* 7/14/46. Rt. at 8 mos. ♂ D. 12/	
	M	4	2	6	3, 5, 13	+	15	28		14/47. ♀ V. 5/19/54.	
95	5 Sa P	?	2	2	7?	+	7	26		♂ *D.* 2/28/45. Le. at 2 yrs. ♂ R.	
	M	4	2	12	29, 26	+	3	11		5/11/48. ♂ J. 4/28/51. ♂ R. 5/3/ 54. d. 2 days. ♀ M. 6/2/55	
96	7 Sa P	?	2	3	2	+	4	3	3	♂ K. 2/8/41. ♂ R. 9/2/42. ♂ *R.*	
	M	?	2	1	1	+	7	13		1/13/44. Rt. at 46 mos. ♀ S. 9/30/ 48. d. at 9 yrs. no eye ca.	
97	7 Sc P	4	2	12	23, 30	+	4	5		♀ *R.* 1/13/48. Bilateral at 6 mos. ♀	
	M	4 (2?)	2	8 (7?)	4, 1	+	5 (half)	5		B. 12/13/52. ♀ D. 8/26/55	

‡ Double first cousins and children of these. Same as those on maternal side.

98	6 Sc	P	4	2	7		+	2 (half) 1 (full)	4		♀ *K.* 5/17/42. Rt at 3 mos. ♂ F. 9/17/56
		M	4	2	3	11, 10, 3	+	2	6		
99	5 Sc	P	4	2	11	18, 28, 2	+	3	4		♀ *L.* 17/18/47. Le. at 1 yr. ♂ N. 9/28/48
		M	4	2	6 (3?)	19, 12	+	2	3		
100	5 Sc	P	?	2	1 (others?)	6	+	8	16		♀ E. 5/23/40. ♀ S. 11/15/42. ♀ *W.* 6/2/50. d. 38 mos. Le. at 24 mos.
		M	4	2	10	26	+	5	7		
101	7 Sh	P	4	2	12	20, 16, 7	+	3	6		♀ *B.* 12/5/46. d. at 4 yrs. 3 mos. Eye removed at 3 yrs. ♂ D. '48. ♀ J. 8/50. ♂ G. '54. by 2nd husband ♂ M. 9/29/55. by 3rd husband ♂ R. 11/4/56
		M	4	2	13	23, 9, 1, others?	+	7	10		
102	8 Sh	P	4	2	4	1	+	2	3		♀ *R.* 9/30/54. Rt. at 30 mos. ♂ G. 11/16/55. ♂ T. 2/18/58
		M	4	2	12	18, 15	+	1			
103	5 Si	P	?	2	1 (others?)	4 (others?)	+	4	7	6	♂ *N.* 4/25/38. Rt. at 2 yrs. ♂ J. 5/5/42. ♂ R. 3/37/46. ♂ ♀ J. and J. 6/27/53
		M	4 (2?)	2	9	23, 29, 1	+	6	5		
104	8 Sm	P	4	2	12 (9?)	6	+	2	1		♀ *M.* 6/30/43. d. at 3 yrs. Rt. at 15 mos. ♀ T. 6/11/46. ♂ J. 4/19/48. ♀ P. 4/28/49. ♀ S. 12/24/52. ♂ M. 2/1/53
		M	4	2	9 (7?)	5	+	6	5		

TABLE 4—*continued*

Fam. No.	Family Name		G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des. P. S. C.	Sibship	Sibs'C
105	5 Sm	P	4	2	14	68, 113,* 92	+	7	21	5	♀ S. 1/13/50. ♀ *S.* 10/23/51. Rt. at	
		M	4	2	14	61, 48†	+	12	21		51 mos. ♂ J. 5/21/54. ♀ S. 9/30/55	
106	4 So	P	4	2	9	20, 6	+	9	5		♀ C. 9/19/47. ♀ *B.* 11/16/48. Rt. at	
		M	4	2	9	34?, 47?	+	2			2 yrs. Le. at 26 mos. ♂ J. 2/22/49. ♀ S. 1/21/50. ♀ N. 4/24/51	
107	6 So	P	4	2	14	38, 57, 7, 1	+	6	14	7	♀ Mrs. N.B. '30. ♀ Mrs. C.S. '32	1, 2
		M	4	2	?	?	+	1	7		Mrs. A.S. '35. ♂ C. '36. ♂ J. '39. ♀ *J.* 3/14/42. Onset 2 yrs. side?	2, 1
108	9 St.	P	4	2	4	1, 3	+	1			♂ *F.* 3/3/57. Bilateral at 2 wks.	
		M	4	2	4	14, 26, 4	+					
109	5 St	P	4	2	13	6, 6	+	7	10		♀ *L.* 1/28/48. Le. at 32 mos.	
		M	4	2	9	6, 3, 2	+	1	1			
110	7 Te	P	4	2	17	15, 4, others?	+	4	12		♀ J. 5/18/47. ♂ *T.* 9/15/50. Bilat-	
		M	4	2	2	2, 6	+	1			eral at 11 mos. ♂ W. 2/4/53	
111	6 Th	P	4	2	19	28, 49, 6	+	5	17		♀ *P.* 4/18/46. d at 31 mos. Bilateral	
		M	4	2	5	7	+	4	5		at 8 mos. ♂ D. 4/10/47. ♀ V. 7/18/48. ♀ P. 7/11/50	
112	8 Th	P	?	2	3	?	+	8	18		♂ J. 5/5/48. ♂ *D.* 4/26/49. Bilat-	
	Negro										eral at 5 mos.	
		M	4 (2?)	2	5	1, 1	+	3				

113	5 To	P	4	2	11	28, 36	+	5	1		½ sib by father. ♀ P. 10/1/39. ½ sib by mother. ♀ E. 2/2/41. Full sibs. ♂ *J.* 6/20/44. Rt. at 2 yrs. Le. involved. ♀ E. 6/22/46. ♀ J. 3/16/50. ♂ P. 5/1/52	
		M	4	2	6	2	+	1	1			
114	7 Tu	P	4	2	10	28, 45	+	3	5		♀ *C.* 8/25/46. d. 39 mos. Unil. at 2 yrs. ♀ 8/25/51. ♂ L. 11/29/56. ♂ T. 11/8/57	
		M	4	2	9 (7?)	12, 13	+	3	3			
115	3 Ul	P	4	2	11	50, 26	+	8	36	6	♀ D. 8/4/52. ♀ B. 3/8/54. ♂ *R.* 12/21/55. Bilateral at 3 wks. ♀ *S.* 4/11/57. Le. at 3 mos. ♀ *N.* 2/59. Rt. at 3 mos.	
	See Fig. 2.											
		M	4	2	11	41, 27 others?	+-	11	22			
116	11 Van	P	4	2	15 (2?)	47, 54	+	2	2		♀ E. 12/17/47. ♂ *R.* 2/21/51. Rt. at 25 mos.	
	Paternal side not shown in figure. See Fig. 8.											
		M	4	2	8	39, 64	+	3	7			
117	10 Van	P	4	2	12	15, 31, 3	+	4	6		♂ *H.* 5/21/32. d. at 2 yrs. Bilateral, onset? ♀ C. 6/10/36. ♂ K. 1/25/37	
		M	4	2	2	11, 15 (8?)	+	3	6	1		
118	7 Va	P	?	2	?	?	+	1	2		♀ Mrs. J.R. 11/10/28. ♂ L. 8/23/30. ♀ D. 10/24/32. ♀ R. 4/37. ♀ *V.* 1/21/51. Rt. at 4 yrs.	2
		M	?	2	?	?	+	9	11	7		
119	5 Vi	P	?	2	?	?	+	1	4	1	♀ J. 2/8/40. ♀ *J.* 8/13/45. Le. at 14 mos.	
		M	?	2	5	4, 3, 4	+	8	12			
120	4 Wa	P	?	2	?	?	+				♀ '50. ♀ '51. ♀ *E.* '52. Unil. at 2 yrs. ♀ '53	
	Negro											
		M	4	2	?	?	+	9 half				

* An additional unknown number not traced.

TABLE 4—*Continued*

Fam. No.	Family No.		G. G. P.	Gr. P.	Gr. P. S.	Des. Gr. P. S.	Par.	P. S.	P. S. C.	Des P. S. C.	Sibship	Sibs'C
121	6 Wa	P	4	2	9	28, 38	+	3	6		♀ *J.* 9/25/37. d. at 4 yrs. Rt. at 3 yrs. ♀ C. 3/7/41. ♀ J. 8/4/42. ♂ R. 12/30/43. ♀ M. 4/17/46. ♀ N. 5/3/47. ♂ J. 2/14/50. ♀ C. 1/25/52	
		M	4	2	10	27, 42, 50, 6	+	4	8	2		
122	5 Wa	P	4	2	11	19, 17, 2	+				♂ T. 1/7/38. ♀ K. 4/18/43. ♀ *S.* 11/27/45. Le. at 8 mos.	
		M	4	2	6	16, 1	+					
123	7 We	P	4	2	17	9	+	1	2		♂ J. 1/8/42. ♂ R. 8/11/43. ♀ *L.* 2/2/46. Unil. at 21 mos.	
		M	4	2	4	4, 4	+					
124	5 Wh	P	4	2	11	7, 17	+	1			♂ M. 7/7/52. ♂ *R.* 8/20/53. Bilateral at 6 wks.	
		M	4 (2?)	2	5	3, 8	+	9	21			
125	6 Wi	P	4	2	10 (4?)	16, 36	+	3 full 4 half	41	11	♂ L. 6/23/42. ♂ *S.* 11/9/44. d. at 41 mos. Bilateral. ♂ D. 11/22/46. ♀ L. 3/3/48. ♂ D. 3/17/51. ♀ P. 6/3/53. ♂ R. 12/8/55	
		M	4	2	9	48, 25 (9?)	+	8	23	4		
126	6 Wi	P	4	2	12	44, 90, 17	+	5	16	2	♀ J. 3/11/49. ♂ *E.* 1/6/51. Le. at 40 mos. ♂ S. 6/6/55	
		M	4	2	10	32, 53	+					
127	7 Wi	P	4	2	22	50, 115, 36	+	5	9		½ sibs by father. ♀ ♀ S. and N. 4/3/44. Full sibs. ♀ *D.* 7/20/50. Eye removed at 5 mos. ♂ D. 1/1/55	
		M	4	2	16	24, 39 (3?), 13 (3?)	+	6	8			
128	7 Wi	P	4	2	9	21, 45	+	2	5		♀ D. 8/13/55. ♀ *D.* 2/16/57. Rt at 6 wks.	
		M	4	2	6	39, 30	+	1				
129	7 Wi	P	4	2	6	12, 19	+	4	13		♂ K. 2/28/51. ♂ D. 2/24/53. ♂ *W.* 5/25/54. Le. at 3 yrs.	
		M	4	2			+	5	5			

130	5 Wo Negro	P	?	2	3 (others?)	1 (others?)	+	4			♂ D. 9/1/44. ♀ *L.* 6/25/52. Rt. at 20 mos. Le. at 4 yrs. Rhabdomyosarcoma knee at 5 yrs. ♂ F. 3/38/55	
		M	4	2	4		+	16	20	5		
131	4 Wo	P	?	2	10	40?	+	5	11		♀ Mrs. C.F. 9/21/30. ♂ *A.* 11/29/35. Bilateral at 14 mos.	3
		M	?	2	5?	7, 14	+	4	5	5		
132	5 Wo	P	4 (2?)	2	2	8, 15, 12	+	2	1		♂ M. 5/31/54. ♀ *N.* 3/23/56. Rt. at 13 mos. Le. at 16 mos.	
		M	4	2	9	16 (9?)	+	8	21			
133	7 Wo	P	4	2	13	15, 21, 1	+	5	11	4	♀ Mrs. T.P. 8/28/36. ♀ J. '37. d. 2 mos. ♂ T. 9/30/39. ♂ D. 5/9/41. ♂ D. 3/28/43. ♂ M. 1/10/49. ♀ *R.* 8/15/53. Rt. at 22 mos.	1
		M	4	2	18	56*, 41, 16	+	5	12			
134	6 Wr	P	4	2	6 (3?)	6, 11 (5?)	+				♂ *D.* 2/11/47. Le. ♂ C. 12/25/48. ♂ G. 7/12/51. ♂ M. 2/12/53	
		M	4	2	10	35, 67, 9	+	3	8			
135	5 Yo	P	4	2	11	30, 57	+	3	4		♀ *C.* 8/2/52. Rt. at 25 mos.	
		M	4	2	15	52, 50	+	2	3			

* Nothing known of descendents of 31.

Explanation of Abbreviations in Table 4

Family Name. The numerals before the letters indicate the number of letters in the surname. The letters are the first two of the name. Thus 5 Bl would stand for Black, Blank, etc.

G. G. P. = great grandparents. *Gr. P.* = grand parents. *Gr. P. S.* = sibs of the grandparents. *Des. Gr. P. S.* = descendants of sibs of the grandparents, with the numbers indicating the number of relatives traced in subsequent generations. *Par.* + = parent contacted. *P. S.* = sibs of parent. *P. S. C.* = children of parent's sibs or first cousins. *Des. P. S. C.* = descendants of first cousins. *P* = paternal relatives. *M.* = maternal relatives. *Sibs'C.* = Sibs' children.

Sibship. ♂ H. a brother whose name begins with H. It is followed by his birthdate. ♂ *R.* a proband, name beginning with R.

12 (8?) = 12 persons, 8 of them not traced. Blank spaces mean that there are no relatives in that category. Families with no ? and no statement that there is no information are complete for all relatives. Number of relatives in the table will most often not be the same as in the figures, which have been drawn as skeleton outlines to make the relationships and number of relatives carrying the gene non-penetrant clear.

further interesting facts about this family. The mother of I-2 in Fig. 4 was a sister of I-4 in Fig. 5. This meant that all four lines of affected relatives were descended from three families, the Lu, the Bl and the St lines, the mother of I-2 in Fig. 4 being an St. It was also shown that all four affected lines were likewise descended from another family whose surname was Ma. Now the relationship between IV-1 and 2 in Figure 4 became clear. This new relationship is shown in Figure 5, where all known consanguineous marriages in the Ma line are indicated by double mating lines.

Only a small part of this family has been traced, although over 4000 relatives have been written to, or interviewed personally, or their parents have been interviewed. Figure 5 shows that IV-1 was descended from one of two Ma brothers. Her husband (IV-2) descended from the other brother, (I-6) on the paternal side, and from a woman who was said to be their sister on his maternal side. Since this relationship is not certain, no vertical line is drawn from the sibship line of I-1 and 2. Her maiden name, however, was the same as their surname. I-6 in Fig. 5 had two wives, and 33 legitimate children and at least 4 illegitimate children who were known to his grandchildren.

The names and some of the descendants of eight of the legitimate children were secured, but they are not shown in Figure 5 since no retinoblastoma was found among them. Three of the legitimate sons and some of their descendants are shown, although again many descendants have been omitted because of no evidence of the disease. This family would make one suspect that there are two genetically different retinoblastomas, the gene being dominant in most families, but recessive in this one. The objection to such an interpretation is that the proband VI-1 in Fig. 5 is not the product of a consanguineous mating. If this family exhibits a recessively inherited condition, V-9 would have to be heterozygous. Most workers agree that retinoblastoma is not a recessive trait, therefore, the recessive gene, if it exists, must be extremely rare. It is highly improbable that a man from a family in which this very rare gene should have already exhibited itself should marry a woman carrying the same gene. It is not impossible, but is less probable than the likelihood that the gene in this family exhibits varying degrees of penetrance, being highly penetrant in two of the four affected sibships, but poorly penetrant in most of the family and in one sibship in which only one of eight children showed the disease.

Families 55 and 62 are shown in Figure 6. Both V-3 and VI-7 were probands in separate families. Neither set of parents knew of the other affected proband. The death certificates of III-3 and III-2 showed that they were brother and sister. This family illustrates the value of obtaining death certificates of all relatives even though they were known not to have the disease in question.

Family 14 is shown in Figure 7. It is one in which a seemingly sporadic case was found to have an affected relative. VI-5 was the original proband. The mother had had one illegitimate child, (the dotted line in the figure should have extended from the dotted mating line) then 15 others by her first legal husband, and then two by her second husband. The second child of the third union developed retinoblastoma. In investigating the father's family (the mother's was

also searched for), there was no evidence of any other child with the same condition. While in Kentucky, trying to find the family of IV-5 in Figure 4, the field worker encountered the grandmother of VII-4 in Figure 7. She had heard that this woman had a grandchild who had died with the disease. Inquiry into the family history showed that there was no relationship to the Lu Family. The family history of the grandchild was collected as a new project after the death certificate was located, stating that the child had died of bilateral retinoblastoma. As the inquiry proceeded, it became evident that the grandmother of the woman being interviewed was the sister of the grandfather of the third husband in the Ohio Family 14. No other cases in either Kentucky or Ohio were found in this family. At the time that the family of the first proband was being traced, the author felt certain that if a collateral line was discovered to have the disease, it would be on the father's side, since the mother had already had 17 opportunities of passing on a gene which she might have been carrying nonpenetrant, and had failed to do so. The finding of the second case here was chance, since it was further removed from the original proband than the investigations usually went.

Family 116 is shown in Figure 8. Here two second cousins have the disease, one bilaterally, the other in the right eye. The mother (IV-2) of the proband stated that two of her cousins each had a child with retinoblastoma. Correspondence with the other branches of the family secured the pathological diagnosis of retinoblastoma in V-4, but the family of V-9 refused to answer. Finally the

DESCRIPTION OF FIGURES

In all figures, squares are males; circles, females. A completely black symbol shows bilateral involvement, a half black symbol a unilaterally affected person, either right or left eye affected. Symbols with figures inside represent a total of that many normal persons. Pedigrees seldom include the full number of relatives investigated, since this is shown in Table 4. When the side of the family through which the gene is transmitted is known, the other side of the family may not be shown at all, although given in full in Table 4. The pedigree is reduced to its simplest outline to make relationships obvious.

The generation numbers in the table do not necessarily correspond to the generation numbers in the pedigrees, which were drawn in most cases to show the latest generation in which the mutation could have occurred in order to be reproduced in the affected persons. This was for ease in counting the number of persons through whom the gene passed nonpenetrant. The first generation in the pedigrees may be one on which no information was secured.

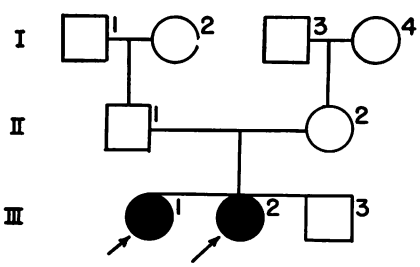

FIGURE 1. Fam. 77. Two sibs affected. Paternal side of family unknown father being an adopted child. Generation I in figure the latest in which mutation could have occurred.

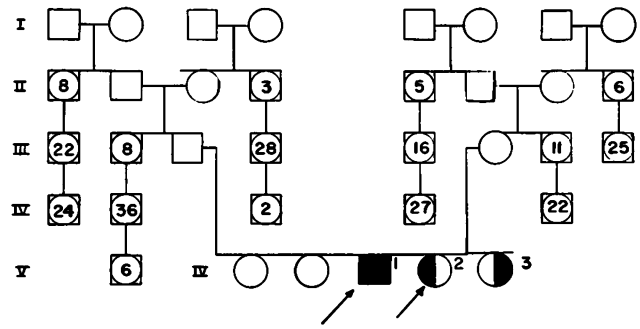

FIGURE 2. Fam. 115. Two affected sibs at time of interview. A fifth child, born in Feb. 1959, showed retinoblastoma in right eye in May 1959.

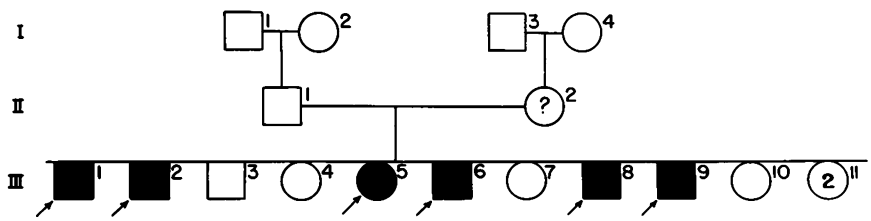

FIGURE 3. Fam. 12. Six in a sibship of ten affected with bilateral disease. Two miscarriages. Mother has microphthalmic eye, no vision, refuses examination. Generation I latest generation in which mutation could have occurred.

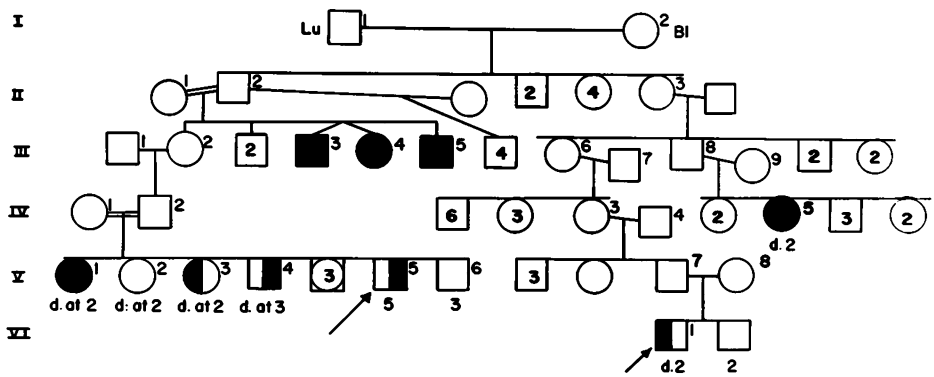

FIGURE 4. Fam. 60 and 63. All four affected sibships are descended from the Lu, and Bl, the Ma and the St lines, I-2's mother being an St. II-1 and -2 are first cousins once removed, I-1 being first cousin to I-2. IV-1 and -2 are third cousins through the Ma line, shown in Figure 5. Over 4000 relatives of the four affected sibships have been traced, but no other affected persons have been discovered.

field worker was sent to southern Tennessee, and found the family, and obtained the pathological diagnosis on V-9. It proved to be glioma of the pons, not retinoblastoma. This is represented by a cross hatched square in the pedigree.

Family 52 is represented in Figure 9. The mother's side of the family is re-

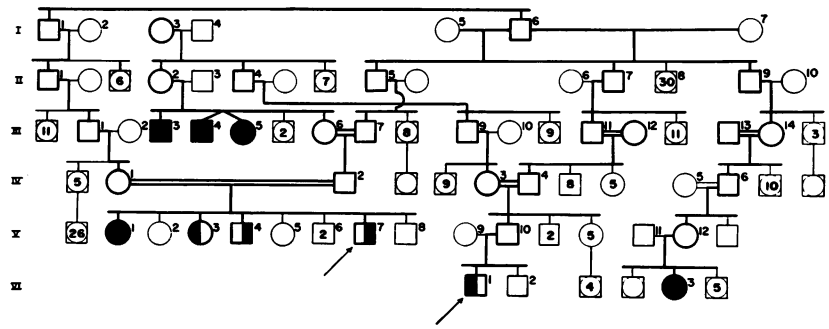

FIGURE 5. Fam. 60 and 63. The relationships are now traced through the Ma line, descent in this line being shown in heavy black lines. I-3 was an Ma, probably a sister of I-1 and I-6. Related parents are joined by a double mating line. Fully a third of the matings in this family are between persons related through one of the four lines from whom all affected children are descended. It has been impossible to show that the four lines all stem from a common ancestor.

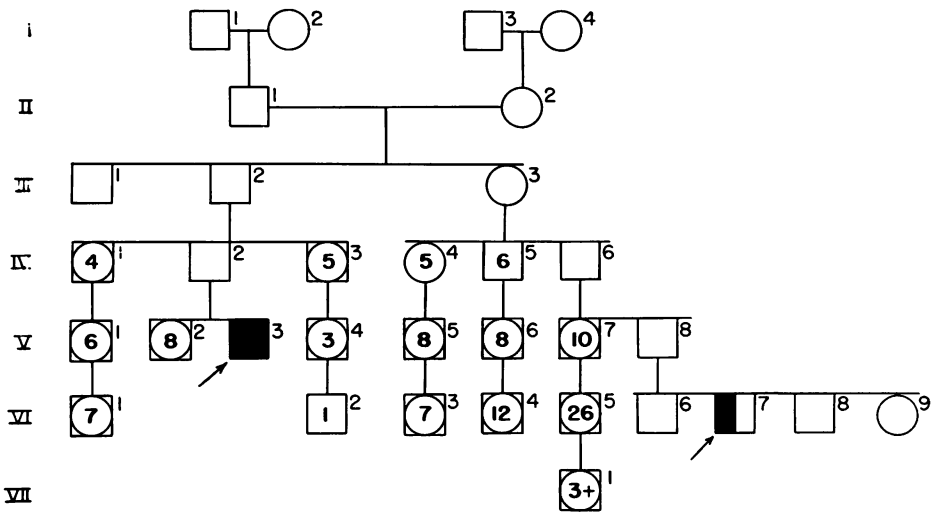

FIGURE 6. Fam. 55 and 62. The probands were in two families not known to be related at the time of the interview.

corded in Table 4. The proband was the first of two children, and no other case was known in the family. A second case was uncovered in a second cousin of the proband. This child had been operated upon for unilateral retinoblastoma some months before. Again what appeared to be a sporadic case proved to be one that was probably inherited.

Family 67 is shown in Figure 10. Two sisters each have produced a child with retinoblastoma. Both children were secured as probands from the hospital in which they were treated. The complete family history is given in Table 4. Neither husband was related to his wife, and they were not related to each other.

III-5 reported that her sister's boy who had been a unilateral case at the

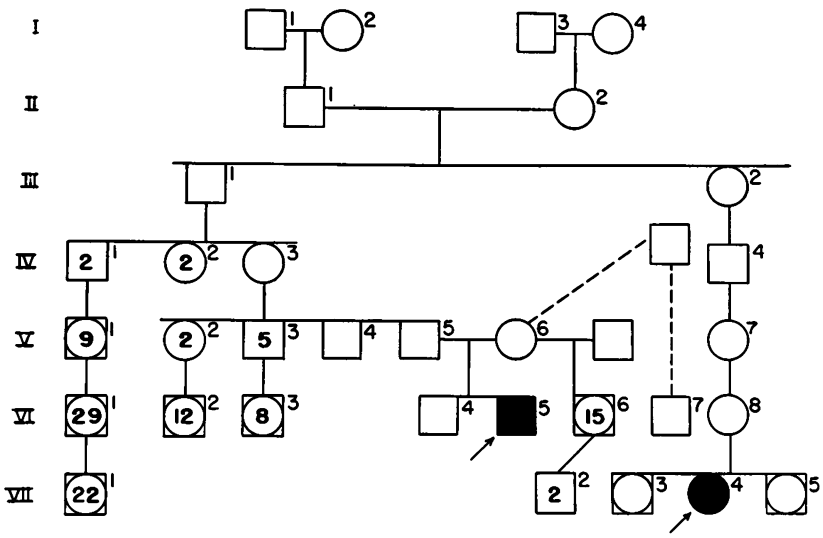

FIGURE 7. Fam. 14. VI-5 was the Ohio proband. VII-4, unknown to the parents of VI-5, was accidentally discovered in Kentucky. The dotted vertical line should have come from the dotted mating line, rather than from the father.

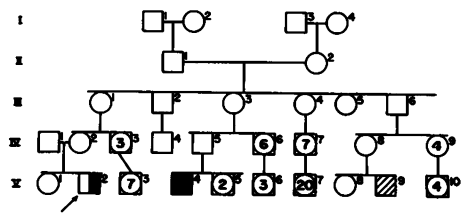

FIGURE 8. Fam. 116. The cross hatched square represents a second cousin of the proband who died of glioma of the pons.

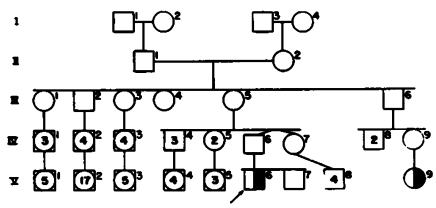

FIGURE 9. Family 52. The parents of the affected children were unaware of the disease in their cousin's child.

time of interview had developed the disease in the other eye, and was given only a few months to live.

Family 40 is shown in Figure 11. The father's maternal uncle was affected. A death certificate was obtained stating that he had died at the age of two years following an operation for cancer of the eye. Again a seemingly sporadic case proved to be otherwise, if one accepts the most probable explanation of this death certificate.

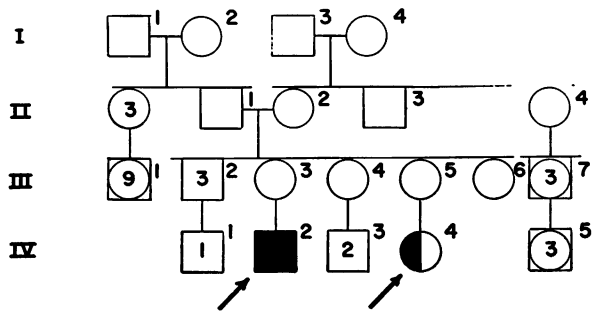

FIGURE 10. The pedigrees of the two fathers of the affected cousins are not shown, nor is the family history of the father of IV-2 recorded in Table 4, since the gene was obviously being carried by the two mothers who were sisters. Family 67.

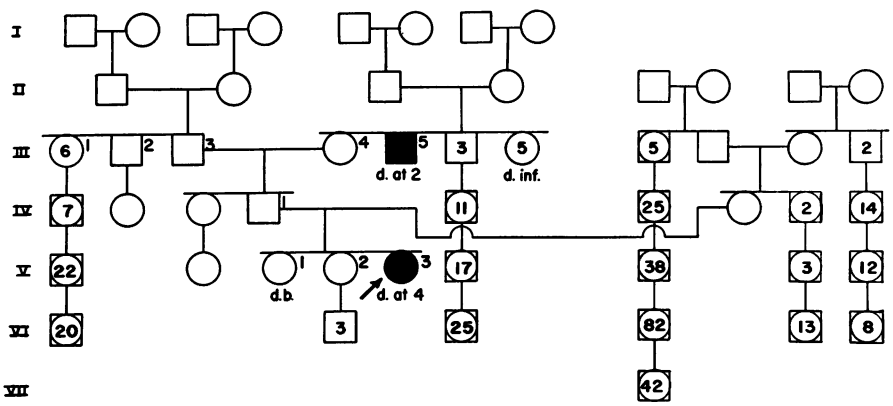

FIGURE 11. Family 40. The proband was first considered to be a sporadic case until her father's maternal uncle was found to have died of cancer of the eye.

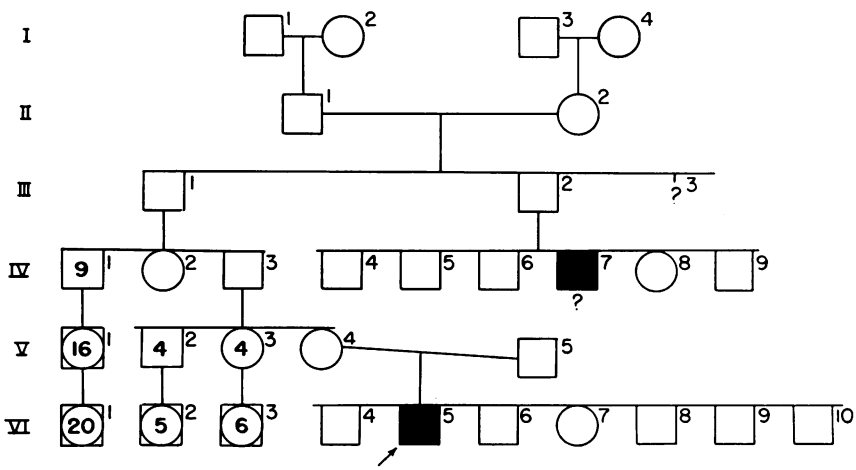

FIGURE 12. Family 65. Diagnosis on IV-7 not confirmed. Family reported eye cancer with death in early childhood in this boy.

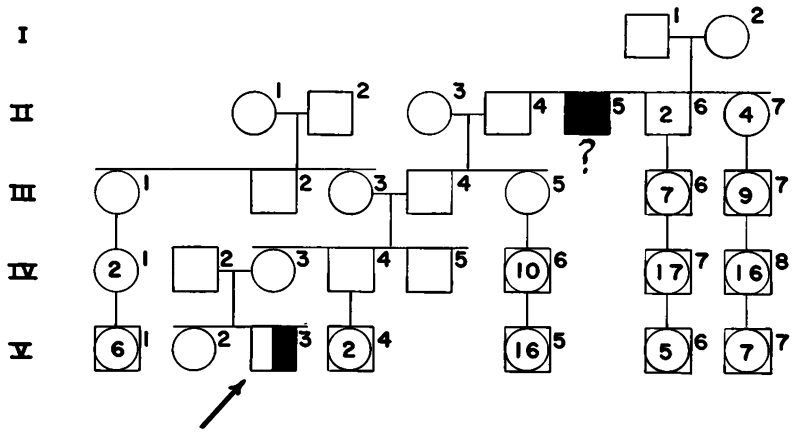

FIGURE 13. Fam. 23. Diagnosis on II-5 not confirmed. Family Bible stated that this child died at the age of 2 after removal of the eyes for cancer.

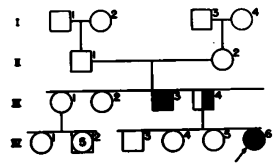

FIGURE 14. Fam. 47. III-4, although a hereditary case, has remained a unilateral one for 43 years.

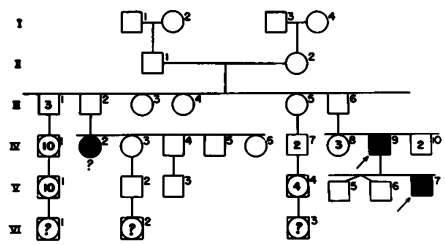

FIGURE 15. Fam. 41. IV-9 was obtained as a proband after his daughter had been found. IV-2 is an unconfirmed case, although all her sibs state that she died at the age of 2 after bilateral enucleation of the eyes for cancer.

Family 65 is shown in Figure 12. This may or may not be an example of an inherited disease, since a confirmation of the diagnosis on IV-7 could not be obtained. IV-2, an aunt of the proband's mother, stated that her father's brother had a son with a very large tumor of the eyes when he was a small child, that "His eyes hung out over his cheeks, they were so swollen, and that he died around the age of two." No death certificate could be found and the physician treating the child was long since dead.

Family 23 (Figure 13) was regarded as representing a sporadic case when a second call for other information upon a paternal aunt of the proband's mother elicited the fact that some of her living uncles had a family Bible with records

in it. This led to further investigation into lines not ordinarily studied because of lack of knowledge of these more remote relatives on the part of the living members of the family. The record stated that a brother of the mother's paternal grandfather had died at the age of four after removal of the eyes for cancer. There is no confirmation that this was a case of retinoblastoma, hence it has been queried in the figure. The age at which the disease occurred, the fact that the eyes had to be removed, and the appearance of the disease in a relative make it quite probable that it was retinoblastoma.

The next two families are the only ones in which parents of the probands were also affected. Figure 14 shows a small part of the paternal side of Family 47. III-3 was an older brother of the proband's father who had died at the age of 4 with bilateral disease existing since the age of two. The father's right eye only was affected; he had survived for 43 years without the other eye becoming diseased. At the time of his marriage he had consulted a physician who assured him that this was not a hereditary case, despite the fact that he had an older brother who died of it. His fourth child had bilateral retinoblastoma.

Family 41 (Figure 15), was another instance of father and child affected. The father was ascertained independently after the daughter had been found. His paternal cousin died at the age of two, but it has been impossible to obtain a death certificate or a record of her operation. The remaining sibs in the family (IV-3–6) all state that their sister died with cancer of the eyes after having been operated upon by a Columbus surgeon, who has long been dead, and whose office records were destroyed many years ago. This may or may not be a true case of retinoblastoma.

PENETRANCE

The problem of penetrance is linked with that of mutation rate, since the lower the penetrance the lower the mutation rate may be. If the gene is almost fully penetrant each sporadic case that is bilateral and some of the unilateral cases will be apt to be dependent upon a germinal mutation. If the gene has a low penetrance many cases may appear to be sporadic that are not so, hence they will increase the estimated mutation rate. The degree of penetrance assigned to the gene for retinoblastoma has varied from 78 per cent (Franceschetti) to 98.5 (Neel and Falls). Neel gives a formula for arriving at a rough estimate for failure of penetrance. First one deducts all families in which a parent is affected. Then one takes the ratio of index cases with affected sibs to all index cases, both sporadic and with sibs affected. In his data there were 58 families with 64 sibships. In five of these the parent was affected. In four of the remaining 59 sibships with normal parents there were affected sibs. The final result was 1/67 or .015 for failure of penetrance, making the degree of penetrance 98.5. He thinks that this estimate may be a little high and that the degree of penetrance may be nearer to 95 per cent.

If this method is applied literally to the present study, calling those cases sporadic in which neither a parent nor a sib is affected, although other collateral branches are affected, one finds that there would be 130 cases listed as

sporadic, and eleven index cases found in four families where other sibs are affected. The figure for non-penetrance would be 11/141, or 7.8 per cent. If, on the other hand, one contrasts the families that appear to be truly sporadic with those in whom some relative not a parent is affected, the present series furnishes 22 hereditary cases against a total of 141, giving a percentage of non-penetrance of 15.6.

Inspection of the families whose pedigrees are shown in Figures 1 through 15 would lead one to question penetrance as high as 95 per cent. An ideal method, if it were possible, would be to determine all those who carried the gene and all those who carried the gene and showed the disease, and to estimate from these figures the degree of penetrance. Unfortunately, one usually does not know how many persons have carried the gene before it becomes evident as the disease in the sporadic cases. One can determine, when two or more collateral branches of a family are affected, what must be the minimal number of persons through whom the gene must have been transmitted if the two affected persons are considered as bearers of the same mutant gene. It is possible that in a rare instance two persons supposed to have derivatives of the same mutant gene from some common ancestor, are, in fact, instances of independent mutations. That this should occur as frequently as it appears to have done in this group of families seems to be most improbable.

In Figures 1 and 2 the gene must have passed non-penetrant through at least one person to have appeared in two offspring. Similarly, it must have been non-penetrant in at least one person to have appeared in six offspring in Figure 3. In Figure 4 it must have mutated at the latest in a parent of I-1 or I-2 to have been present in segregating form in either I-1 or I-2. If then one counts the number of persons through whom it passed in order to show up in the four collateral lines, and if one assumes that on the average it should appear in half the offspring of a parent carrying the gene, we have 30 carriers of the gene but only nine showed it, making the penetrance 30 per cent. If it is assumed that the sibs of the carriers should not be included, it went non-penetrant through nine persons to show up in nine, a penetrance of 50 per cent.

Studying the family from Figure 5 as if the gene had descended not through the Lu, the Bl or the St lines, but through the Ma line one finds that the number of persons through whom the gene went non-penetrant to be evident in nine persons varies from 37 to over 40, if the half of the sibs of carriers are regarded as carrying the gene also. It has been pointed out that two of the four sets of parents of affected offspring are related, but although as shown in Figure 4, II-1 and 2 are related as far as the St line is concerned, they do not appear to be related if the gene was transmitted through the Ma line. The affected sibship of four (V-1–8) comes from the Ma line through the mother, and from the Ma line through the father's father and mother. The degree of penetrance in this family, if the gene is to be regarded as a dominant, and if the four sibships are not to be thought of as caused by independent mutations, ranges from below 25 to about 30 per cent.

If all the families shown in the figures are counted, omitting Figure 5 which deals with the same family as Figure 4, and if the number of affected and

normal sibs are counted in each sibship in which an affected child occurs, one finds 44 affected children plus two who had to be carriers and 88 sibs who were normal. This gives a penetrance of 34.3 per cent, a figure much lower than that reported by other workers. Using the Yates correction in estimating $\chi^2_{(1)}$ gives a value of 12.54 ($P < .001$) if it is calculated on the basis of full penetrance, and a value of 5.74 ($P < .02$) if only 90 per cent penetrance is expected.

If the estimate of penetrance is made from those normal sibs who must have been carriers in order that the mutant gene from a common ancestor appear in two collateral lines, the degree of penetrance is much lower. In four families, the gene may have been transmitted from either the paternal or maternal line, thus making a different number of sibs to be counted as normal. Using the maximal number of sibs it was found that there were 37 who had to be carriers and 163 who were normal, making a penetrance of 18.5 per cent. If the minimal number of sibs is used there were 37 carriers and 148 normal sibs, giving a penetrance figure of 20.0 per cent.

It would appear that in the families in which some estimate of penetrance is possible the average figure is very much lower than that advanced by other workers. The degree of penetrance of any partially penetrant gene in man must have rather ill-defined limits, since the genetic background in which the gene operates is different in all families and in individuals within a family except in the case of identical multiple births. In this series, the gene was probably fully penetrant (if a dominant) in Family 12 in the sibship, and also in sibships of three and four affected in Family 60, while being markedly reduced in penetrance in the rest of Family 60. The average degree of penetrance deduced from one author's series of cases may well differ from the average in another author's series, not only because of the extent to which the family history is investigated, but because the degree of penetrance is a variable with a wide range.

If this investigation had stopped where many of the studies of this type do terminate, namely with the grandparents, parents, aunts, uncles, cousins and sibs of the affected child, the only families listed as showing hereditary retinoblastoma would have been those in Figures 1, 2, 3, part of Figures 4 and 5, with the two single sibs each being counted as sporadic cases, Figures 8, 10, 14 and 15. Twelve cases listed in the figures would have been classed as sporadic instances of the disease.

It is impossible to state what factors make the gene so highly penetrant in some families, and so low in penetrance in others. Despite the low degree of penetrance, and the fact that a large percentage of families continue to produce more children without their developing the disease, the tragedy to the child whose case may be bilateral, should the parents persist in having more children after one has become affected, would appear to justify counselling the cessation of child-bearing on the part of the parents, and to advise those affected cases, who live to maturity, to refrain from producing offspring.

MUTATION RATE

Several estimates of the mutation rate for retinoblastoma have been made. Philip and Sorsby (cited by Falls and Neel 1951) estimated that it was 1.4×10^{-5}

for England; Neel and Falls (1951) that it was about 2.3×10^{-5} for Michigan, with 95 per cent confidence intervals of 1.7 to 3.1×10^{-5}. Vogel's (1954) estimate was much less, being $.4 \times 10^{-5}$. If one considers that all the sporadic cases are examples of germinal mutation, the estimated mutation rate will be high. On the other hand, if one believes that many of the seemingly sporadic cases are such because the degree of penetrance is low, and that the germinal mutation has probably occurred some generations earlier rather than in the germ cells which made up the population under study, the estimated rate will be much lower. It is difficult, if not impossible, to decide which sporadic cases, especially the unilateral ones, may be germinal mutations, and which may be somatic mutations or phenocopies. Because the bilateral cases are much more frequent among the hereditary group, it is usually assumed that the bilateral sporadic cases are germinal mutations. It is possible to set two arbitrary limits to the mutation rate in a given population; the highest being obtained by counting all sporadic cases as germinal mutations, the lowest by counting only the bilateral sporadic cases.

It is quite evident that some unilateral cases belong in the hereditary group whether as germinal mutations occurring in the germ cell of an unaffected parent, or as the result of previous mutations some generations earlier, because persons who have remained affected in only one eye have reached maturity, married and produced bilaterally or unilaterally affected offspring. It is reasonable, therefore, to conclude that some of the unilateral sporadic cases are in truth germinal mutations, not somatic mutations, nor phenocopies. When one considers that a somatic mutation, to become evident as the disease, must arise in the cells of the organ which can show the disease, it is amazing that somatic mutations for retinoblastoma should arise so frequently in the cells of the retina that they are more numerous than the hereditary cases, in which the mutation is limited to a germ cell.

In estimating the possible mutation rate in Ohio, all hereditary cases had to be discarded, since the mutation did not involve the germ cells which made up the present population. All sporadic cases which were born outside the state of Ohio had to be excluded. The mutation rates might be different for the white and Negro races, so that the number of births and the number of retinoblastoma cases in the two groups had to be treated separately. Although the plan at the beginning of the study embraced only the years from 1940 through 1953, the number of cases found after that, and the delay in preparing the study for publication permitted the years 1954, 55 and 56 to be included. This gave two and a half years after the end of 1956 for children born in that year to develop the disease.

The children dying under one year of age are not likely to have had the disease and to have died of it, so that the number of deaths under one year was deducted from the total number of births for the year, to estimate the number of children in whom the disease might appear.

During the 17 years under study there were 2,720,929 white children born in Ohio who lived as long as one year. There were 92 white children born in Ohio who appeared to be sporadic cases, and whose names had been encountered. This,

of course, was a minimal number, since not all such cases might have been found, although probably a very large percentage was obtained. This means that one in every 59,150 genes was mutating, or a rate of 1.60×10^{-5}. Similarly, there were 213,318 Negro children born during those years, who lived to be more than one year old. Among this group, 11 children with sporadic retinoblastoma were encountered. One in every 38,785 genes was mutating, a rate of 2.58×10^{-5}. Combining the two groups, the total mutation rate was 1.76×10^{-5}.

The mutation rate was higher among the Negro race than among the white. One explanation may be that the mutation rate is higher; another might be that physicians might not hesitate to send in names of clinicals cases, among which all the Negro children in this group would fall, while they might not be so likely to send in the names of private patients who might resent their names being given for a research project. Falls and Neel (1951) found the mutation rate somewhat less in the Negro than in the white.

If only the bliateral cases are considered, there were 33 of the 37 sporadic bilateral cases that were white, and 4 that were Negro. The mutation rate based on these figures would be 6.1×10^{-6} for white, and 9.4×10^{-6} for Negro. The combined rate is $.63 \times 10^{-5}$. This is doubtless too low. The real value probably lies somewhere between the first and second estimates given.

Fifty-eight point eight per cent of the hereditary cases were bilateral. If this figure is accepted as typical of this series and if one assumes that no non-hereditary cases are bilateral, one would expect that, in a group of 117 sporadic cases, the proportion of bilateral cases could vary between 58.8 per cent $\pm 2 \times 4.55$ per cent, the latter figure being standard error of the proportion. This gives upper and lower limits of 67.9 and 49.7 per cent of bilateral cases which could reasonably be expected among genetically determined sporadic cases. Thirty-seven bilateral cases were found among the sporadic instances of the disease. Equating 37 first to 67.9 per cent; second, to 49.7 per cent, gives a range of 55 to 74 of the 117 cases that might reasonably be expected to be hereditary, hence caused by germinal mutations. These figures give mutation rates of $.94 \times 10^{-5}$ and 1.26×10^{-5} respectively. The range of mutation rates runs from 1.76×10^{-5} when all sporadic cases are considered, to only $.63 \times 10^{-5}$ when only bilateral cases are considered, with 1.26 and .94 (both $\times 10^{-5}$) as intermediate estimates. The highest estimate is within the lowest range of Neel and Fall's figures for Michigan, (1.7×10^{-5}), and the lowest is not remote from Vogel's estimate ($.4 \times 10^{-5}$). Vogel's estimate is based upon an almost exclusively white population, while the combined rate here is for white and Negro, the latter having an appreciably higher rate. If one considers only the percentage of those sporadic cases which live who produce offspring showing the disease, the estimated mutation rate would be much lower. In this series there have been four affected persons who lived to reproduce. One in Family 47 was not a sporadic case since his brother also had the disease. A second in Family 41 thought himself to be a sporadic case since it was the investigation carried on by this study that uncovered the unconfirmed case in a cousin. Accepting him as a sporadic case, as he might have

been accepted in many studies, he produced an affected child. Two other cases, both unilateral, see Families 4 and 74 have married and each has had one child, neither of whom was affected at the time of the interview. The child in Family 4 was 13 months old two years ago, and the child in Family 74 was normal at 2½ years. The net result is that from among the 134 families interviewed in which the parents either were, or thought they were, sporadic cases three affected parents at the most have produced children, and only one of these, so far, has produced *affected* children.

The conclusion from this necessarily incomplete estimation of the mutation rate of the gene for retinoblastoma in Ohio is that it is much lower than that found by Neel and Falls in Michigan, and that this in turn is largely dependent upon the lower penetrance rate found existing among these Ohio families, which in turn may depend, in part at least, on the more intensive efforts expended in this study to trace antecedents as far as possible.

SUMMARY

A study of as complete a roster as possible of children born in Ohio in a 17 year period, and who developed retinoblastoma, was made. In 119 of 133 families, the disease appeared to be sporadic, despite intensive investigation into the family history. Hereditary cases (those in which sibs, parents or collateral lines were similarly affected) were significantly more often bilateral than were the sporadic cases. Bilateral cases have a much higher risk of dying with the disease. Only two instances of consanguinity were found. The degree of penetrance varies widely not only in different families but in different sibships in the same family. The families here presented indicate that the degree of penetrance may range as low as 20 per cent. The estimated mutation rate is of necessity most tentative, ranging for the total population from 1.76×10^{-5} to $.63 \times 10^{-5}$, depending upon whether all sporadic cases, or only bilateral sporadic cases are interpreted as germinal mutations. The rate for Negroes is higher than it is for the white race. The risk of sporadic cases producing affected children cannot be determined from the very small number of such cases in this study. The risk of normal parents producing more than one affected sib depends upon one's method in determining the risk. In this study, the ratio of families in which normal parents produced more than one affected sib to all families of normal parents producing any affected sibs was one in 15.

ACKNOWLEDGMENTS

1. This work was sponsored by a grant from the Department of Health, Education and Welfare, Field Investigations and Demonstrations Branch, from 1956 through May 1959.

2. The author desires to express her gratitude to those physicians and hospitals who so generously responded to requests for names of patients, and to the Director of the Columbus School for the Blind and to the Directress for the Ohio Services to the Blind for their co-operation.

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