THE PRACTICAL MANAGEMENT OF RETINOBLASTOMA*

BY *Robert M. Ellsworth*, M.D.

RETINOBLASTOMA IS A HIGHLY MALIGNANT congenital tumor arising multicentrically in one or both retinas. It usually remains confined to the eye for a relatively long period of time, but then may metastasize rapidly by a variety of routes and is almost invariably fatal if untreated.

The following material is based on an experience with 900 cases of retinoblastoma seen through 1968 at the Institute of Ophthalmology of the Columbia-Presbyterian Medical Center in New York.

INCIDENCE

FREQUENCY

Our cases are useless for a computation of frequency since we draw patients from an undefinable population base. There are numerous, well studied population groups in the literature reporting a frequency varying from one in 17,000 new births to one in 34,000 new births.[1–10] A recent suggestion[11] that retinoblastoma is increasing in frequency around the world is not proved by the data presented, but would seem to be a reasonable expectation for at least one reason. As more patients with retinoblastoma survive the disease and grow into adulthood to produce children of their own, the gene frequency in the general population will certainly increase. It is a reasonable guess that the frequency of retinoblastoma might double over the next hundred years due to this factor. The ultimate cause of retinoblastoma is just as unknown as the ultimate cause of any other spontaneous mutation. In an age in which we can expect higher radiation exposure, however, basic mutation pressure could well increase.

*From the Institute of Ophthalmology of the Presbyterian Hospital, and the College of Physicians and Surgeons, Columbia University, New York, N.Y.

TR. AM. OPHTH. SOC., vol. 67, 1969

AGE

The average age at the time of diagnosis in our series was eighteen months. In two cases, the disease was present at birth. Our oldest patient was 34 years of age. In the latter case, spontaneous regressions were present in both eyes and the diagnosis was made certain by the fact that this woman produced children with retinoblastoma by two different husbands. In the literature the oldest cases reported have been 48 years,[12,13] 52 years,[14] 53 years,[15] and 62 years old.[16] When retinoblastoma is suspected in an adult on the basis of ophthalmoscopic examination, it would seem irrelevant to remove that eye to establish a diagnosis, if useful vision were present. If a patient survives retinoblastoma to adulthood, the factors governing spontaneous regression would seem very well in command of the situation and it is hard to imagine that a tumor at that age would pose any threat to life.

SEX

While several series in the literature suggest a slight preponderance in males, there has been no sex predilection in our series.

RACE

It has been reported that this disease is rarer in Negroes than in Caucasians, but there are no hard figures to substantiate this and it is our feeling that there is no racial predilection.

"Clustering" has been noted both in the literature and in our series, and the occurrence of numerous cases in one area over a brief period of time can suggest racial preference. This phenomenon of clustering deserves attention for it could someday suggest an etiologic clue.

BILATERALITY

Although most cases of retinoblastoma are unilateral, it is the bilateral cases that present problems in management. Various authors have estimated the incidence of bilaterality to vary from 20–35 per cent. A figure of 30 per cent is consistent with our experience. Over 80 per cent of the cases currently seen have bilateral retinoblastoma, but this bias is unquestionably explained by our interest in the treatment of this disease.

HEREDITY

In a given family line, the tumor originally arises as a spontaneous mutation. Ambient radiation may be a theoretical cause and we have

quizzed mothers of retinoblastomic children about possible irradiation, especially to the abdomen during the period of gestation, and have not found any positive correlation. There is no evidence that the age of the mother or the rank of birth is of any importance. It has been reported that retinoblastoma is more common in the last born child, but this may well be explained by voluntary birth control.

The first involved patient in a family is termed a "sporadic" case and may be either unilaterally or bilaterally affected. It has often been observed that patients with bilateral disease transmit the disease to their progeny much more frequently than those affected unilaterally[19] and this has led to the concept that unilateral cases may frequently represent somatic rather than germinal mutation. It is uncommon in medicine to find a tumor produced by both somatic and germinal mutation so that there is no particular precedent for this notion. There is absolutely no doubt that many unilateral sporadic cases are germinal mutations as proved by the subsequent pedigree.

It would seem more logical to consider all retinoblastomas as germinal mutations and to postulate that the manifestation or penetrance may vary from individual to individual or from family to family. If a single enzymatic defect is responsible, it is possible that associated genes on the involved chromosome may modify the effect of the defective gene by providing alternative metabolic pathways, thereby circumventing the faulty biochemical reaction.

In the earlier series, the manifestation of this gene was estimated at 80 per cent[17] to 95 per cent.[3] It has been suggested more recently that in certain families the degree of manifestation may be as low as 20 per cent.[18] A dramatic variability in manifestation from less than 20 per cent to nearly 100 per cent in different families fits well with our experience.

The pedigrees of our familial cases have not been previously published and are appended as a reservoir for future calculations. Only 8 per cent of all cases seen present a family history of the disease.

Kitchin[31] has analyzed our data in considerable detail and has noted that manifestation may vary with the clinical presentation (Table 1). These cases were ascertained from an involved child and, therefore, there were no families with no affected children. This bias was corrected by the Fisher method, but the small numbers led to a considerable standard error. In an effort to lower this, our data were combined with Hemmes'[6] series and again corrected by Fisher's method (Table 2). While the standard error remains large, variable manifestation seems certain.

TABLE 1. VARIABLE MANIFESTATION IN FAMILIES WITH RETINOBLASTOMA

Clinical presentation	Manifestation (%)	Standard error (%)
Bilaterally affected parent	89	22.5
Unilaterally affected parent	54	17.9
Normal parent with 2 or more affected children	48	26.1
Carrier parent	39	15.9

TABLE 2. COMBINED ESTIMATE WITH HEMMES SERIES

Clinical presentation	Manifestation (%)	Standard error (%)
Bilaterally affected parent	99	16.9
Unilaterally affected parent	56	14.8

In an effort to verify this truncate distribution, an unbiased series was assembled by polling survivors of bilateral retinoblastoma who had lived to have children. Out of 70 such survivors of reproductive age, five were located with a total of five children. These cases were combined with ten other survivors in the literature (Table 3). The data in Table 3 reinforce the inference that sporadic bilateral retinoblastoma is a germinal mutation with nearly 100 per cent manifestation.

The survivors of sporadic unilateral disease are plentiful in the literature (Table 4).

If the average manifestation in sporadic unilateral retinoblastoma is about 15 per cent, then less than 10 per cent of their progeny would be affected. Since the truncated distribution suggested a possible manifestation as high as 56 per cent, and since some of the sporadic unilateral cases are indisputably germinal mutations with low manifestation, all must be so considered from the point of view of genetic counselling.

The following scheme seems a reasonable basis for such advice (Figure 1).

When hereditary retinoblastoma does occur in an affected family, it is particularly likely to be bilateral. Kitchin[31] has analyzed this point as follows (Table 5). Whenever bilateral retinoblastoma is present, its transmission should be highly suspected. If retinoblastoma is to be detected early, unilateral cases should be considered germinal mutations, albeit of low manifestation, and afforded the same vigilance.

TABLE 3. RETINOBLASTOMA IN THE OFFSPRING OF SURVIVORS OF THE SPORADIC FORM OF THE DISEASE*

Author	Sporadic bilateral					
	No. of parents	No. of parents having healthy children only	No. of parents having children with retinoblastoma	No. of children	No. of healthy children	No. of affected children
Vogel, 1957	2	2		3	3	
Smith & Sorsby, 1958	1		1	1		1
Hemmes et al., 1964	7	2	5	22	10	12
Eye Institute, P & S	5	3	2	5	3	2
TOTAL	15	7	7	31	16	15

*Segregation ratio, $p = 0.4838$; manifestation, $2p = 96.76$ per cent.

TABLE 4. RETINOBLASTOMA IN THE OFFSPRING OF SURVIVORS OF THE SPORADIC FORM OF THE DISEASE*

Author	Sporadic unilateral					
	No. of parents	No. of parents having healthy children only	No. of parents having children with retinoblastoma	No. of children	No. of healthy children	No. of affected children
Krause, 1939	3	3		6	6	
Badtke, 1940	1	1		4	4	
Herm Heath: Tucker, Steinberg Cogan	8	6	2	18	16	2
Vogel	34	33	1	70	68	2
Hemmes, 1964	68	58	10	177	161	16
TOTAL	114	101	13	275	255	20

*Segregation ratio, $p = 0.0727$; manifestation, $2p = 14.54$ per cent.

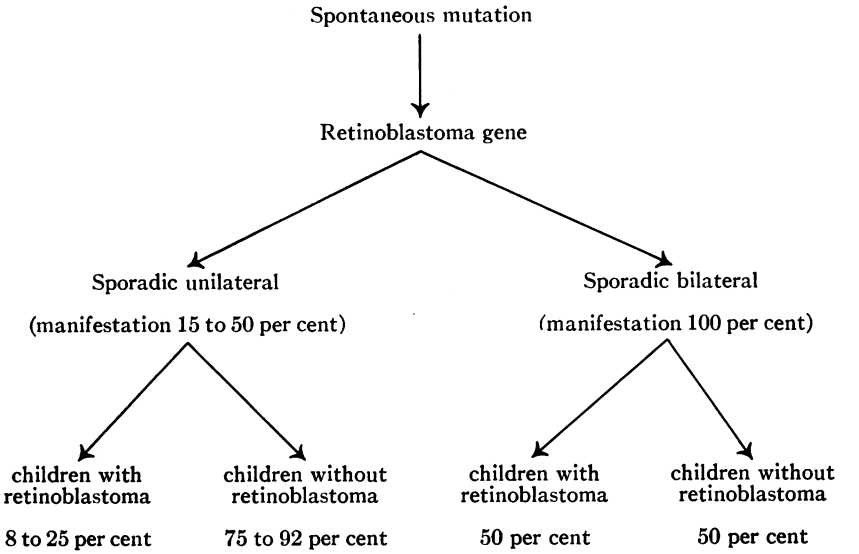


FIGURE 1
Heredity of retinoblastoma.

TABLE 5. BILATERALITY IN HEREDITARY RETINOBLASTOMA

Child with retinoblastoma with	Bilaterality (%)
One parent affected	
bilaterally	95
unilaterally	92
No parent affected but	
2 or more siblings affected	83
distant relative affected	60

There are numerous pedigrees in the literature and in our own series where the disease has been passed down through three or more generations indicating that it is a dominant characteristic. There are eight cases in the literature in which both monozygotic twins were involved with tumor and there is one such pair in our series. The absence of sex predilection suggests that an autosomal chromosome is involved and there is no question that certain individuals carrying the defective gene show no retinal tumor and no other manifestation of the disease.

To our knowledge there is no other characteristic associated with

retinoblastoma. Some years ago Weiner *et al.*[20] studied twelve of our families with hereditary retinoblastoma and found no gross chromosome defect. Stallard and Penrose[21] reported chromosome deletion in one case, but this information is merely suggestive at best. With more sophisticated methods of chromosome analysis, it is hoped that a characteristic change may be demonstrated in patients with retinoblastoma. This would be of inestimable value in genetic counselling. We are currently studying 14 known chromosomal markers in the hope that we may establish an association between retinoblastoma and some other enzymatic reaction. To date we have not been able to make any positive correlations.

There must be some biochemical stigma of retinoblastoma potentially detectable in blood or urine. Our studies[22] on vanillylmandelic acid (VMA) and homovanillic acid (HVA) excretion have been inconclusive, but further efforts along this line are indicated. The only known manifestation of the gene, then, is a retinal tumor capable of metastasis.

Since the gene is so rare in the general population, all affected patients may be assumed to be heterozygous in nature. Since blind people do congregate, however, a homozygous individual may well be born someday.

We now have a dozen families in which more than one child with retinoblastoma was born to normal parents with no other family history of the disease. In this situation, we assume that the mutation to the retinoblastoma gene occurred in one of the parents, but failed to penetrate, and produced no known clinical or biochemical sign. The abnormal gene was, however, passed down to the children as would be expected for an autosomal dominant characteristic.

Analyzing our figures, we deduced that there was a 4 per cent chance that normal parents, having produced one child with retinoblastoma, would subsequently produce another child with the disease. Macklin[7,18] found that of the families in which subsequent pregnancies occurred, 6.8 per cent had one or more affected children somewhere in the ensuing family line. It would seem that the carrier state for retinoblastoma is well established and it is unfortunate that it is clinically unrecognizable.

PATHOLOGY

STEM CELL

The stem cell initiating this tumor has been widely discussed in the literature with a vague, general conclusion, at least in the American

literature over the past two decades, that the responsible cell comes from the glial elements and is in the spongioblastic series. The principal basis for this notion arises from the fact that only the glial elements in the retina are capable of reproduction after complete differentiation of the retina. This argument is not particularly germane to practical management except for the rather secure clinical observation that certain retinoblastomas are more sensitive to radiation than others. This suggests that there may be certain histological differences, or at least biochemical differences, between one retinoblastoma and another, and it is possible that certain retinoblastomas arise from glial elements and others from receptor cells. If it could be proved that retinoblastoma can arise from two different lines of cells and that one group was more radiosensitive than the other, this would, indeed, be valuable clinical information. Tsukahara[23] has shown that in bilateral cases of retinoblastoma the histological type is generally the same in both eyes. If, therefore, one eye were enucleated and the histological type identified, we might be able to draw certain conclusions about the radioresponsiveness of the opposite eye and might vary the treatment program accordingly.

The cell most commonly seen in retinoblastoma is a uniform, small, round or polygonal cell with scant cytoplasm and a large chromatin-rich nucleus, which stains deeply with hematoxylin. Popoff,[24] working with our group, has studied with the electron microscope the typical cell found in intraocular retinoblastoma and characterized it in some detail. In studying normal, retinal precursor cells in the 7-cm human embryo, she finds striking similarities in cells in the outer retinal layer and feels that the cells in a typical retinoblastoma are nearly identical to primitive cells which will later form rods and cones. The mitochondria show similar polarization and numerous centrioles are present. The latter expand into cilia which may differentiate into outer rod segments. A peculiar folding or reduplication of the nuclear membrane is seen in both cells. Whether the responsible mutation produces a type of dedifferentiation into a primitive retinoblast, or into an entirely new and different cell, is uncertain at this time.

MACROSCOPIC TYPE

When retinoblastoma arises in the internal nuclear layers of the retina, a mass extends into the vitreous cavity where it can be readily seen with the ophthalmoscope. This has been called the endophytum type of retinoblastoma and is the more common. When the tumor arises from the external nuclear layers, it may grow in the subretinal space, detaching the retina ahead of it. These tumors growing beneath a

detachment are called exophytum retinoblastomas and, since the tumor cannot be seen directly, they lead to greater problems in diagnosis. Whether a tumor is endophytum or exophytum in nature makes little clinical difference because neither tumor responsiveness to irradiation or chemotherapy, nor prognosis in general, has been related to this growth characteristic.

MICROSCOPIC TYPE

In the past, retinoblastomas have been divided into two histological groups; one, the undifferentiated retinoblastoma type composed of the small cells noted above, and two, the neuroepitheliomatous type in which the cells assume a larger, columnal shape and arrange themselves radially around a central cavity to form true rosettes. This behavior has been taken as an effort toward differentiation and this may or may not be significant. It is thought that this differentiation is in the direction of mature rod or cone cells, but it is possible that rosette formation simulates the primitive neural tube rather than normal, mature, receptor elements in the retina.

It is a general concept in oncology that more differentiated tumors are less radiosensitive and Tsukahara[23] seemed to bear this out, namely, that tumors with definite rosette formation were less sensitive to irradiation, whereas the more undifferentiated, anaplastic tumors were more radiosensitive. The histological characteristics of the tumor, however, seem to have little bearing on response to therapy or to ultimate prognosis.

Retinoblastomas have very definite histological similarities to neuroblastomas in the peripheral nervous system and to medulloblastomas in the central nervous system. All three are highly malignant tumors which occur in infants and young children; all are relatively radiosensitive; and all undergo necrosis and calcification and show a tendency toward spontaneous regression. These generalizations have little clinical value, but, perhaps, indicate exciting prospects for the future.

BIOCHEMISTRY

Children with neuroblastoma have been shown to excrete excessive amounts of VMA and HVA, as well as other pressor substances in the urine. Because of the histological similarities between retinoblastoma and neuroblastoma, it was felt that children with retinoblastoma might secrete substances of a similar nature and gas chromotographic analysis of urine speciments from twelve patients was done. Three of these patients showed high total levels of HVA and VMA excretion, although,

because of the small sample, these results were not statistically significant. There was a suggestion that tumors with true rosettes produce more VMA and HVA than less differentiated tumors and that radiation therapy of the tumor produced a decrease in urinary excretion of these metabolites. This information is fragmentary at the moment, but further biochemical studies are of considerable importance. If it could be shown that retinoblastoma produces a characteristic metabolite, this would be most helpful in initial diagnosis, in measuring the response to treatment, and as an index to metastatic spread.

MULTIPLE FOCI

Retinoblastoma characteristically arises in multiple foci in an involved retina. In the last 100 cases seen in our clinic, multiple foci were present in 84 per cent of the eyes examined. There are two possible explanations for this phenomenon. The first, and most probable of these, is true multicentric origin in various areas of the retina. An alternative, and possible explanation, is tumor spread in the potential subretinal space, either in the presence or absence of frank retinal detachment. There is no particular area of predilection for retinoblastoma over the entire area of the fundus except at the ora serrata. Of our cases, 75 per cent show tumor at the ora, either as a feature of massive involvement, or as small localized tumors. Numerous histological specimens bear out the presence of small foci at the ora serrata suggesting that cells might spread in the subretinal space to become mechanically trapped at the ora where they give rise to localized tumor masses.

Perhaps 30 per cent of retinoblastomas involve both eyes and in these cases there is a distinctly separate origin in each eye. There are a few cases on record in which retinoblastoma spread from one eye via the optic nerve and across the chiasm into the other optic nerve and into the fellow eye, but these cases are exceptions to the general rule where true multicentric origin in each eye has been well documented.

DIFFUSE TYPE

There is another rather unusual clinical variant in which the entire retina is more or less uniformly replaced by tumor cells without marked tumefaction. This has been called diffuse infiltrating retinoblastoma[25] and may pose a difficult clinical challenge. There is a faint clinical suggestion that this type of retinoblastoma is particularly apt to spread into the uvea and outside the eye, making it analogous to

the flat type of diffuse uveal melanoma which carries with it a definitely increased risk of extraocular extension.

SEEDING

The stroma is poorly developed in retinoblastomas and the cells are not particularly cohesive. As the tumors grow larger within the eye, peripheral portions tend to break away from the parent mass to float about freely in the vitreous producing the clinical phenomenon of vitreous seeding. This is a very bad prognostic sign and markedly decreases the chance for successful treatment. In general, only large tumors seed and, in a sense, seeding is a reflection of a considerable tumor mass in the eye. On rare occasions a relatively small tumor will show some mild seeding in the overlying vitreous and, while this is alarming to a degree, it does not carry with it the dire significance of more extensive seeding. Vitreous seeds have been divided into three groups.

(1) Active tumor seeds are opaque, gray masses which float about in the vitreous over the surface of the tumor, or, in more advanced cases, may fill the entire vitreous space. The larger ones are sometimes fairly sharply demarcated, while the smaller seeds may have feathery outlines suggesting that there are detached tumor cells along the borders.

(2) Calcified tumor seeds are characteristically seen after the radiation treatment of retinoblastoma. Some three or four weeks after radiation therapy, the tumors may rather suddenly become heavily calcified and shrink in size. As this happens, the calcific remnants may break apart and calcified seeds spread about in the vitreous. This is not particularly dangerous and many eyes in which this has occurred have survived. Occasionally, a tumor, prior to any treatment, will show a considerable amount of calcification and there may be some glistening, white, sharply demarcated, calcified seeds in the vitreous. This particular type of seeding is not as ominous as the active tumor seeds described above.

(3) Amorphous tumor seeds occur as a response to radiation therapy. Large tumors, following irradiation, will occasionally show little calcification, but the entire tumor mass will fall apart and large remnants will float about in the vitreous. This is opaque, gray, tumor tissue of irregular shape and with soft outlines. It produces a frightening picture indeed, and it is impossible to tell clinically whether these floating tumor remnants have been sterilized by irradiation, or whether they may have the potential for growth. These eyes must be followed

especially carefully with frequent examinations under anesthesia and prompt treatment of further tumor activity. Some of these eyes will show progressive resorption of the floating vitreous masses without incident, whereas others may show regrowth of tumor at a later date.

When active tumor seeds are present in the vitreous, they have no active blood supply and grow little, if at all. The vitreous seems to be able to maintain viability for relatively long periods of time, however, and these tumor seeds may subsequently settle on some distant area of the retina where they receive a better blood supply, begin to grow more rapidly, and establish implantation growths. These implantation growths initially may appear as flat, or very slightly elevated, "greasy," gray areas in the retina which are often confluent. As they grow, they become more elevated, take on a more solid, pink-gray appearance and neovascularization appears on the surface. The vascular stroma of retinoblastomas frequently exhibits telangiectatic and microaneurysmal vessels which are probably a reflection of venous stasis and relative hypoxia within the tumor.

ROSETTE FORMATION

Retinoblastoma, characteristically, shows pseudorosette, as well as true rosette formation. Pseudorosettes are perivascular cuffs of cells arranged in a palisade up to 15 or 20 cells in thickness around a capillary. Remote from the capillary itself, and between these pseudorosettes, extensive areas of necrosis occur. Necrotic retinal tissue does not seem to be particularly toxic and rarely excites a clinically apparent inflammatory reaction. This same type of focal necrosis characteristically occurs in melanomas, but in the latter tumor tends to produce clinically recognizable intraocular inflammatory disease with cells in the vitreous and anterior chamber, and an injected and painful eye. It must be emphasized, however, that necrosis in a retinoblastoma does occasionally produce an inflammatory reaction of considerable severity, resulting in the picture of endophthalmitis, panophthalmitis, or orbital cellulitis. The clinical characteristics of this phenomenon will be described later, but a recognition of this potential should lead to the suspicion of retinoblastomas in any severely inflamed eye in a child.

SPONTANEOUS REGRESSION

A considerable amount of calcification occurs in necrotic areas of the tumor. A specific sequence of calcium and phosphate ions and of alkaline phosphatase and other enzymes is necessary for the produc-

tion of soft-tissue calcification and the exact sequence of events producing calcification in retinoblastoma is not well understood. It has been thought that a considerable amount of calcification in a tumor might lead to toxic concentrations of calcium and self destruction of the tumor. This concept has never been substantiated and is probably inaccurate. It is true that spontaneously regressed retinoblastomas are often heavily calcified, but there is no reason to argue that the spontaneous regression is an effect of the calcification.

It is easy to imagine that some local factor in a particular tumor could cause it to regress spontaneously. There is one example of a bilateral spontaneous regression in the literature[26] and there is one well-documented case in our own series. This would lead us to believe that there may be some systemic factor, immunological, or otherwise, that allows tumors in certain individuals to be destroyed spontaneously. These patients deserve particular study since the behavior of their tumors could provide some clue to a new therapeutic approach.

We are currently attempting to make an antigen from human retinoblastoma tissue. We hope to identify a tumor-specific antigen and then to produce antibodies to this in animals or in human beings. If we cannot find a tumor-specific antigen, but can isolate a retinal-specific antigen in these tumors, even this would be a great help in identifying retinoblastoma cells in extraocular locations. Because retinoblastoma in metastatic sites rarely produces rosettes, its identification in bone marrow and lymph nodes, especially, and in other organs, is most difficult. If we could produce a specific antigen-antibody reaction employing a fluorescent antibody, metastatic cells might be distinguishable.

CHOROIDAL EXTENSION

Extension of retinoblastoma through the lamina vitrea into the choroid is of considerable significance. Clinically, there are three signs of choroidal extension: (1) rapid growth over a period of days or weeks, (2) high elevation on a narrow, pedunculated stalk, and (3) a yellow color at the summit suggesting that the lamina vitrea has been pushed forward ahead of the tumor. It has been stated[27–29] that choroidal extension is associated with increased mortality and, in general, this is true. A definitive study has never been done to document this point. In order to accurately gauge choroidal extension, it is necessary to examine all the serial sections in an eye and to make a three-dimensional reconstruction of the choroid to appreciate its total involvement.

We are currently involved in such a study and, while the final results have not been fully delineated, there are certain important suggestions at the moment.

It appears that choroidal extension occurs almost regularly in Group IV and Group V cases. In many such eyes choroidal involvement was not recognized until the entire globe was sectioned in the course of this study.

Choroidal extension is by no means tantamount to clinical hematogenous metastasis since the majority of children with choroidal involvement have survived. Retinoblastoma cells apparently do not share with melanoma cells the capacity to remain fixed in a stage of "suspended animation" to a capillary wall for many years, retaining the potential for late regrowth and metastasis.

Mortality roughly varies from 10 per cent in cases with no choroidal involvement to over 60 per cent in eyes with considerable choroidal extension. A quantitative factor must be present and will hopefully be delineated by the study in progress. The problem of choroidal extension is of considerable importance because it could indicate long-term chemotherapy.

Extension into the sclera is very important prognostically, and may occur either by direct extension from the choroid, or along the emissary vessels. While extension along the emissary vessels is very common with melanomas, it is a relatively rare method of extension in retinoblastoma and has been seen in only a handful of cases.

Howard[30] has suggested that light coagulation may destroy the lamina cribrosa, which acts as a natural barrier, and permit extension into the choroid, which may lead to orbital spread and death. In analyzing the eyes that Howard reported, we found that in all cases seen personally, there was definite evidence of choroidal extension prior to the light coagulation. In these cases, there had been intensive prior treatment with irradiation and chemotherapy, and light coagulation was used as a desperate alternative to enucleation of an only eye with tumor recurrence. There is no question but that these cases showed massive choroidal extension and spread into the sclera. The most significant feature in this paper is the demonstration of scleral necrosis which is rarely seen in retinoblastoma without light coagulation and which may be a major factor in orbital extension. It must be stressed that these patients did not satisfy the usual criteria for light coagulation and this experience should not be construed as a condemnation of light coagulation as a treatment modality. It does stress the importance of choroidal extension and would tend to dissuade one

from "last ditch light coagulation" in advanced, recurrent tumors. There is some evidence that cryotherapy does not have a similar destructive effect on the lamina cribrosa and this might be an argument for the use of cryotherapy rather than light coagulation in the treatment of small tumors. This point has not been sufficiently elaborated and requires considerable further experience.

NERVE INVOLVEMENT

As this tumor involves the peripapillary portions of the retina, it may grow down into the papilla, then through the lamina cribrosa and into the nerve. In enucleated eyes it is common to find tumor extending for only a few millimeters behind the lamina cribrosa at the time of enucleation. As the tumor grows further back into the nerve, it eventually involves the subarachnoid space with dissemination of tumor cells into the spinal fluid and seeding along the base of the brain to produce the clinical picture of basal meningitis. When the tumor extends back some 10–12 mm behind the eye, to the point where the central retinal artery enters and the central retinal vein leaves the nerve to cross the subarachnoid space, the tumor almost invariably gains access to the spinal fluid and the mortality rate increases to 90 per cent or more. When eyes with retinoblastoma are enucleated, it is important to obtain a long optic nerve, since the tumor may be, thereby, completely removed in those eyes with extension of tumor beyond the lamina cribrosa, but without extension into the subarachnoid space. Once the latter has occurred and tumor cells are seeded into the spinal fluid, removal of even the entire nerve would not stay the danger of progressive involvement of the central nervous system. For this reason, craniotomy has no place in the surgery of retinoblastoma.

METASTASIS

Metastasis occurs by three general routes. The most celebrated of these is direct extension into the optic nerve and then into the subarachnoid space as noted above. Of at least equal importance, although less emphasized in the literature, is the extension into the uvea with hematogenous metastasis. Retinoblastoma cells in the general circulation seem to show a predilection for certain tissues over others. The tissue most commonly involved in the early stages of metastasis is the bone marrow. Whether this is due to tissue affinity or to rheological factors is uncertain, although the latter is probable. On the other hand, retinoblastoma is never seen in the lung except

as extension by direct contiguity from involvement of ribs or other adjacent structures. Tumor cells undoubtedly pass across the lung, but the factors that dissuade their growth there are unknown. In the latter stages of metastasis, the tumor may involve marrow and bone throughout the body and almost all of the lymph nodes and visceral organs.

When isolated tumor cells are seen in bone marrow, or in lymph nodes, it is impossible to distinguish them from cells normally present in these locations. It is only when clumping occurs in the bone marrow, or when gross disorganization of a lymph node by tumor cells has occurred, that a definite diagnosis of metastatic retinoblastoma can be made.

DIAGNOSIS

The diagnosis of retinoblastoma depends on the index of suspicion of the observer. Almost invariably there is a history that the initial sign or symptom was ignored by the general practitioner or pediatrician to whom it was pointed out, thereby delaying treatment for a critical length of time. This is by no means an indictment of the general practitioner or pediatrician, because they are presented with the story of a transient cat's eye reflex in the pupil, or an intermittent esotropia among a beguiling myriad of other and, usually, trivial complaints and when looked for in a crying, unco-operative infant they are not seen. Were retinoblastoma a commoner disease, this would not be the case, but, as it is, many pediatricians never see a case during an entire life of practice and the possibility of a life-threatening tumor is certainly not uppermost in their minds.

By the time the ophthalmologist is consulted, the area of interest is clearly defined and the possibility of retinoblastoma should be considered first because it is a life-threatening, as well as an eye-threatening, condition.

The following list of signs and symptoms will form a frame of reference for evaluation of the presenting situation (Table 6).

"CAT'S EYE REFLEX"

The most common presenting sign of retinoblastoma is a white reflex in the pupil, described in the German literature for over a century as a "cat's eye reflex." When a tumor arises in the macular region, it will present this reflex when it is relatively small, perhaps 3 or 4 disk diameters in size, and is seen when the child looks straight ahead toward the observer. On the other hand, when the tumor arises in the

TABLE 6

Presenting sign or symptom	Percentage
White reflex or "cat's eye reflex"	56
Strabismus	20
Esotropia 11 per cent	
Exotropia 9 per cent	
Red, painful eye with glaucoma	7
Poor vision	5
Routine examination	3
Orbital cellulitis	3
Unilateral mydriasis	2
Heterochromia iridis	1
Hyphema	1
"Strange expression"	0.5
Nystagmus	0.5
White spots on iris	0.5
Not eating, failure to thrive	0.5

retinal periphery, it must grow to a very large size before it presents such a white reflex in the pupil and then the reflex is seen only when the child looks in a certain direction. This explains the fact that the mother, or father, or grandmother sees the white reflex at home, but when the child is brought to the pediatrician, it is not seen unless the child happens to look in a particular direction. When the pupil is dilated with mydriatic drops, the reflex is much more obvious and this should be a routine procedure by any physician when this complaint is presented.

Although a white reflex was the presenting complaint in 56 per cent of the over-all series, it has been a more frequent complaint over the past decade, perhaps indicating that the diagnosis is now being made at an earlier stage than it was in years past.

STRABISMUS

The second most common presenting sign of retinoblastoma is strabismus and, although esotropia has been much more common in the most recent series of cases, on analyzing the over-all series, it was found that esotropia showed a very slight preponderance over exotropia.

When a small tumor arises in the macula, strabismus may be a very early sign of retinoblastoma. In many cases, however, esotropia is seen only after the disease has reached an advanced stage in one or both eyes.

It is well to consider that any child with strabismus, and especially any child with strabismus and a poorly fixating eye, has retinoblastoma until proved otherwise. If the disk and macular area can be seen well

with the indirect ophthalmoscope in a co-operative child, this is probably sufficient, but if there is the slightest difficulty in examining the posterior pole of the eye, the child should be seen under anesthesia.

INFLAMMATION

A red, painful eye, often with accompanying glaucoma, is a common presenting sign of retinoblastoma and it is these children who are frequently treated for a long period of time for inflammatory disease before the correct diagnosis is made. The injection and pain may be secondary to uveitis following spontaneous necrosis of the tumor, or may be related to glaucoma. In the absence of uveitis, the glaucoma may be secondary to hemorrhage into the vitreous or may follow venous obstruction in the posterior segment complicated by rubeosis iridis. These eyes almost constantly show widespread extension into the choroid and it would seem that almost any mass lesion in the choroid may be associated with secondary glaucoma on a neurohumoral basis.

VISION

Poor vision is the presenting symptom, or sign, in only two situations. Occasionally, the slow-growing type of retinoblastoma will increase in size slowly over a period of years and will ultimately involve the macula and lead to a spontaneous complaint of poor vision. More commonly, poor vision is seen in infants with massive bilateral tumors producing extreme bilateral loss of acuity and a floundering behavior.

ROUTINE EXAMINATION

Three per cent of the children with retinoblastoma were identified on routine ocular examination, half of these by the pediatrician, family doctor, or ophthalmologist on routine visits, and the other half studied because of a family history. The necessity for examination of other members of an involved family deserves reiteration if early diagnosis is to be made.

ORBITAL CELLULITIS

Spontaneous necrosis is almost the rule with malignant melanomas of the choroid if they achieve any size. It is not widely enough recognized that spontaneous necrosis can occur in retinoblastoma to produce the picture of a violent endophthalmitis, panophthalmitis, or orbital cellulitis. Two clinical features of this process are noteworthy.

The first is rapid development suggesting an active inflammatory process extending from the adjacent sinuses or by infected emboli from a distant source of infection. The second, and more amazing characteristic, is the rapid resolution over a period of a few days without treatment. On one occasion, two infants with an almost identical picture of orbital cellulitis were admitted to the nursery on a Friday. One of these patients was thought to have infectious cellulitis extending from the sinuses, was treated with vigorous antibiotic therapy and was much better by the following Monday. In the other child a rather typical retinoblastoma had been identified several days before the development of the orbital cellulitis and he was consequently not treated with antibiotics or in any other fashion and he, too, was almost completely recovered the following Monday. This shows that response to antibiotics must not necessarily be taken as evidence for infectious rather than neoplastic origin. In general, any child with violent, inflammatory disease should be at least suspected of having retinoblastoma. It is in this particular circumstance that tap of the anterior chamber for tumor cells may be of value.[36] While puncture of the sclera to obtain a sample of subretinal fluid may carry the danger of extension into the orbit if the choroid is involved, there seems to be very little danger from puncture of the cornea for anterior chamber tap. A positive test for tumor cells is diagnostic, but a tap revealing only inflammatory cells must be interpreted with some circumspection.

MYDRIASIS

Unilateral mydriasis is an occasional presenting sign and is usually seen with extensive tumor and total retinal detachment. Often, when a parent states that the first noticed sign of abnormality was an enlarged pupil, he frequently means, on further questioning, that the pupil was unusual in appearance and, on further questioning, often states that there was a white reflex in the pupil.

IRIS COLOR

A difference in the color of the iris is an occasional presenting sign, but this is not "heterochromia iridis" in the sense that there is any difference in the pigment distribution in the iris, but is rather an indication that there has been previous bleeding into the anterior segment with changes in iris color due to residual hemoglobin, or to a secondary inflammatory reaction. In all of the cases observed first-hand, the involved iris was darker in color.

HYPHEMA

Hyphema may occur during the recurrent course of retinoblastoma following treatment and it is an uncommon and embrangling presenting sign. The confusion arises because there is commonly a history of actual or alleged injury which beclouds the true source of the bleeding. It has become a maxim to ignore a history of injury when one is presented and to always suspect injury, if there is no history, in dealing with ocular disease in children.

OTHER SIGNS

A "strange expression" of the child, apparently not related to an abnormal pupillary reflex, or to strabismus, is occasionally presented and is noteworthy merely to emphasize that the first clue to this disease may be nebulous.

When nystagmus occurs, it is a manifestation of very far advanced bilateral disease, but in a very young child, it may be observed when the lack of vision is not obvious.

White spots on the iris are an occasional first sign of the disease and represent implantation growths on the surface of the iris stroma or, more commonly, are small, circumscribed masses of tumor tissue floating in the anterior chamber where they frequently settle in the angle below. If the child is turned upside down, the tumor material floats about in the anterior chamber to settle in the dependent part of the angle. Generally, anterior segment seeding is present only with very large tumors, but, occasionally, the tumor cells find their way into the anterior chamber with a tumor of moderate size and with only moderate seeding in a limited sector of the vitreous.

Failure of a child to eat, gain weight, and to thrive may be a first, but very discouraging, intimation of retinoblastoma. Occasionally, children have metastatic disease when retinoblastoma is first discovered and the early signs of metastasis may be extremely vague. Two cases are known in which metastatic retinoblastoma was present at birth and, in this circumstance, it is conceivable that the systemic involvement will become manifest before any ocular abnormality is noted.

Although the aforementioned signs and symptoms will be the ones commonly noted in the practice of medicine in the United States, or other socially advanced countries, it is almost the rule that orbital extension or metastatic involvement is present when medical aid is sought in more primitive societies. In the latter situation, the children usually present with an orbital mass sometimes protruding so mas-

sively from the orbit that no normal ocular structures can be identified. Other children die of metastatic involvement without the true cause of death becoming evident unless a postmortem examination is performed.

DIAGNOSTIC CLUES

The problems involved in the diagnosis of retinoblastoma fall naturally into two groups; one, those cases in which the retinal tumor itself can be seen with the indirect ophthalmoscope and, two, those in which the primary tumor is obscured by retinal detachment, vitreous haze, vitreous hemorrhage, or some obscuration in the anterior segment.

When an elevated, endophytum tumor projects into the vitreous, the diagnosis is usually straightforward. The tumor, generally, has a creamy, pink color with neovascularization on the surface which is not part of either the normal retinal or choroidal circulation. The internal vascular stroma of retinoblastomas frequently contains many microaneurysms, and microaneurysmal, telangiectatic, and large aneurysmal vessels may frequently be found on the surface of the tumor. The major vessels supplying the tumor may be extremely large and, if accompanying detachment is present, the tumor may mimic a retinal angioma. About 5 per cent of retinoblastomas will show demarcated patches of typical yellow, fatty exudate adjacent to the tumor and this is usually present in extensive retinoblastomas with large, nutrient vessels and is probably a reflection of a vascular shunt in the tumor itself. A large vein apparently arising de novo in the tumorous mass and then draining into the retinal venous circulation is typical of retinoblastoma. If, in the region of the equator, a vein that appears larger than it should be is seen in surveying a retina for retinoblastoma, then a peripheral tumor may be present in this area and the entire retina out to the ora serrata should be very carefully studied.

About 5 per cent of retinoblastomas will have small areas of spontaneous hemorrhage on the surface and these are commonly seen after treatment either with radiation or with light coagulation. About 10 per cent of retinoblastomas have an atrophic annulus with pigment disturbance involving the retinal pigment epithelium at the border of the tumor and this is interpreted as a favorable sign indicating that the tumor is in a regressive stage.

There is another kind of retinoblastoma, which appears, clinically, not as a pink, vascularized tumor, but as a snowy-white, elevated mass that is completely avascular. This type of retinoblastoma is

typically seen in older children at the age of six or eight years and often arises in the retinal periphery where it apparently grows very slowly during a long period of time. When this occurs, the presenting sign is usually visual loss related to increase in the size of the tumor, or accompanying detachment, or is related to vitreous floaters which the child reports as dots dancing before his eyes. This particular appearance should not be regarded as a sign of benignity, since a number of children with this presentation have ultimately had fatal metastasis.

Retinoblastoma has no predilection for any particular geographical area in the retina, but it occurs very commonly in the region of the ora serrata. Over 75 per cent of our patients have tumor at the ora serrata in the involved eye and this is generally a reflection of a very large tumor that is mechanically restricted at the ora. In a considerable number of the children, however, there are isolated tumors at the ora serrata and we feel that there may be spread of tumor cells in the potential subretinal space out to the ora where they are mechanically trapped and grow to form an elevated mass.

The frequent presence of retinoblastoma at the ora stresses the need for optimal conditions during the examination. It is manifestly impossible to examine the entire retina of a child without anesthesia. The pupil must be maximally dilated and a sympathomimetic drug is not satisfactory for use with the indirect ophthalmoscope. The latter instrument is indispensable for the detection of these tumors. Very early endophytum tumors are seen as tiny, gray mounds, and early exophytum tumors are almost impossible to distinguish with the direct ophthalmoscope. Slight abnormality in the retinal vascular pattern, very slight elevation, or a faint color change at the border of the lesion are the only clues. The entire retina must be systematically surveyed and scleral indentation around the entire circumference of the ora is vital. A 28- or 30-diopter aspheric lens enables the observer to see a wide area of the retina at one time and the size and location of the tumors can be accurately diagrammed.

Eighty-four per cent of our cases have more than one tumor in an involved eye and examination of the retina should not be concluded with the identification of a single retinoblastoma.

The real problems in the diagnosis of retinoblastoma come when the tumor itself cannot be satisfactorily seen. The most common cause of this is exophytic growth behind the retina which causes serous detachment of the retina ahead of the mass and obscures its coloration and outline. When the tumor produces hemorrhage into the vitreous,

or excites an inflammatory response to cloud the vitreous, the problems are even more difficult. In these situations some ancillary help is most valuable.

Retinoblastoma occurs in eyes of normal size and microphthalmos is rarely, if ever, present. The one exception to this rule involves those eyes that undergo spontaneous regression and phthisis bulbi. Indeed, it is well to suspect any phthisical eye in a child as harboring a retinoblastoma.

Cataracts are never seen with retinoblastoma except as a late complication of hemorrhage or inflammatory disease in the vitreous. Eyes that have undergone spontaneous regression and phthisis bulbi may have cataracts, but this is a very late development and, in general, any eye in which a cataract can be unequivocally identified is not highly suspect of containing a retinoblastoma.

There are two features of retinoblastoma that are almost pathognomonic of this disease. The first of these is calcification and the second is the seeding of tumor cells into the vitreous.

Calcification may occur as the result of any type of advanced, intraocular, hemorrhagic, or inflammatory disease, but the particular pattern of calcification in retinoblastoma is typical. This can be appreciated either with the ophthalmoscope or on roentgenograms. Calcium can be detected with the ophthalmoscope in over 50 per cent of retinoblastomas and Pfeiffer[32] has reported that calcium could be identified in roentgenograms in 75 per cent of cases. He stresses that the roentgen technique is critical and expert radiological advice and consultation is important in exposing these films. It is not uncommon to encounter eyes with extensive tumor calcification which has been missed in improperly exposed roentgenograms. Bone-free films of the anterior segment have been of little value and the injection of air and contrast media has not been employed.

Calcium on the surface of a tumor is sharply demarcated and has the appearance of "cottage cheese," whereas calcium occurring deeper within the tumor is seen as a change in gray color values or in translucency and the outlines of the calcium are muted. Differential histochemical staining[33] and electron micrographs[24] have suggested that a good portion of the glistening, white material seen in retinoblastomas either before or after treatment represents precipitated desoxyribonucleic acid rather than calcium. It is probable that the "cottage cheese calcium" which makes a dramatic appearance three or four weeks after irradiation is largely or entirely precipitated DNA.

This material may then secondarily bind calcium to form a radiodense complex.

Vitreous seeds may be divided into three types: (1) active tumor seeds, (2) calcified seeds, and (3) amorphous tumor seeds. Active tumor seeds are usually seen with large tumors. They are composed of groups of detached tumor cells that float on the surface of the retina or out into the vitreous and, indeed, in advanced cases may entirely fill the vitreous space. The cellular conglomerations are of various size and move freely about as the eye is agitated. The vitreous can apparently support growth of these tumor seeds for a fairly long period of time, but they do not grow luxuriantly in the vitreous. If tumor seeds settle on a viable area of the retina where they obtain a good blood supply, they may establish implantation growths. These implantations may be confluent and may involve large areas of the retina in an extensive, but only slightly elevated, mass with an avascular "greasy" gray appearance. Vitreous seeding is an extremely dangerous prognostic sign. Occasionally, a small retinoblastoma, some 4 or 5 disk diameters in size, will be accompanied by slight seeding into the overlying vitreous and, in this particular situation, the seeding does not have quite the same ominous significance.

Calcified seeds are seen after radiation treatment and may come about in two ways. The first of these is calcification taking place in the tumor seeds themselves. They become inspissated, sharply demarcated, and glistening white. It is possible that this material in the vitreous is DNA rather than calcium. Secondly, as larger tumors respond to irradiation, they may become heavily calcified, and disintegrated calcified seeds may spew out into the vitreous. These glistening, calcified seeds apparently have no growth potential and rarely lead to implantation growth.

"Amorphous tumor seeds" are seen following radiation therapy of large tumors. The entire tumor mass itself seems to break apart and huge clouds of tumor tissue float about in the vitreous. These fragments are dull gray in color with fuzzy outlines and show no bright, glistening calcification. This is a frightening ophthalmoscopic picture and these patients must be watched very carefully, perhaps at intervals of three or four weeks. While these amorphous seeds may be truly sterilized and may be gradually absorbed over long periods of time, they carry a special threat of implantation and tumor recurrence.

The presence of a large number of tumors in the retina is usually explained by tumor seeding, but "diffuse, infiltrating retinoblastoma,"[25]

which may involve almost the entire retina, produces very little tumefaction and is not the result of seeding and confluent implantations. This type of clinical picture leads to great difficulty in diagnosis and ancillary methods of study are of little help.

When the tumor itself cannot be seen, diagnostic roentgenograms may be of considerable value. Retinoblastomas accumulate ^{32}P in a characteristic fashion and ^{32}P uptake may be helpful in selected cases. In the past, transillumination has been non-contributory, but with the development of very brilliant fiberoptic transilluminators, the evaluation of detachments and solid lesions can be considerably enhanced. Fluorescein angiography produces a typical pattern when the tumor can be seen well, but this adds little to the typical ophthalmoscopic picture, and, when the retina is totally detached, or the vitreous opacified, fluorescein offers little help.

A diagnostic trial of roentgenography is never justified in this disease. If there is widespread, unilateral disease and a normal fellow eye, enucleation is in order and, if both eyes are massively involved, enucleation of one will establish the correct diagnosis.

When one eye is extensively involved and the responsible process obscure, careful study of the fellow eye may be invaluable, for detection of a tiny, typical retinoblastoma will immediately clarify the problem.

DIFFERENTIAL DIAGNOSIS

Reese and Blodi coined the term "leukokoria," meaning "white pupil," and the differential diagnosis of retinoblastoma involves an assortment of lesions presenting this sign. These eyes have a clear cornea and a clear lens and congenital cataract should not be included in this problem. It is to be re-emphasized that cataract is not a part of the picture of retinoblastoma and occurs only in the very late stages in eyes that have had severe intraocular inflammation or which have become phthisical. When the tumor itself can be seen through clear media, there is little problem with diagnosis in most cases, but when the tumor is obscured by detachment or vitreous haze, errors may easily occur.

The following fourteen conditions have been those most often confused with retinoblastoma.

LARVAL GRANULOMATOSIS

Many eyes with larval granulomatosis have been mistakenly enucleated with the diagnosis of retinoblastoma. Larval granulomatosis

presents a whole spectrum of clinical pictures ranging from a quiet, solitary, retinal nodule to a violent, widespread uveitis or endophthalmitis with opacification of the vitreous.

The larvae of *Toxocara canis* are ingested by children who play with dogs and who, unconsciously, swallow eggs present in the dog's feces. There is often a history of dirt-eating in the involved children. Infestation by *Toxocara canis* is prevalent among dogs around the world and is particularly common in young puppies where the incidence may reach 90 per cent. There is, therefore, widespread exposure to this potential hazard. The ingested eggs hatch out in the intestine, bore through the wall, and migrate throughout the body in a pattern typical of "visceral larva migrans." It is peculiar that children with proved *Toxocara* granulomas in the retina or choroid seldom have other clinical manifestations of visceral larva migrans. They may, or may not, have eosinophilia; there is rarely any radiologic evidence of migration through the lungs; the liver is generally normal; and, since the parasites do not complete their life cycle in the child's intestine, no larvae or eggs are found in the involved child's stool. Clinically, the diagnosis is difficult to substantiate even with laboratory help. In enucleated eyes, as well, the diagnosis may be difficult to substantiate because the larval fragments initially present in an eosinophilic granuloma dissolve with time, so that at a later stage no larval fragment will be seen even if the eye is meticulously sectioned serially. Efforts have been[34] and are being made to develop reliable serological reactions to help with this diagnosis. It appears that exposure to *Toxocara* larva is universal and that many clinically normal individuals are positive reactors, analogous to the situation with tuberculin testing. It is hoped that fractionation of larval antigens will lead to a more specific test.

The larvae apparently enter the eye through the short ciliary arteries and, therefore, the lesions are most common in the macular and peripapillary areas. If the larvae enter the central retinal artery, they may lodge in a temporal arteriole and give rise to a characteristic granuloma in the retinal periphery.[35] The intraocular picture would seem to depend on the number of larvae which arrive in the eye and upon the individual immunological response to the larvae. If a solitary larva enters the eye and there is no violent antigen-antibody reaction, a solitary, quiet, retinal nodule may be produced. An important clinical characteristic of such a picture is a small, translucent "core" in the center of a white granuloma. Such a lesion very closely resembles a retinoblastoma and can be differentiated only with the

passage of time. If larval granulomatosis is suspected, examinations at intervals of two or three weeks should be made before enucleation is considered.

If numerous larvae enter the eye and there is a violent inflammatory reaction, a severe uveitis will be produced with vitreous opacification. When this occurs, it is common to see long, straight strands in the vitreous emanating out from an elevated, gray-yellow chorioretinal lesion. These radiations into the vitreous are uncommon with retinoblastoma.

The larval fragments in the granuloma are gradually absorbed and an eye can apparently survive this insult, in contrast to the problem with cysticercosis where degeneration of the *Taenia solium* larva produces enough toxic reaction to destroy function of the eye, if not the globe itself. The ocular lesion of cysticercosis, if intra- or subretinal, can exactly resemble a retinoblastoma, but this disease is uncommon in the United States. In our series, one eye in a six-year-old Costa Rican child was enucleated with a mistaken diagnosis of retinoblastoma.

UVEITIS

Granulomatous uveitis of any cause can easily be confused with retinoblastoma. Küchle *et al.*[36] and Weizenblatt[37] have presented two very instructive cases among many in the literature and one case in our series presented with a typical picture of granulomatous uveitis which later proved to be retinoblastoma with massive involvement of the choroid. Left esotropia was present at birth and vitreous haze made examination of the fundus impossible.

It is well to consider as retinoblastoma any major disease in the eye of a child that precludes a view of the fundus, that will certainly render the eye functionally useless, and in which the sequence of events is obscure. Despite the doubt that may exist in such a situation, enucleation is the wisest and best course.

COATS'S DISEASE

Coats's disease can simulate retinoblastoma better than any other condition except larval granulomatosis. The typical features of Coats's disease are telangiectatic and aneurysmal vessels in the retina with progressive subretinal exudate and detachment. The involved retina often has a characteristic greenish-yellow sheen. The peripheral detached portions of the retina may be dark gray or black due to proliferation of the retinal pigment epithelium, and scintillating crys-

tals may be present in or behind the retina. When large vessels are present later in the course of the disease, there may be widespread, bright yellow, fatty exudate in the involved area. Retinoblastoma, too, is frequently accompanied by microaneurysmal and telangiectatic vessels on the elevated surface of the tumor and, occasionally, by the presence of yellow, fatty exudate. While the green-yellow sheen seen in Coats's disease is not present in retinoblastoma, there is occasionally a faint, transparent, lemon-yellow color over the surface of a retinoblastoma in a sharply delimited area, which has never been recognized histologically, and the basis of which is not clear.

In the far advanced stage of either retinoblastoma or Coats's disease, when there is total detachment of a retina thrown forward behind the lens in multibullous folds and there is a creamy gray-pink mass behind the retina with abnormal vessels, it is extremely difficult to make an accurate diagnosis.

ANGIOMATOSIS RETINAE

Although in a typical early case angiomatosis retinae cannot be confused with retinoblastoma, in the later stage, when extensive detachment is present, it can be. Pleomorphism is the rule in angiomatous lesions of the retina and a small angioma responsible for a detachment may be obscured. Only miliary aneurysms and telangiectatic vessels are visible on the surface. In this situation the picture can well simulate a retinoblastoma. Meyer-Schwickerath[38] has stressed the occurrence of large vessels with retinoblastoma and has especially noted that huge veins occasionally seem to arise *de novo* and drain into the venous circulation. When such large vessels are present with retinoblastoma, they may well suggest angiomatosis retinae.

In either advanced Coats's disease, or advanced angiomatosis retinae, where there is confusion with retinoblastoma, it is difficult to temporize, because if it should prove to be retinoblastoma there is extreme danger of extension into the choroid and metastasis. In this situation, diagnostic roentgenograms for calcification and ^{32}P uptake may be useful.

METASTATIC RETINITIS

Metastatic retinitis refers to spread of infectious emboli to the eye usually during the course of one of the exanthematous diseases of childhood, producing widespread, violent chorioretinitis with severe vitreous reaction, and often yellow-white, opaque tissue behind the lens. External inflammatory signs are present and a temporal history

usually links the eye condition to the underlying disease. This entity has been repeatedly discussed in the European literature and unquestionably does exist, but the history linking the ocular pathology to an underlying viral disease should always be suspect. The correct diagnosis of retinoblastoma has often been delayed by a presumption that the inflammatory, ocular signs were related to a viral disease and not to spontaneous necrosis of tumor.

PERSISTENT HYPERPLASTIC PRIMARY VITREOUS (PHV)

Persistent hyperplastic primary vitreous refers to a gray, retrolental membrane composed of remnants of the primary vitreous, the vasa hyaloidea propria and the tunica vasculosa lentis. The condition is usually noted at birth, or within the first few weeks of life, and well over 90 per cent of cases are unilateral. There are no inflammatory signs and microphthalmos is the rule, although it may be slight in degree. It occurs in full-term infants of normal birth weight and no unsual features have been noted in the pre- or postnatal course. The cornea and lens are clear initially and the anterior chamber may be slightly shallow. The retrolental membrane varies considerably in density. There is often a rather dense, yellow-gray, oval plaque in, or nasal to, the center of the membrane and vessels may radiate out into this central area. The membrane may be several millimeters thick, completely precluding a view of the fundus, or may be thinner peripherally where normal retinal markings can be discerned. In general, the optic nerve and retina of these children are normal and these eyes are worth a considerable effort at salvage. The ciliary processes are abnormal and are long and the lens may be small, the equator visible over a considerable portion of the circumference. The iris is frequently normal, although large radial vessels may be present on the iris, or in the area of the pupil, and the iris may show some atrophy and posterior synechiae and may dilate poorly. A pupillary membrane is rare. Behind the retrolental mass, persistence of the hyaloid artery is often present.

It has been observed that these eyes do not survive into adult life[39] and they are usually lost through one of two mechanisms. During early life, often at about the age of six months, the fibrovascular tissue behind the lens invades the posterior lenticular capsule, producing swelling of the lens cortex. As the lens swells, the anterior chamber becomes shallow and the trabeculum is blocked, producing acute glaucoma and corneal edema. This can occur very rapidly over a period of several days and a salvageable eye is rapidly converted

into a surgical emergency where the risks are extreme. For this reason, needling of these lenses is indicated when the diagnosis is made. If the majority of the lens substance is removed, the danger of acute glaucoma is obviated. The second threat to eyes with persistent hyperplastic vitreous is late hemorrhage into the vitreous and anterior chamber. This is presumably caused by traction on large vessels in the retrolental membrane. There is, thus, a rationale for discission of the secondary membrane in an area away from the large vessels. When the membrane is thin, this is no problem, but with very thick membranes discission is difficult and excessive manipulation should be avoided.

Persistent hyperplastic primary vitreous commonly produces a white reflex in the pupil, but is seldom confused with retinoblastoma when an optimal examination can be performed under anesthesia.

RETROLENTAL FIBROPLASIA

Retrolental fibroplasia produces a membrane similar to PHV and, indeed, Grade 5 retrolental fibroplasia and advanced PHV are very difficult to differentiate. Persistent hyperplastic primary vitreous is almost always unilateral, whereas an eye with Grade 5 retrolental fibroplasia will almost certainly show some pathology in the fellow eye.

It is Grade 4 retrolental fibroplasia with gray, elevated mounds in the periphery of the retina and abnormal vessels on the surface that can be confused with retinoblastoma. The history of prematurity and of incubation in oxygen and the pathology in the fellow eye will usually make the differentiation clear.

At the present time, there is renewed interest in retrolental fibroplasia, since many children with the "respiratory distress syndrome" are being saved by the use of high concentrations of oxygen. If too little oxygen is given, the infants may have damage to the brain, and if too much oxygen is given, they may become blind. The "middle-ground" of safety has not been definitively established, but, at the moment, it seems reasonable to maintain umbilical arterial pO_2 at 100 mg of mercury, or less in children with respiratory distress and to maintain the incubator concentration of oxygen at 40 per cent or less with infants who have no cardiovascular disease.

Three retinoblastomas have been seen in premature infants.

RETINAL FOLDS

Retinal folds may occur in the following conditions: (1) grade 3 retrolental fibroplasia (RLF), (2) congenital retinal fold, (3) retinal

dysplasia, and (4) toxoplasmosis. The retinal fold seen in RLF is typical in appearance with traction on the nervehead and with, generally, a similar abnormality in the other eye. Ninety per cent occur temporally.

A congenital retinal fold, as described by Mann[40] is seen in normal infants with no history or sign of inflammatory disease and with a normal fellow eye. This fold extends out from the optic nerve into the periphery of the retina and may occur anywhere around the circumference of the retina.

"Retinal dysplasia" is a syndrome described by Reese, Blodi, Straatsma,[41,42] and others. It refers to a severe, bilateral, ocular disease present at birth in full-term infants of normal birth weight. There is frequently a family history and associated systemic anomalies. Microphthalmos is usually present and there is a clear cornea and a shallow anterior chamber. There may be abnormal vessels in the iris with posterior synechiae and a persistent pupillary membrane. While cataract may be a late feature, it is rarely present early and a vascularized, white, retrolental mass can be seen. Remnants of the hyaloid system are often present as are abnormal retinal folds composed of branching retinal tubules and large, irregular rosettes. Zimmerman[43] has preferred to consider retinal dysplasia a histological rather than a clinical term and notes that it is present in many different conditions. The entity called "retinal dysplasia" by Reese and Straatsma may certainly be a manifestation of 13–15 trisomy and there may be other etiological factors. Associated anomalies are usually present, if sought, and include cerebral agenesis, internal hydrocephalus, anomalies of the heart and vascular system, polydactylism, harelip, cleft palate, malrotation of the gut, etc.

The retinal fold seen with toxoplasmosis is different from the foregoing three conditions because the fold does not originate at the disk but at the area of a former granuloma from which it extends out into the retinal periphery. If the original toxoplasmosis granuloma was in the peripapillary area, it may appear that the fold did arise at the disk.

HEMORRHAGE

A vitreous filled with blood may be an uncommon presenting sign of retinoblastoma. When this picture is encountered clinically, careful temporization is in order, especially in very young infants. Persistent vessels of the hyaloid system can bleed following birth and usually, as they undergo regression, the blood will clear, revealing a normal fundus. Unrecognized contusive trauma to the eye of a child can also account for vitreous hemorrhage which will clear with time. It is

possible that "hemorrhagic disease of the newborn" with factor VII and prothrombin deficiency can produce bleeding in the eye as in other organs. It is conceivable that the very common retinal hemorrhages of the newborn may occasionally be extensive enough to break into the vitreous and produce this picture.

Ultrasonography may be able to differentiate a tumor mass from loculated hemorrhage in the vitreous and diagnostic roentgenograms for calcification and radioactive phosphorus uptake may be helpful. It is certainly permissible to observe such an eye over a period of several months and, if cells occur in the anterior chamber, an anterior chamber tap may be diagnostic.

Retinal hemorrhages occur in 30–40 per cent of newborn infants, more commonly following difficult delivery. They are extremely rare following cesarean section and are almost the rule following suction delivery. If these retinal hemorrhages are extensive, they could become organized and result in a gray mass in the retina. This mechanism undoubtedly can occur, but several cases so categorized at first examination have later proved to be retinoblastoma or *Toxocara canis* granulomas.

OTHERS

Extensive areas of medullated nerve fibers, large colobomas of the choroid, especially those incorporating the optic nerve, and, occasionally, high myopia may produce a white reflex in the pupil, a "leukokoria," demanding examination under anesthesia. When these eyes are carefully studied, the diagnosis is immediately obvious.

SUMMARY

Table 7 summarizes the common diagnostic dilemmas. When the differential diagnosis is uncertain, the presence of seeding and calcification are almost pathognomonic. "Snowball floaters" seen in the presence of sarcoid and some granulomatous uveitis may be confused with the seeding of retinoblastoma, but this is rare. The typical radiologic picture of fluffy calcium in these tumors is not seen in other conditions and, if present, is most helpful. The absence of calcification on the roentgenogram, however, is not helpful in making a definitive decision.

TREATMENT

By all means the most significant factor in the treatment of retinoblastoma is the stage of the disease at the time treatment is undertaken. The approach to this disease depends on whether the tumor is

TABLE 7. SUMMARY OF THE COMMON DIAGNOSTIC DILEMMAS

Differential diagnosis of retinoblastoma
A. Lesion visible
1. Solitary retinal mass
a. larval granulomatosis
b. retinal astrocytoma
B. Lesion not visible
1. Total retinal detachment
a. congenital retinal detachment
b. juvenile retinoschisis
c. Coat's disease
d. angiomatosis retinae
e. Norrie's syndrome
2. Vitreous haze
a. larval granulomatosis
b. granulomatous uveitis
3. Vitreous hemorrhage
a. At or soon after birth
1. persistent hyaloid arterial system
2. hemorrhagic disease of the newborn
3. retinal hemorrhages of the newborn
b. At a later age
1. spontaneous from a retinoblastoma
2. following treatment with x-ray or light coagulation
3. trauma

confined to the eye, whether it has extended locally to the orbit, or whether there is already evidence of metastasis when the diagnosis is made. It is rare in the United States to have a child present with obvious orbital tumor and, consequently, the basic problems are those involving intraocular tumor and those with microscopic evidence of extension into the orbit. In contrast, in many other countries the most common clinical presentation of retinoblastoma is an orbital mass with considerable proptosis and a virtually hopeless prognosis.

INTRAOCULAR TUMOR

When a child with retinoblastoma is seen for the first time, examination should be conducted under anesthesia, with full mydriasis and with the indirect ophthalmoscope. It is important to make a detailed drawing of both eyes, charting the precise size and location of the tumors. It is vital to note all tumors present because, if a lesion is missed at the first examination and is subsequently seen after initial treatment has been delivered, there is no possible way to be certain whether it is truly a new recurrent tumor, or whether it was a lesion overlooked before treatment was instituted. A system using a grid projected onto the retina to gauge size was used for a period of time,

TABLE 8. PROGNOSIS

Group I—Very favorable
a. Solitary tumor, less than 4 disk diameters in size, at or behind the equator
b. Multiple tumors, none over 4 disk diameters in size, all at or behind the equator

Group II—Favorable
a. Solitary tumor, 4 to 10 disk diameters in size, at or behind the equator
b. Multiple tumors, 4 to 10 disk diameters in size, behind the equator

Group III–Doubtful
a. Any lesion anterior to the equator
b. Solitary tumors larger than 10 disk diameters behind the equator

Group IV—Unfavorable
a. Multiple tumors, some larger than 10 disk diameters
b. Any lesion extending anteriorly to the ora serrata

Group V—Very unfavorable
a. Massive tumors involving over half the retina
b. Vitreous seeding

but was found to be unsatisfactory. With the large field of the binocular indirect ophthalmoscope, the size can be estimated quite readily by comparing the size of the tumor with the diameter of the optic nervehead, and the position in the fundus can be noted with some precision by noting the specific distance of the tumor margin from known landmarks, i.e., the optic nervehead, the fovea, the long posterior ciliary nerves, the vorticose ampullae, and the ora serrata. By noting several of these key distances at the time of examination, an accurate drawing can be reconstructed.

Some years ago, when a decision was made to treat more advanced intraocular cases, it was obvious that some type of quantitative scheme was necessary to compare the results using different treatment modalities and the following, purely arbitrary, scheme was adopted (Table 8).

In Group I an arbitrary figure of 4 disk diameters was selected because it seemed apparent that tumors smaller than this could easily be handled by one of a variety of methods, and multiplicity per se did not seem to adversely affect the prognosis as long as the tumors were in the posterior portion of the eye.

In Group II are larger tumors in the posterior segment, and these carry a slightly less favorable prognosis, probably because of an increased over-all tumor mass.

Two features that cause problems are noted in Group III. In analyzing treatment failures, it became obvious that an anterior location, especially in the nasal half of the retina, had unfavorable prognostic

significance. There would seem to be three possible explanations for this. The first of these is the difficulty in examining the ora serrata and the possibility of missing a small lesion in this area. With the binocular indirect ophthalmoscope and scleral indentation, this should no longer be a problem. Second, in an effort to miss the lens, a therapeutic x-ray beam may be directed too far posterior when a temporal portal is used, resulting in a non-homogeneous dose to the annulus of retina near the ora. The third problem with an anterior location is the difficulty in light coagulation, but with practice, with either the xenon-arc or the laser coagulator, burns can be made 2 or 3 mm up onto the pars plana, so this, too, should be no real problem. Indeed, in our most recent series of cases, awareness of these difficulties encountered with anterior tumors has led to a significant increase in the cure rate of cases in Groups III and IV.

In Group IV the anterior location is accentuated with tumors extending all the way up to the ora. It is common to see peripheral tumors scalloped at their distal margin to conform to the normal configuration of the ora.

In Group V are very large tumors involving over half of the retina, and these are often accompanied by total retinal detachment. In Group Vb the danger of vitreous seeding is documented. As a rule, seeding is a reflection of large tumor size and, in those occasional cases in which a small tumor is accompanied by limited seeding directly over the tumor, the prognosis is not nearly so bad.

UNILATERAL CASES

Unilateral retinoblastoma is probably best treated by prompt enucleation, after the fellow eye has been thoroughly studied and a search for metastasis is complete. In the usual unilateral case, the tumor has grown to considerable size before the diagnosis is made and the risks involved with treatment can hardly be justified in the presence of a normal fellow eye. In only two situations will small, unilateral tumors be detected, and in both of these, we have no hestitation in treating the unilateral case if it falls into Groups I, II, or III. When there is a family history of retinoblastoma, and routine examinations of siblings and other relatives are conducted, small early tumors are frequently found which can be treated with radiation plus adjunctive measures. A tumor arising in the macula may produce a squint which leads to the proper diagnosis when the tumor mass is still relatively small and treatment is possible.

BILATERAL CASES

In bilateral retinoblastoma, the eye in which the disease was detected is generally far advanced and usually comes to enucleation, while the remaining eye, hopefully, has a more favorable prognosis. This type of asymmetrical, bilateral involvement is the rule in retinoblastoma. Any time retinoblastoma is treated, life is gambled for sight, and so, if an eye is massively involved with little hope for useful function, the main tumor mass in this eye should be removed and efforts at treatment directed toward the more favorable fellow eye where useful vision may be salvaged.

There are two situations in which both eyes of a bilateral case might be treated. The first of these are small, bilateral tumors which are not uncommonly seen in hereditary cases. A number of cases have been seen in which a newborn sibling of a child with retinoblastoma has been examined under anesthesia with perfectly normal retinas on at least three occasions and has subsequently developed small tumors in both eyes requiring treatment. This is the reason that dogged follow-up of siblings is so vital. There are no special problems involved in treating both eyes, if both fit into Groups I, II, or III.

The other situation, where treatment of both eyes may be justifiable, is that group of cases with advanced and more or less symmetrical involvement of both eyes. The common problem here is very large tumors in the macular area precluding any view of the fovea and often of the nervehead. With radiation treatment these tumors shrink and it is possible that they may spare the fovea in one or both eyes, but it is impossible to make this decision initially. In these patients, both eyes are treated with a therapeutic dose of radiation and they are watched very carefully as the tumors respond. If both eyes react favorably to treatment it is most fortunate, but often the "proper eye" is salvaged even though one ofthe globes eventually comes to enucleation.

In general, any eye falling into Groups I, II, and III may be treated whether the disease is unilateral or bilateral. In advanced, bilateral cases the more involved eye is enucleated and treatment is directed at the remaining retina. A trial at treatment of an only eye is justified if there is a segment of retina, measuring 60 degrees or so, which is not obviously involved with tumor and which may function normally if the tumor is controlled, even though this "normal segment" of retina is detached at the time the diagnosis is made. Some retinoblastomas are exquisitely sensitive to radiotherapy and the delay of several

TABLE 9. THE TREATMENT OF RETINOBLASTOMA

1. *General agents*—treating the entire retina
   a. Irradiation
   b. Chemotherapy
2. *Local measures*—treating only the tumor-bearing area of the retina
   a. Diathermy
   b. Radon seeds, cobalt-60 applicators
   c. Light coagulation
   d. Cryotherapy

months needed to assess the initial response to irradiation will probably not adversely affect the prognosis for life.

TREATMENT MODALITIES

The following modalities are available for the treatment of retinoblastoma (Table 9). Radiation and chemotherapy can affect the entire retina and we feel that irradiation alone, or combined irradiation and chemotherapy, should be the primary form of treatment in almost all cases of retinoblastoma. In cases treated with light coagulation alone, or with radioactive applicators alone, there is a high incidence of new tumors arising following the completion of the original course of therapy. Over three-fourths of patients with retinoblastoma have more than one tumor in the affected eye, and involved retinas have a tendency to develop new tumors. A potential new tumor site may not be obvious ophthalmoscopically at the first sitting, but will blossom into a new retinoblastoma if not discouraged by irradiation.

All cases are treated with irradiation alone in Groups I, II, and III, and irradiation combined with intracarotid triethylenemelamine (TEM) in Groups IV and V. With experience it was found that small tumors could be controlled by irradiation alone, or irradiation combined with light coagulation or cryotherapy, and it was felt these children could be spared the hazards of TEM without adversely affecting the prognosis. Cobalt-60 applicators, light coagulation, and cryotherapy are extremely valuable adjunct measures.

IRRADIATION

Radiotherapy is by far the most valuable weapon against retinoblastoma. Crying, irritable children are difficult to deal with and precise radiation dosage must be given with patient, loving care. It is imperative that an interested radiotherapist be completely familiar with ocular anatomy, and work in close co-operation with the ophthalmol-

ogist so that the precise location of the tumor is understood as radiation therapy is planned. The fundus sketch plus an anteroposterior cross section is available to the radiotherapist drawing the isodose curves and planning location of the beam.

At one time the children were treated under anesthesia but this presented problems with fractionation on one hand and with cardiorespiratory safety on the other. It has been found over the years that even sedation is not necessary with most infants. Children may be frightened by the imposing apparatus, and they are occasionally placed under the machine the first day to become accustomed to the situation and not given any radiation therapy. On return the following day, they are often calmer and treatment goes along without difficulty. A "Flexicast," made by the Picker X-Ray Corporation, is indispensable for positioning these children. This is a thick-walled, but very pliable, plastic bag forming two long arms and filled with tiny beads. The child's head can be positioned on the main portion of the bag as on a pillow and the long arms wrapped around head, neck and shoulders in a comfortable fashion. When the bag is evacuated with a vacuum pump, the Flexicast itself does not move at all but becomes absolutely rigid and holds the child's head comfortably in place without any possibility of movement.

Slides, or movies, projected on the ceiling may interest older children and keep the eye fixed straight ahead, or a mobile may attract the attention of a smaller infant. With the use of a monitoring television camera, it was found that Bell's phenomenon and rotation of the eyes were not significant factors and positioning of the eyes with sutures and the fixation device has been largely abandoned. In an occasional hyperactive child, sedation or a fixation device will be of value.

There are two distinct advantages of supervoltage over orthovoltage apparatus. The first of these is a razor-edge beam, which, using a temporal portal, can be brought up to the ora serrata, to irradiate the entire retina without significant lenticular dosage. Because no epithelial cells are present, the posterior portion of the lens can probably be irradiated with impunity, giving an additional millimeter or two leeway in the positioning of the beam. If the tumors are confined to the posterior segment of the eye behind the equator, the lens is intentionally spared by several millimeters and, if there is extensive seeding in the anterior vitreous, the beam is moved forward to irradiate a portion of the lens with an increased risk of cataract formation.

The second advantage of supervoltage irradiation is the more favorable isodose curve with maximal irradiation occurring, not at the surface of the skin, but at a depth of several centimeters. With the 22.5 MeV betatron used in the current series, the maximal depth dose is at 4 cm. Unit density material is used between the child's temple and beam to bring the point of maximal ionization into the plane of the tumor. With orthovoltage apparatus, the surface skin receives the maximal dose, which then falls off rapidly as the beam penetrates into the eye. With supervoltage irradiation, using the betatron, the skin and bone at the entering temple receive approximately 40 per cent of the tumor dose and only the tumor-bearing area of the eye receives 100 per cent of the dose. Because of the high energy of this supervoltage beam, the midline dose and the exit dose through the opposite side of the head is higher than it is with orthovoltage irradiation, but does not approach 100 per cent and has not caused any problems.

An ideal apparatus for the irradiation of retinoblastoma would be an accelerator with an energy of at least 4 to 6 MeV and high output. The higher the output, the shorter is the exposure time, and the fewer the problems in positioning and restraining a child.

Various fractionation schedules have been used and the most common formulas are daily treatments for five days of the week, or treatments three days a week. An attempt is made to keep the exposure per treatment at less than 400 R and the weekly dosage at less than 1200 R.

The average total dose to the tumor is 3500 R in three weeks. This is an empirical dose found to cure the average retinoblastoma and not to produce untoward complications. If irradiation is given properly, the eye can usually withstand a total dose of up to 5000 R with impunity and it has been tempting to increase the average dose to a level of 4500 to 5000 R. This has not been done because of the possible occurrence of radiation-induced fatal tumors at this level and, for the time being, an average dose of 3500 R is being maintained. When the eye under treatment is in Group v and massive tumor is present, the initial dose is often increased to 4500 R because it is felt that these situations are desperate and an increase in risk is justifiable.

A single 3 $\times$ 4 cm temporal portal is used in all cases and is, usually, the only portal used. In cases with extensive, anterior tumor near the lens, it is combined with a round, anterior portal, but attempts are made to keep the dosage through the anterior segment at less than 1000 to 1500 R.

The initial effects from radiation are usually seen about three weeks

after the beginning of irradiation. The most difficult single problem in the treatment of retinoblastoma is the interpretation of regression patterns following irradiation. If a child is seen by a new observer for the first time six months after irradiation, it may be manifestly impossible for him to decide whether the child is doing badly or doing well. For this reason, the same observers must follow these children serially to assess the result and to make a decision concerning further treatment. Because these lesions are considerably elevated, fundus photography is not satisfactory for the follow-up of the majority of cases.

REGRESSION PATTERNS

Regression patterns have been divided into three types.

Type 1: "Cottage cheese calcium." This is the most common regression pattern and means that the tumor shrinks down in size and assumes an irregular, glistening white appearance that is similar to cottage cheese. Because of this glistening white appearance, because eyes with retinoblastoma commonly show a fluffy type of opacification in roentgenograms, and because amorphous, necrotic areas in an enucleated retinoblastoma pick up a great deal of hematoxylin, it has been assumed that this white, "cottage cheese" material is calcium. The pathogenesis of soft-tissue calcification is not well understood and it has always been somewhat baffling to understand how this could occur so rapidly in an irradiated eye. It would now seem that this glistening white material may be precipitated desoxyribonucleic acid (DNA) resulting from destruction by radiation of many cells in this "nucleus rich" tumor. These masses of calcium, or DNA-calcium complexes, are gradually absorbed with time. Tumors up to 3 or 4 disk diameters in size may disappear entirely leaving no trace in the irradiated retina. Larger tumors are usually represented by an area of white residual tumor for the remainder of the patient's life.

Type 2. This regression pattern is much more difficult to interpret. The tumor shrinks down in size to perhaps one-half or three-fourths the initial volume and loses the pink color of capillary injection. The surface is gray and homogeneous and some areas may be markedly translucent. The normal retinal vessels loop up over the surface of the tumor, which may show considerable elevation. No calcium, or precipitated DNA, is seen. As the tumor regresses, an annulus of pigment disturbance may be exposed around the border. As long as the tumor remains smaller than the original lesion and shows no sign of growth, it is assumed that it has been controlled by irradiation. This

type of regression pattern is much more disturbing than is Type 1 and must be watched more closely.

Type 3. This regression pattern is extremely common and is a combination of Types 1 and 2. There is a glistening white nidus of calcium, or DNA, in the center of amorphous, translucent, gray remnants which may be rather highly elevated. The lesion loses its pink, solid appearance and it is often possible to see right through the translucent tumor and identify normal choroidal markings. A pigment disturbance is often seen around this lesion and, while it is occasionally fairly dark, there is usually less pigment proliferation than occurs after light coagulation or diathermy. It is usually possible to distinguish with the ophthalmoscope between pigment disturbance seen following irradiation and that seen following light coagulation. As long as the ophthalmoscopic changes are in a regressive direction, no further treatment is given. Should there be enlargement of the tumor, or other signs of regrowth, additional therapy is then instituted.

IRRADIATION COMPLICATIONS

The ocular complications of irradiation have, perhaps, been overemphasized and, certainly, the danger of cataract has been overstressed. The blood vessels of the retina and choroid are the most radiation-sensitive structures in the eye, whereas the neural elements of the retina are relatively resistant. Radiation vascular necrosis is the most common and most dread complication. While this rarely develops with a total dose to the retina of under 5000 R, it has been observed infrequently with doses as low as 3500 R. Intraretinal and preretinal hemorrhages occur and, if more severe, massive hemorrhage into the vitreous supervenes. The bleeding is noted most commonly about six months after the completion of irradiation, but may occur as long as four or five years following irradiation. If there is one limited episode of retinal or vitreous hemorrhage, this may clear and the eye may weather the storm. When there is considerable vitreous hemorrhage, and especially when this is complicated by secondary glaucoma, the prognosis is very bad. When vitreous hemorrhage occurs, it is impossible to assess tumor activity and this presents a very difficult clinical dilemma.

One course of irradiation with a retinal dose below 5000 R is attended by few significant complications. If a recurrence requires a second course of irradiation, the damaging effects to ocular structures are cumulative, and with a second course of irradiation with a total

tumor dose of over 7000 R, there is an 85 per cent chance of functional loss of the eye due to radiation vascular complications. In eyes so lost, 50 per cent have had active, residual tumor, whereas the other 50 per cent have been cured of retinoblastoma, but have been lost to hemorrhage and secondary glaucoma.

It is common to see changes in the retinal pigment epithelium following irradiation,[30,44,45] especially when the irradiated retina has been detached. This usually assumes the form of diffuse salt and pepper pigmentation, but the pigment clumping may be more gross in pattern and macular damage can occur. At retinal doses below 4000 R the changes are not extreme.

Radiation dermatitis and atrophy of bone over the temporal area were rather severe problems with orthovoltage irradiation, but are no longer troublesome with supervoltage irradiation. There is a decrease in orbital volume which usually ranges between 10 per cent and 30 per cent in irradiated sockets, but skin changes are not marked, there is no loss of lashes, and there are no cosmetic problems resulting from this decrease in orbital size. Keratinization of the conjunctiva and cornea is not a problem since the anterior segment is spared. When an anterior portal with a total dose of 1200 to 1500 R is employed, there are rarely any signs or symptoms, at least during a period of five to ten years following irradiation. A number of cases of orbital rhabdomyosarcoma have been treated with a dose of 5000 R to the entire orbit and these children do have some injection and discomfort.

Glaucoma is a complication of irradiation when secondary to intraocular hemorrhage, or when the anterior segment has received extensive exposure.

Cataract is a rare and mild complication of properly delivered supervoltage irradiation. With orthovoltage apparatus and a temporal beam positioned at the ora serrata, there will be a tremendous dose to the lens and invariable cataract formation. External beam cobalt radiation produces a penumbra that is difficult to trim and a considerable dose to the lens, and there is no doubt that many cataracts will be seen if external beam cobalt radiation is used. With the betatron, or other types of supervoltage apparatus, one occasionally sees a stellate posterior subcapsular cataract, especially when massive tumors, or seeding near the lens, has been treated. These cataracts are usually mild and progress slowly, if at all. The important fact is that they do not occur for several years following irradiation and, therefore, do not preclude a view of the fundus when a judgment of tumor

regression must be made. Even if cataracts inevitably would occur, they would be a justifiable risk in treating a malignant disease, but with careful irradiation technique, cataract is not a problem.

Radiation-induced tumors are a most important problem and this risk has not been totally clarified. In 1960, Forrest[46] reported nine cases of radiation-induced tumors among children treated for retinoblastoma with an over-all incidence of 5.3 per cent. In 1968, the same group of cases was again analyzed[47] and it was found that there were now fourteen cases of radiation-induced tumors, or an incidence of 8.3 per cent. This stresses the long latent period between irradiation and the development of a radiation-induced tumor, which has varied from four to thirty years in our series. It must be immediately emphasized that these were cases treated many years ago wtih very high doses of radiation. The total dose in air ranged from 12,000 to 20,000 R and this experience is by no means representative of the irradiation techniques and dosages in use at the present time.

In 1968, Sagerman *et al.*[47] reviewed our entire series and discovered nineteen radiation-induced tumors for an over-all incidence of 4.9 per cent. The danger of radiation-induced neoplasia with the current technique is felt to be in the range of 1 per cent. In the cases irradiated before 1945, there was a 30 per cent incidence of secondary radiation-induced malignancy, although the numbers involved are quite small.

Of nine osteogenic sarcomas arising as the result of irradiation, none occurred with a tumor dose of less than 6000 R. The latent period averaged thirteen years and did not appear to be shortened by higher doses of radiation.

If tumor recurs following an initial course of irradiation with a tumor dose of 5000 R, or less, and the recurrence cannot be controlled by light coagulation, cryotherapy, or local radioactive applicators, there is little rationale for giving a second course of irradiation. If a second complete dose of external beam radiation is delivered with a cumulative total of over 7500 R, only 15 per cent of eyes at most will survive with useful vision. It is doubtful whether the danger of a radiation-induced tumor many years later is balanced by this salvage rate, but there may be an occasional situation where a second course of external beam irradiation is justifiable.

CHEMOTHERAPY

Although many chemotherapeutic agents have a profound effect on retinoblastoma, the precise role of chemotherapy has not been pre-

cisely defined. There is evidence that many of the chemotherapeutic agents act at a different point in the dividing chromosome than does radiation and, for this reason, the combined effects of irradiation and chemotherapy may be additive, if not synergistic. Since we have two, proved, effective agents, i.e., irradiation and chemotherapy, it seems reasonable to use them together in desperate situations. Combined therapy is used in the advanced Group IV and V ocular tumors and in the treatment of residual and recurrent orbital disease. Chemotherapy is the mainstay in the treatment of metastatic retinoblastoma with the adjunctive use of irradiation to control pain. The use of chemotherapy in the treatment of metastatic retinoblastoma is purely palliative and there is no rationale for the use of chemotherapy alone without concurrent irradiation in the treatment of intraocular retinoblastoma. With the agents available at the present time, chemotherapy cannot cure retinoblastoma alone, but, combined with irradiation, it may tip the scales favorably in advanced intraocular tumors or in early orbital tumor.

Among the drugs known to have an effect on retinoblastoma are nitrogen mustard, thio-TEPA, triethylenemelamine, Cytoxan, methotrexate, vincristine, and dactinomycin. The use of triethylenemelamine has been continued in our series so that the results of combined treatment may be comparable and because no more specific agent has been found. Because triethylenemelamine is relatively rapidly fixed, it is effective by intracarotid injection. By this route, the tumor receives a higher dosage and the bone marrow is relatively spared. If a nontoxic alkylating agent could be found which could be fixed in the matter of seconds, it might be possible to inject the drug into the ophthalmic artery following craniotomy, or by retrograde catheter through the supraorbital artery and deliver a tremendous dose to the tumor without systemic complications.

Since Cytoxan apparently requires a trip through the liver to be fully activated, this is a poor drug for intra-arterial injection.

Convulsions have been reported following the intrathecal use of alkylating agents and methotrexate is the drug of choice if tumor cells are present in the cerebrospinal fluid.

In treating Group IV and V intraocular cases, triethylenemelamine is injected into the internal carotid artery under direct exposure. If this drug is given percutaneously, it may be inadvertently injected into the wall of the artery and may produce an aneurysm. A ligature is placed beneath the artery, below the injection site, and the artery entered with a small hockey stick No. 25 needle. A dose of 0.08 to 0.1

mg per kg is injected over a period of several minutes and the ligature released. The neck wound is closed with subcutaneous sutures and a pressure dressing is placed over the neck. The injection is given on the same side as the tumor in most cases, although there is evidence that there is good exchange across the circle of Willis in children and both sides will receive an adequate level of drug. If possible, the intra-arterial injection is given on the day before the start of irradiation. In an earlier series, a second injection of TEM was given at a later date, when the marrow had recovered, but this has been found to be unnecessary and has been discontinued.

The principal complications of TEM therapy are leukopenia and thrombocytopenia, which are manifest in the first two weeks following injection. The children are treated with a prophylactic broad spectrum antibiotic when the white blood count drops below 2,000 and oral steroids are given when the platelet count drops below 100,000. This systemic therapy is continued until the white blood count is rising and is above 3,000 and until the platelet count rises above 100,000.

During the period of hematologic depression, exposure to infection should be minimized, and no operative procedures should be planned during the several weeks of risk following TEM injection.

The route, dosage, and complications of other chemotherapeutic agents are extremely varied and are functions of the agent itself. It is certainly possible that a less toxic or a more specific drug will eventually be the principal weapon against this disease.

DIATHERMY

There have been numerous reports in the literature of retinoblastoma cured by diathermy.[48–50] There is no doubt that diathermy may cure small tumors, but there are usually easier, more precise methods available. Surface diathermy is inadequate to cure the larger tumors and penetrating diathermy carries the threat of dissemination of tumor into the orbit and should be strictly avoided. There is histologic evidence that tumor can grow through the sites of perforating diathermy and, once the tumor has extended to the orbit, the prognosis is nearly hopeless. The scarring produced within the eye is greater with diathermy than with either light coagulation or radiation therapy.

RADIOACTIVE APPLICATORS

Stallard[51–53] in London has pioneered the use of radioactive applicators with outstanding success. The current applicators are platinum disks containing radioactive cobalt and are made in various sizes and con-

figurations to conform to the tumor present within the eye. Three objections and four possible indications for this technique come to mind.

The high dosage of radiation to the sclera at the base of these applicators, approximating 30,000 R to 40,000 R, would seem to predispose to scleral necrosis, or to radiation-induced neoplasia, but this has apparently not been a problem in Stallard's series. The principal objection is the inability of cobalt applicators to treat the large tumors that are present in most eyes. In general, lesions up to 6 disk diameters in size can be treated with a radioactive applicator, but lesions larger than this should be treated by external beam radiation. When multiple tumors are present, and this obtains in over 80 per cent of eyes, there is difficulty in calculating overlying isodose curves produced by applicators and in this situation it would seem, too, that external beam irradiation is preferable.

Cobalt applicators would seem to have four specific indications. The first of these is choroidal extension. Clinically, it is impossible to make this diagnosis with certainty, but the signs of choroidal extension are rapid growth over a period of days or weeks, very high elevation on a narrow, pedunculated stalk, and a yellowish color on the surface, which may be the lamina cribrosa pushed forward by the choroidal mass. It is possible that the tremendous dose delivered by an applicator to sclera and choroid at the base of such a lesion may be just what is needed to cure choroidal extension. However, once there has been massive extension into the choroid, it is probable that any and all methods will be unsuccessful.

The second specific indication for a cobalt applicator is the local recurrence of a tumor too large to be controlled by light coagulation, after an initial course of external radiation therapy. If, for example, five tumors are present in an eye and four are controlled by the first course of irradiation, but one lesion some 4 to 8 disk diameters in size recurs, it is possible that a radioactive applicator can control this recurrence with less danger of radiation-induced vascular necrosis than would be attended by a second course of external beam irradiation.

Thirdly, with a solitary anterior tumor at the ora serrata, especially on the nasal side, it is possible that the lesion may be controlled with an applicator with less danger of cataract. Certainly, large recurrent tumors at the ora should be treated in this fashion and it is very easy technically to place the applicators in these instances.

If, with future experience, the specter of radiation-induced neo-

plasia increases, it may be possible to minimize this complication with the more frequent use of radioactive applicators in cases in Groups I, II, and III.

For the treatment of retinoblastoma, a dose calculated at 4000 R at the tumor apex is desirable. The plaque is left in place until this dosage is obtained and is then removed at a second operation.

The complications of radioactive applicators are generally the same as those of external beam irradiation, and vascular necrosis, with hemorrhage into the retina and the vitreous, is the most serious. Eyes treated with localized radioactive applicators must be surveyed carefully and frequently for the development of new tumors.

LIGHT COAGULATION

Light coagulation is a most valuable adjunct in the treatment of retinoblastoma. All cases of retinoblastoma in our series are currently treated with external beam radiation with a tumor dose of 3500 R in three weeks. The eyes are then examined under anesthesia in six to eight weeks. If, at that time, there are any tumors anterior to the equator that remain pink, opaque, and suspicious, they are treated with light coagulation. Light coagulation in the anterior retina carries very little threat of hemorrhage or other complications and does not produce a huge field defect. In many of the cases treated with these criteria the light coagulation may not be strictly necessary, but because it is relatively harmless, it is justified if it may conceivably obviate a second course of irradiation.

The second indication for light coagulation is recurrent retinoblastoma, either at the original site or elsewhere in the retina, following external beam radiation therapy. Tumors up to 4 disk diameters in size can be controlled nicely with light coagulation if they are well separated from the optic nervehead. If they are near the nerve and nourished by the large vessels, it is difficult to control them with light coagulation.

Retinoblastomas depend on the retinal circulation for nutrition for a considerable period of time and can, therefore, be destroyed by obliterating the retinal vessels. A double, or triple, row of coagulations is made entirely around the tumor and carried proximally along vessels where this will not produce a much larger field defect. The children are treated at intervals of three or four weeks until all the vessels to the tumor are destroyed. It is not necessary to treat the tumor itself, and, indeed, it is almost impossible to influence most retinoblastomas with light coagulation because their white color

reflects the beam and the tumor itself is not heated to a sufficient degree for cell destruction. The tumor within the light coagulation scar gradually becomes more translucent and is absorbed over a period of several months. As long as all of the retinal vessels in the area are destroyed, further coagulation is not necessary. If the tumor has extended into the choroid, light coagulation will be ineffective.

The immediate complications are retinal detachment and hemorrhage, which frequently occurs on the surface of the tumor but is rarely a major problem. The blood vessels nourishing a retinoblastoma can usually be treated directly without any great danger of hemorrhage. With large tumors and extensive light coagulation, a limited retinal detachment may occasionally occur, but it usually resolves over a period of several weeks or several months with good function. Occasionally, yellow, fatty exudate may appear following light coagulation of a retinoblastoma, especially if large, nutrient vessels are present. The most serious complication of light coagulation of retinoblastoma has been stressed by Howard,[30] who has shown that light coagulation can break down the lamina vitrea and, perhaps, cause dissemination of tumor into the choroid and even through the sclera. In reviewing the material that Howard studied, it was found that most of the cases had clinical evidence of choroidal extension before the light coagulation. In these cases, light coagulation was used as a desperate, last ditch measure only in eyes that had two courses of irradiation, or extensive treatment of other sorts. For this reason, it is difficult to evaluate the role of light coagulation in fostering choroidal extension. Howard's finding of scleral necrosis, however, does seem significant and it may be well to avoid light coagulation in advanced, recurrent tumors. When tumors do recur and behave unpredictably, choroidal extension is often the cause and light coagulation, irradiation, and anything else are almost doomed to failure.

If light coagulation is confined to the treatment of tumors smaller than 6 disk diameters in size, there would seem to be little danger of encouraging choroidal extension.

If light coagulation is used as a primary form of treatment, new tumors may crop up in other areas of the retina and require further treatment. Very close supervision of these children is mandatory. Tumors behind the equator should not be treated with light coagulation because huge field defects will be produced, because there is a danger of hemorrhage, and because lesions in this part of the eye can be treated more easily with radiation. In general, an eye successfully treated by radiation will show less damage to normal retinal structures

than will an eye successfully treated by light coagulation, cryotherapy, diathermy, or radioactive cobalt applicators.

CRYOTHERAPY

Cryotherapy is about as effective as light coagulation in the treatment of retinoblastomas and small tumors can be well controlled in this fashion. Cryotherapy is effective in lesions up to about 4 disk diameters in size and is easily applied in the anterior portion of the retina where light coagulation is somewhat difficult. For this reason, light coagulation and cryotherapy are, to a certain degree, complementary. It is possible that cryotherapy will leave the lamina vitrea intact and carry less danger of choroidal extension than does light coagulation. If the proper indications for both of these modalities are observed, choroidal extension will probably not be a major problem.

SUMMARY

To summarize the current approach to the treatment of retinoblastoma, cases in Groups I, II, and III are treated initially with radiation alone, and cases in Groups IV and V with combined radiation and intracarotid TEM. When examined under anesthesia six or eight weeks later, light coagulation is applied to suspect tumors lying anterior to the equator. When there is recurrence of tumor within the eye, light coagulation is used if feasible, and if the recurrent tumor is larger, or unfavorably located, a ^{60}Co applicator is applied. Should these local measures fail to control the recurrence, a second course of external beam irradiation and intra-arterial TEM must be considered, although the chance of salvaging such an eye with useful vision is in the range of 15 per cent.

RESULTS

The results of the treatment of retinoblastoma, using a combination of the methods outlined, were reported at the Gonin Meeting and at the International Congress of Ophthalmology in 1966, and in the American Journal of Ophthalmology.[54]

Table 10 presents the most recent cases for which adequate follow-up is possible. These are cases treated between 1960 and 1965 for which an average follow-up of five years, and a minimal follow-up of three years, is available.

Several notations should be made in connection with the above table. The failures in Groups I and II are explained in many cases by mortality resulting from metastasis from the fellow eye. These cases

TABLE 10. RESULTS IN 192 CASES TREATED BETWEEN 1960 AND 1965

	Number of cases	Cure (%) rate
Group I	20	95
Group II	32	87
Group III	24	67
Group IV	32	69
Group V	74	34
Orbit	10	30

are classified as failures even though the treatment directed to the remaining eye was successful at the time the child was last examined.

The advanced Group V contains the largest number of cases. This group can be treated only by external beam radiation and these difficult cases do not appear in those series treated with light coagulation, diathermy, cryotherapy, or cobalt applicators alone.

The risk to life does not seem to be increased significantly by the period of delay occasioned by treatment. There is no way to control this factor, however, and it is undeniable that a certain risk is present. Certainly, if an eye fails to respond favorably to treatment and has no chance of survival as a functionally useful organ, prompt enucleation should be advised. There comes a time when the risks involved outweigh the possible gains and only a considerable amount of clinical experience can indicate the moment for this decision.

ORBITAL TUMOR

The treatment of orbital retinoblastoma is discouraging, but an occasional success justifies vigorous delineation of the problem and maximum therapy.

When a child presents with an obvious orbital mass and proptosis, the probabilities are overwhelming, nearly 100 per cent, that there has already been extension into the cranium, or generalized hematogenous metastasis. Exenteration may be necessary to prevent a massive, fungating growth, but there is little or no chance for survival.

A more common presentation is an enlarged nerve at the time of surgery, or the presence of tumor cells outside the globe on histological section of the enucleated eye, or a suspect, recurrent mass in the orbit following enucleation. In all of these situations, vigorous efforts should be made to detect metastatic disease, for, if such is present, heroic efforts in the orbital area are unwarranted. These studies should include careful roentgenograms of the optic canals, orbital tomography, and examination of bone marrow and spinal fluid for tumor cells. If

a mass is present in the orbit, it should be promptly biopsied, and if the biopsy is positive and there is no evidence of metastasis, exenteration should be performed, followed by intra-arterial TEM, with a dose of 0.1 mg per kg given into the internal carotid artery on the same side, and irradiation.

In the past, head perfusion was used in about a dozen cases for the treatment of orbital tumor. Because complications were encountered, and because the results could not be shown to be better than with simple intra-arterial injection, perfusion has been, at least temporarily, discontinued.

When the evidence for orbital involvement is more spurious, consisting of the presence of questionable tumor cells outside the globe on the routine sections, it is felt that exenteration is not justifiable. These children are treated with radiation with a tumor dose of 5000 R to the entire orbit combined with intra-arterial TEM.

When the optic nerve is involved with tumor at the line of section, there has usually been extension of tumor into the subarachnoid space and along the base of the brain. Very careful studies should be done for the presence of tumor cells in the cerebrospinal fluid. If none is present, and if the optic canal is completely normal, exenteration with section of the nerve at the orbital apex, followed by irradiation and intra-arterial TEM, probably gives the best chance for survival. Because the results in this series of cases has been so poor, some clinicians prefer not to subject the child to exenteration under these circumstances. This is a matter of judgment.

There is absolutely no rationale for combined orbital and intracranial surgery to cut an enlarged optic nerve at the chiasm. Because this is a completely sensible approach to a glioma or astrocytoma of the optic nerve, the same argument has been carried over to the treatment of retinoblastoma where it has no application. By the time retinoblastoma enlarges the optic canal, there is a 100 per cent chance of orbital, cranial, and distant extension and no hope for cure. Once the tumor has extended back into the nerve 12 mm or so behind the eye where the major retinal vessels enter and exit from the nerve, it invariably gains access to the subarachnoid space and removal of the remaining proximal portion of the nerve is irrelevant. Since retinoblastoma often extends back into the nerve in limited fashion for several millimeters behind the lamina cribrosa, it is well to always obtain a long nerve at the time of enucleation. This can be done by inserting 0000 black silk traction sutures into the stump of the medial

and lateral rectus muscles to draw the eye forward as gently curved scissors are passed down the medial wall into the orbital apex. Because the optic nerve is firmly fixed to the dura in the optic canal, there is little danger of traction on the chiasm, if reasonable force is employed.

METASTATIC TUMOR

The documentation and treatment of metastatic retinoblastoma is a devious and disappointing challenge. The diagnosis is essentially academic since the treatment is entirely palliative and the result is inevitable death.

SIGNS

The early clinical signs of metastasis may be extremely obtuse. Failure to thrive, vague central nervous system symptoms, either irritability or increased somnolence, and, occasionally, nausea and vomiting may be presenting signs either of metastasis, or the initial clinical sign of retinoblastoma itself. Firm nodules over flat or long bones and bone pain with difficulty in movement can be the first indication of tumor spread.

Immediate documentation of these clinical signs is imperative, not only to establish the prognosis, but also to rule out a possible alternative explanation. One child with retinoblastoma had previous enucleation of one eye and successful treatment of the other with x rays and intra-arterial TEM. Several years later a call was received from another hospital indicating that the child had been admitted because of "rheumatic fever." The problem was narrowed down to difficulty in walking and some pain over the femur, and roentgenograms revealed a lytic bone lesion in the leg. With that history, the child was admitted to our hospital where work-up for tumor cells elsewhere in the body was completely negative. The radiologists insisted that the signs were diagnostic of eosinophilic granuloma of bone, and a separate, coin-shaped lesion was found in the skull. Despite acknowledgment by the ophthalmologists and pediatricians that this had to be metastatic retinoblastoma, the radiologists were adamant and when the femur was biopsied eosinophilic granuloma of bone was discovered and the disease has now been controlled by irradiation and the child is completely healthy with a relatively good outlook. Another child with apparently cured retinoblastoma developed the picture of transverse myelitis with the presumption of metastasis to the cord. She proved

to have Guillain-Barré syndrome and recovered completely. These cases serve only to illustrate that a child with retinoblastoma may develop other simulating and potentially curable conditions.

DOCUMENTATION

When metastasis is suspected, a complete skeletal survey should be made, with special attention to the skull and optic canals. Enlargement of the canals is a late, but very significant sign. Retinoblastoma metastasizes to bone marrow early and there is probably a rheological explanation for this preference. Tumor rarely, if ever, involves the lung except by continguity from a focus in a rib, but involves lymph nodes and the abdominal viscera late in the course of hematogenous metastasis. The disease kills about half the time by extension via the optic nerve into the meninges with a CNS death, and about 50 per cent of the time by widespread metastases to bone marrow, lymph nodes, and viscera. If neither optic nerve has been clinically involved by tumor, it is unusual for the central nervous system to be involved except by direct extension from a marrow lesion in the skull. The lesions seen in bone may be lytic or may be subperiosteal thickening which is often associated with pain. The involvement of bone marrow is irregular and, if metastasis is strongly suspected, marrow punctures should be done at several sites, perhaps both iliac crests, the sternum, and a spinous process. Abnormal bone marrow will be seen long before radiologic evidence of bone lesions can be detected.

The findings in bone marrow of patients with retinoblastoma have been divided into the following groups (Table 11).

The marrows in Group 0 are completely normal, whereas in Group 1 excessive lymphocytosis is seen. At one period it was suspected that this lymphocytosis might be the harbinger of marrow invasion, but

TABLE 11. BONE MARROW IN RETINOBLASTOMA

Group	Characteristics
0	Less than 8 per cent blasts
I	Over 8 per cent blasts with "atypical cells" and lymphocytosis (over 40 per cent before age two and over 30 per cent in older children)
II	Single, "tumor like" cells with bizarre nuclei and nucleoli with, or without, atypical cells and lymphocytosis
III	Definite single tumor cells and clumps containing up to four cells
IV	Many small clumps, or one clump with more than four cells

this has not proved to be the case. In Group 2 are single, suspect cells, but nothing diagnostic of marrow invasion by tumor. We have attempted to grow the bone marrow of patients with retinoblastoma in tissue culture in the hope that this might have the same diagnostic significance as the culture of marrow in patients with neuroblastoma, but technical problems have been encountered. If a specific retinoblastoma, or even a specific retinal antigen can be isolated from tumor cells, it should be easy to identify these unwelcome inhabitants in the bone marrow where blast cells can mimic tumor cells to an extraordinary degree.

In Groups 3 and 4, clumping occurs, which is diagnostic of marrow invasion. It is not until many typical tumor cells are seen and definite clumping occurs that a definitive diagnosis of marrow invasion is made.

In patients with neuroblastoma, HVA and VMA, along with other pressor substances, are excreted in abnormal amounts in the urine. Because of the histological similarities between neuroblastoma and retinoblastoma, it was felt that the same substances might be found in the urine of children with retinoblastoma, and 17 patients were studied.[20] While several of these patients did have elevated HVA and VMA excretions, they were not diagnostic, and it is suspected at the moment that retinoblastoma and neuroblastoma are biochemically enough different so that this test will not be of clinical value. It was hoped that quantitative measurements of HVA and VMA might be used as an index of metastatic involvement, but this has not proved to be the case. It is interesting, however, that HVA and VMA excretion in children with retinoblastoma decreased after the lesions were treated with radiation.

Circulating retinoblastoma cells in the peripheral blood have been studied[57] using a modified millipore technique. While tumor cells can be identified, their prognostic significance is uncertain and the mechanical effect of enucleation has not been documented. It is suspected that manipulation of the globe during enucleation might produce a shower of tumor cells into the peripheral blood and might adversely affect the prognosis. If this is true, the central retinal vein and the vorticose veins should be ligated early in the operation and, perhaps, a systemic chemotherapeutic agent should be instilled at the time of enucleation. This area deserves further study.

TREATMENT

Metastatic retinoblastoma was originally treated with intramuscular or oral TEM and, more recently, with systemic Cytoxan. In an effort to

minimize side effects "triple therapy" was then employed using a combination of Cytoxan, methotrexate, and dactinomycin.[56] More recently, alternative weekly courses of Cytoxan and vincristine have been used with the same schedule as has been employed in the treatment of neuroblastoma. It is the current impression that all three regimens are roughly equivalent, although we tend to slightly favor alternative courses of Cytoxan and vincristine at the present time. One-year palliation is the average expectation in the treatment of metastatic disease. Although the number of children involved with retinoblastoma is small, it is hoped that the treatment of metastatic disease may give us some insight into better chemotherapeutic agents.

If a fungating orbital mass or painful bone lesions are present, a course of localized radiotherapy will often be helpful.

MORTALITY

The over-all mortality in our series is 18 per cent. This is regarded as a minimal value since future complications will develop in a few patients, who will die. The latent period from the initial treatment to the time of death has been less than one year in 47 per cent of cases, less than three years in 66 per cent of cases, and less than five years in 77 per cent of cases.

Of those who die, 10 per cent live more than ten years and then succumb to their disease or to the complications of the treatment thereof, and 2 per cent live over twenty years and then succumb to the late complications of therapy.

Of 16 patients who expired after a period of ten years, 2 died of recurrent metastatic retinoblastoma, 1 died in an auto accident, 1 died of pulmonary tuberculosis, and 12 died from other neoplasms. The 3 who survived for twenty years died of neoplasms, 1 of thyroid carcinoma and 2 of osteogenic sarcoma.

Four other patients died of new and, apparently, entirely separate primary tumors. Two of these were osteogenic sarcomas developing in the distal femur, seven years following treatment in one patient and nine years in the other, with absolutely no evidence of any primary lesion in the area of irradiation in the skull. Another patient developed a Wilms's tumor and died five years after treatment for retinoblastoma.

The cause of death of patients with retinoblastoma is shown in Table 12.

If a patient with retinoblastoma is to die of that disease, he will usually do so within 2.4 years of the time of diagnosis. Late and

TABLE 12. MORTALITY IN RETINOBLASTOMA

Cause of death	Cases	Percentage	Average interval
Retinoblastoma	126	83	2.4 years
Radiation-induced tumor	18	12	13.0 years
New primary tumor	4	3	10.0 years
Others	3	2	10.0 years

malicious threats to these patients are completely separate primary neoplasms and radiation-induced tumors, which may have a latent period up to 30 years. Adults with one primary neoplasm commonly develop a second unassociated neoplasm. This phenomenon has not been widely observed in children probably because they have not lived long enough to develop a second neoplasm and because many of the cancers of childhood are fatal. It is possible that there is such a thing as a "cancer diathesis" and that patients with retinoblastoma may be predisposed to develop other malignancies later in life. There are two patients in our series who have developed fatal central nervous system neoplasms which have been biopsied at craniotomy and are extremely anaplastic. Despite the help of expert pathologists, it has been impossible to decide whether these are metastatic retinoblastomas manifest at a late date, whether they are radiation-induced tumors, although they did not arise in the area of the radiation beam, or whether they are unassociated, highly malignant, round-cell sarcomas. All three explanations are very disquieting in terms of the ultimate fate of children with retinoblastoma.

It is tragic that patients afflicted with this disease, who have fought and won a long and trying battle early in life, are again, many years later, visited by a specter which proves more virulent than retinoblastoma itself.

SUMMARY AND CONCLUSIONS

Retinoblastoma is inherited as an autosomal dominant characteristic. A sporadic unilateral case will transmit the disease to 10 to 20 per cent of his children, whereas a sporadic bilateral case will pass it on to nearly 50 per cent of his progeny. When a family history is present, retinoblastoma is particularly apt to be bilateral. All retinoblastomas may be considered to be germinal mutations, albeit of highly variable manifestation. When one child with retinoblastoma is born to normal parents with no family history of the disease, there is a 4 per cent chance that future siblings will be affected.

Retinoblastoma cells closely resemble primitive retinal cells that are destined to become receptor cells. The diagnosis is difficult when the tumor itself is not ophthalmoscopically visible. Typical calcification and seeding are almost pathognomonic signs.

The fourteen conditions most commonly confused with retinoblastoma are briefly outlined. When the diagnosis is in doubt, when the pathogenesis is unclear, when the eye is functionally lost, and when the fellow eye is normal, enucleation is the only safe course.

Precise irradiation is the cornerstone of the treatment of intraocular retinoblastoma. Light coagulation, cryotherapy, and ^{60}Co applicators are valuable adjunctive measures, and chemotherapy can palliate metastatic disease.

The current results in 192 cases are presented.

Pedigrees of the familial cases are appended as a reservoir for future calculations, since they are relatively rare.

ACKNOWLEDGMENTS

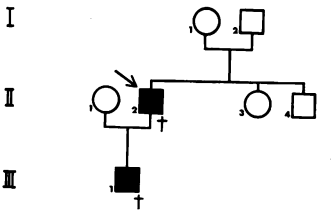
The treatment of retinoblastoma is a team effort and one member is indispensable to the others. Dr. James Wolff initially studies the children for systemic involvement and manages the metastatic cases. It is Dr. Patricia Tretter who supervises the irradiation with loving care and who is actually responsible for most of the good results. Dr. George Hyman, along with Dr. Wolff, supervises the chemotherapy, and Drs. Carl Feind and Alfred Markowitz perform the carotid injections.

The center of the group is the Tumor Clinic. Here Drs. A. B. Reese, Ira Jones, William Cooper, and Robert Ellsworth diagnose and follow patients with ocular tumors. Dr. David Kitchin investigates the pedigrees of involved families and supervises numerous experimental studies. Children could not be examined without the help of anesthesiologists, Drs. Herman Schwartz and Daniel Pino, and the clinic could not run at all without expert administration by Mrs. Lee Jones, jack-of-all trades, Mrs. Rita Johnson, and Mrs. Rita Dolan, who has literally worked day and night to make these studies possible. The unflagging help of my personal secretary, Mrs. Elsie Donohue, and Miss Kathy Donohue, has been invaluable. My wife Grace, who drew the appended pedigrees, has been a constant and understanding helper whenever needed.

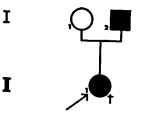
Lastly, Dr. Reese must be acknowledged as the true source of erudition, charm, and inspiration that drives the entire group along.

APPENDIX

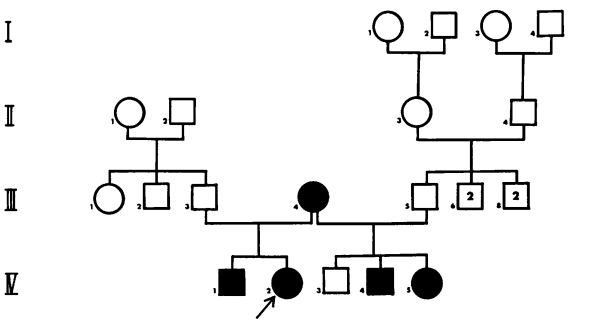
The pedigrees of all cases with familial retinoblastoma are appended. They are labelled with a "retinoblastoma number" (RB) for purposes of identification.



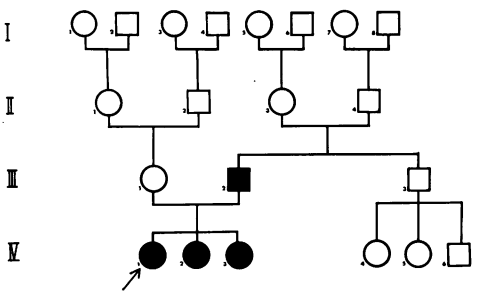
RB 66 D.S.



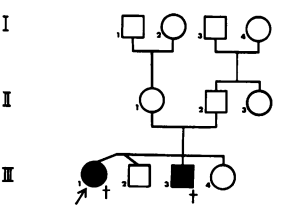
RB 123 N.D.



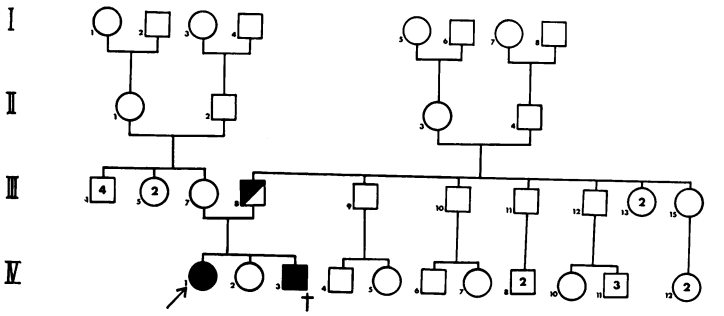
RB 124 C.Y.



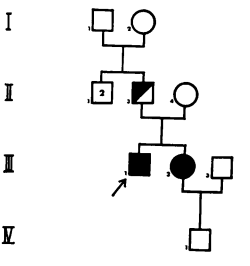
RB 131a M.D.



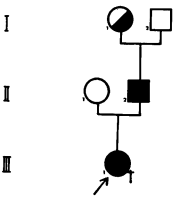
RB 153 G.R.



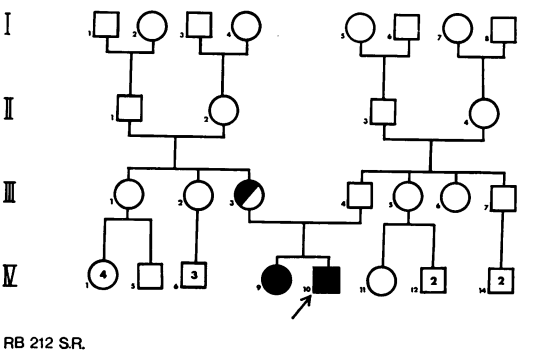
RB 175 M.C



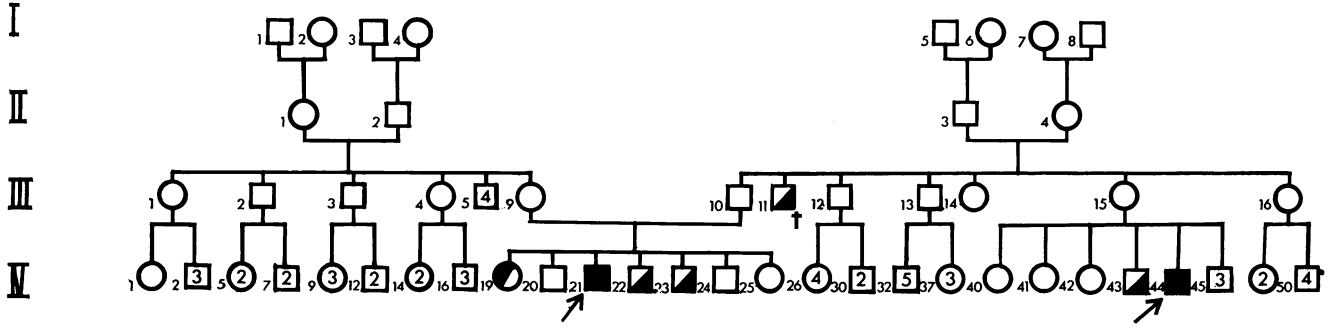
RB 181 M.G.



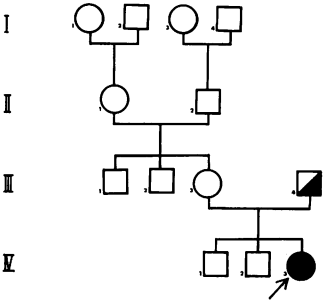
RB 190 B.R.



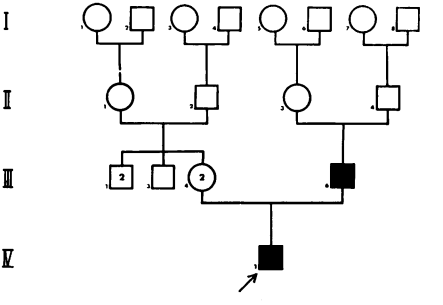
RB 212 S.R.



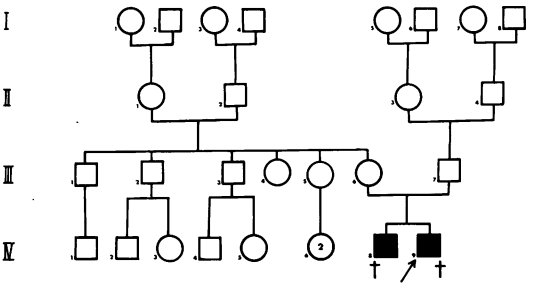
RB 330 T.K.
RB 225 D.C.



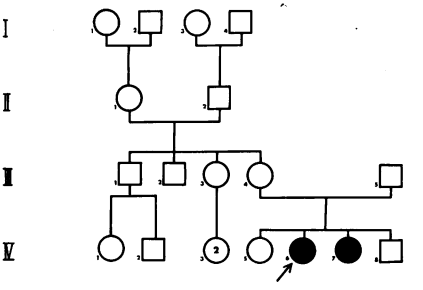
RB 236 L.P



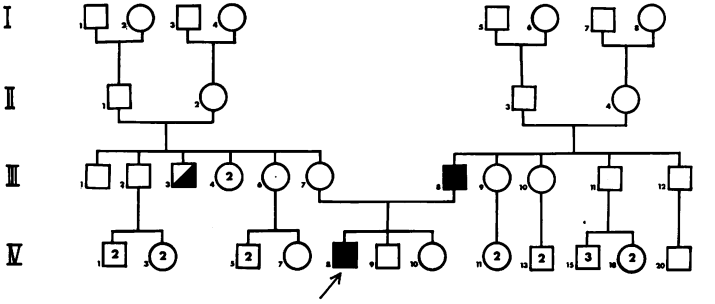
RB 258 P.A.



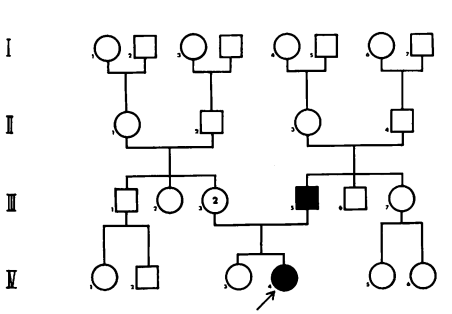
RB 268 J.Q.



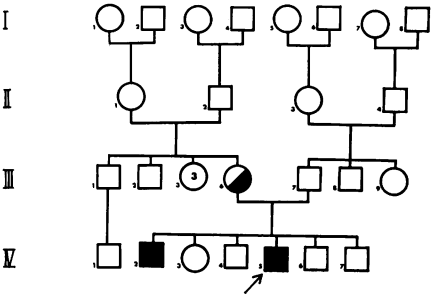
RB 288 T.H.



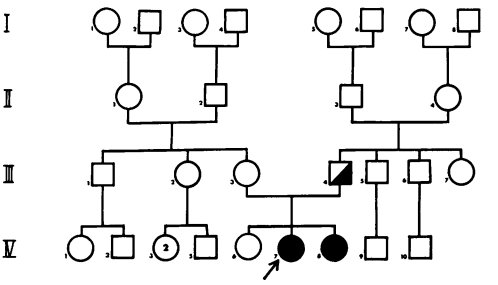
RB 307 R.G.



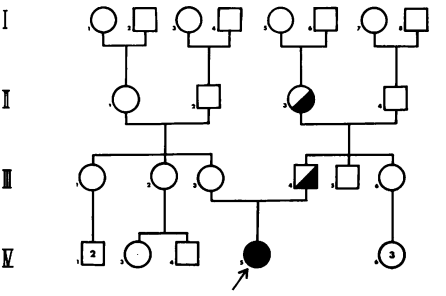
RB 313 D.B.



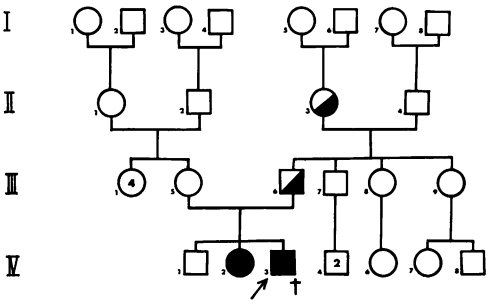
RB 324 M.F.



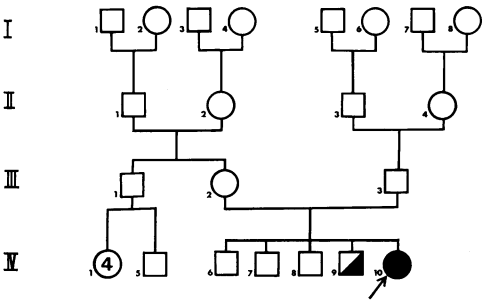
RB 336 R.M.



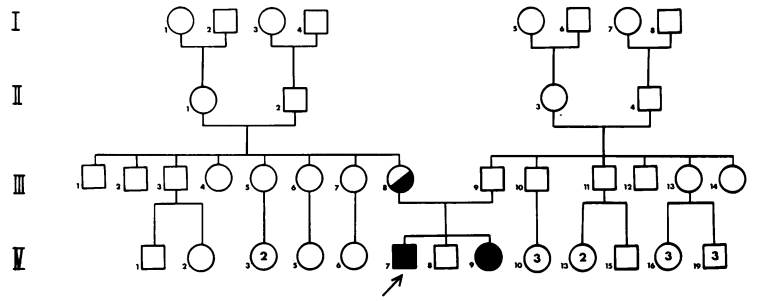
RB 344 K.J.



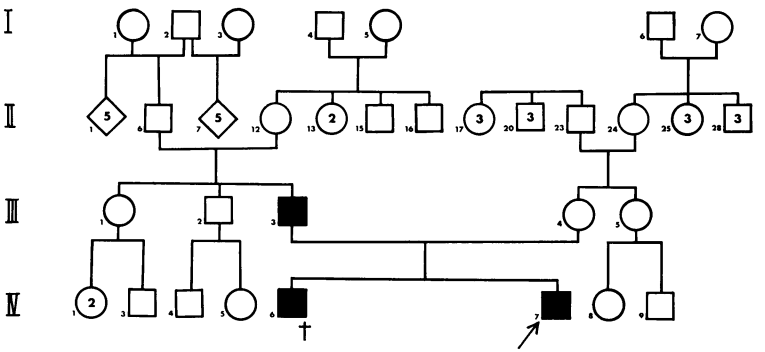
RB 409 H.T.



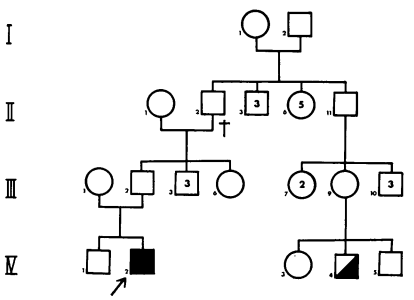
RB 415 L.T.



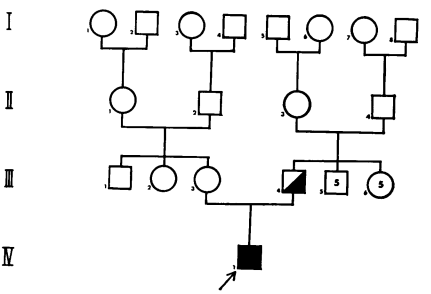
RB 420 E.M.



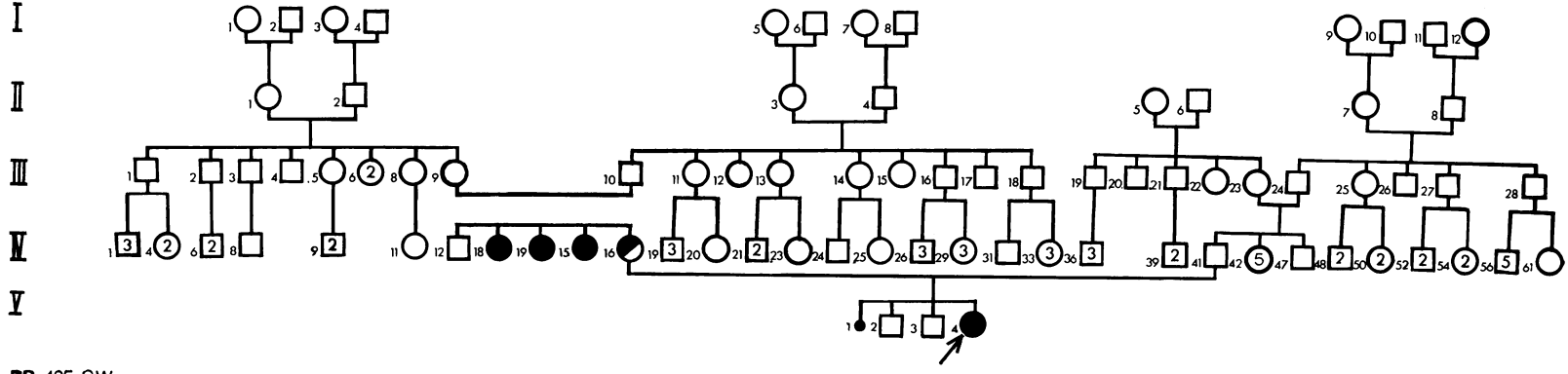
RB 449 W.S.



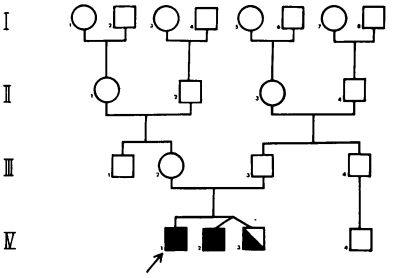
RB 458 G.H.



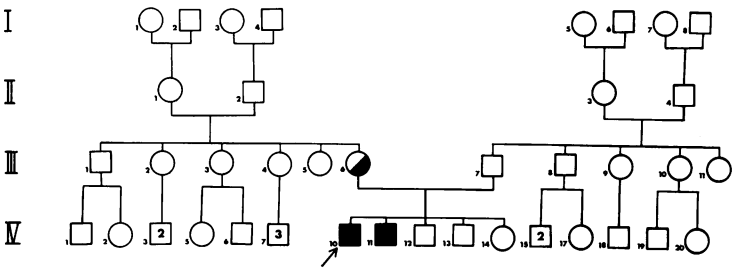
RB 464 J.D.



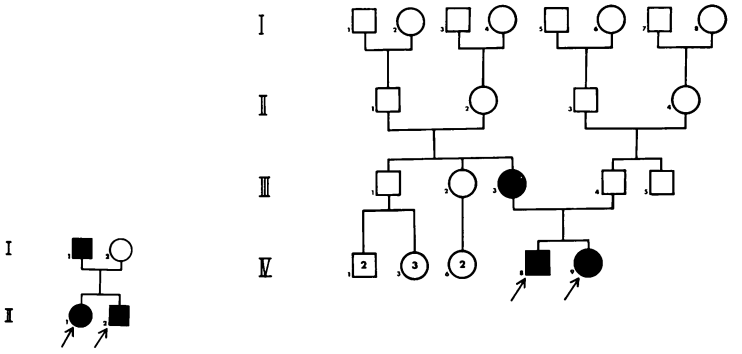
RB 425 C.W.



RB 490 J.L.

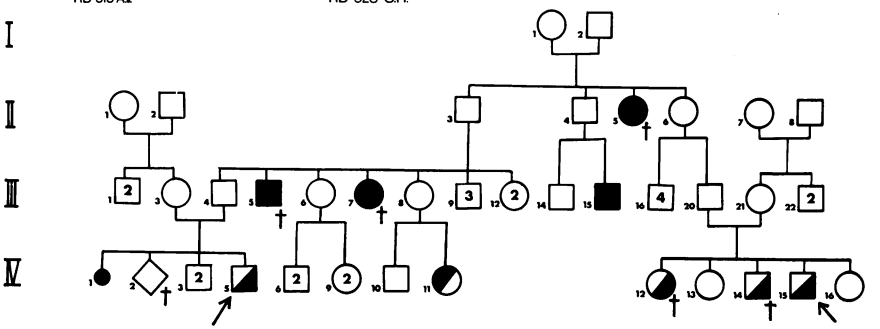


RB 507 R.N.

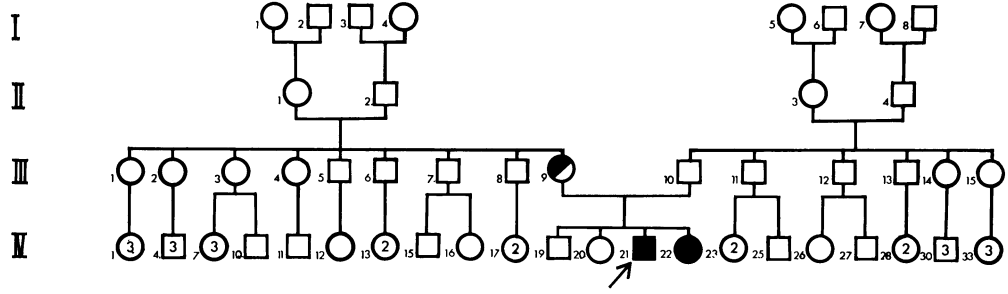


RB 515 A.V.

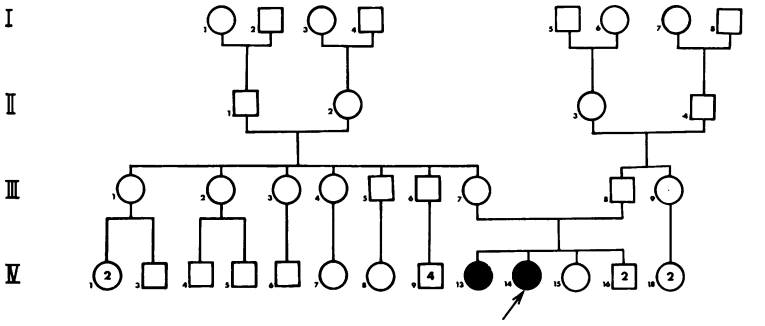
RB 529 C.H.
RB 528 O.H.



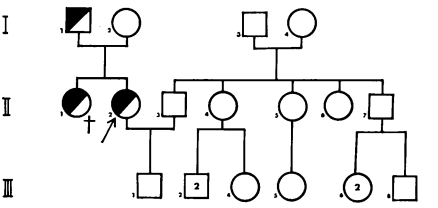
RB 537 T.C.



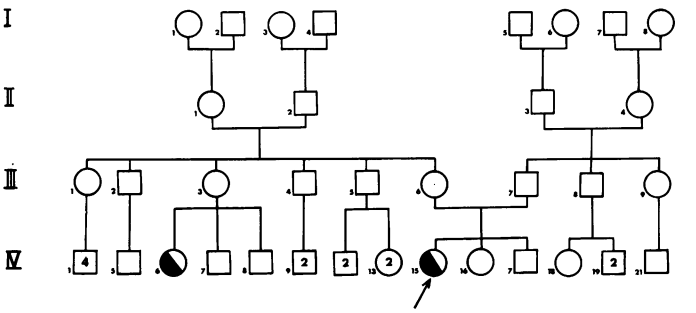
RB 575 R.S.



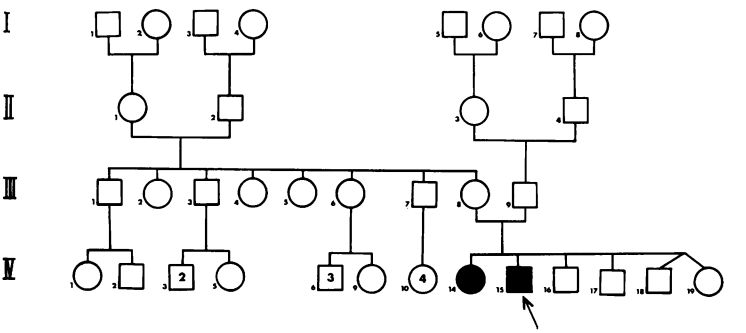
RB 541 D.C.



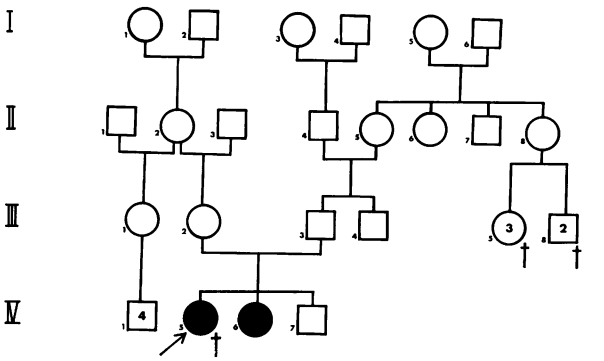
RB 577 S.T.



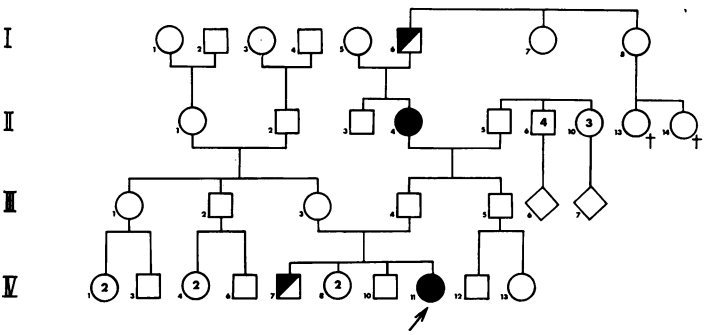
RB 612 R.R.



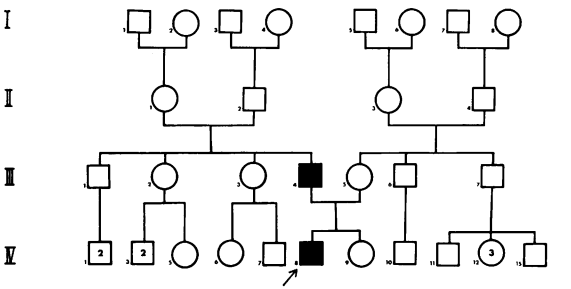
RB 639 R.B.



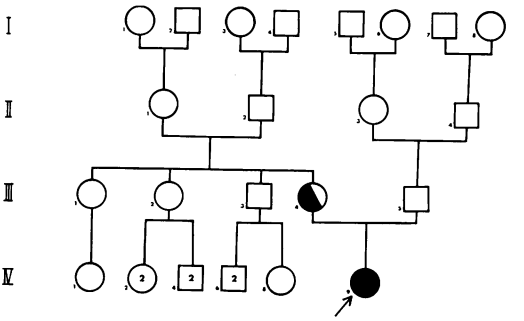
RB 655 M.W.



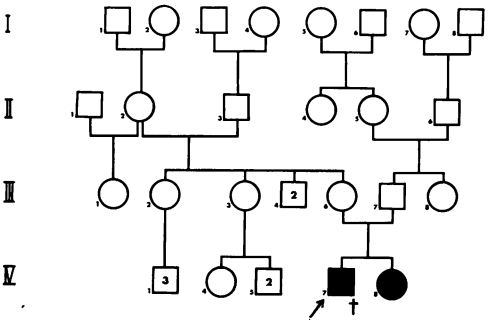
RB 717 A.C.



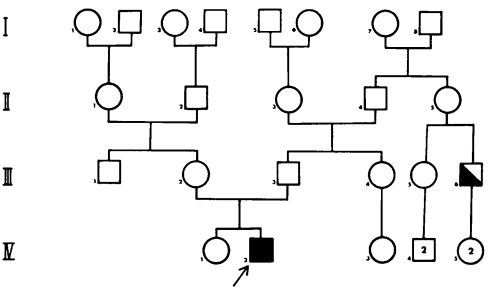
RB 719 K.B.



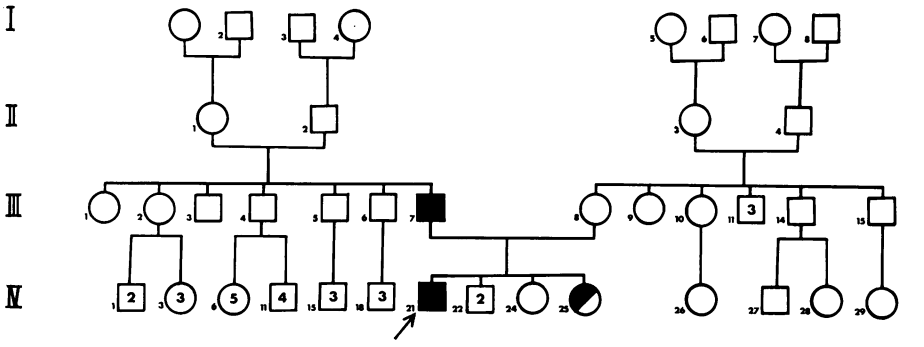
RB 743 S.P.



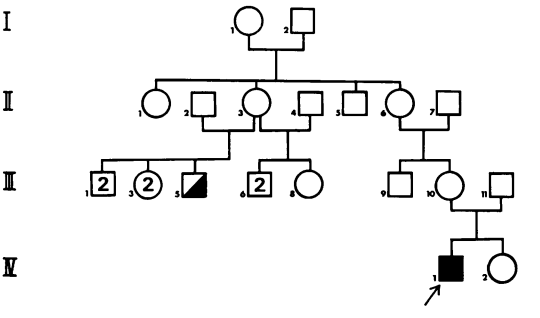
RB 789 J.F.



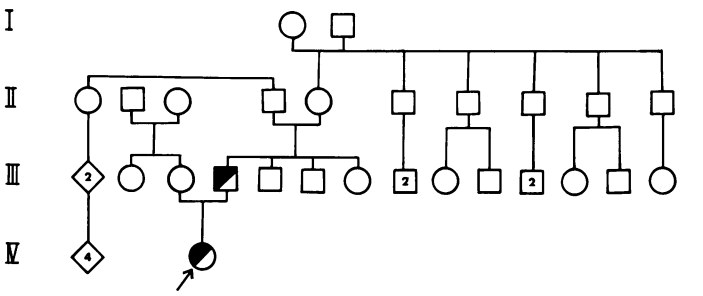
RB 792 C.K.



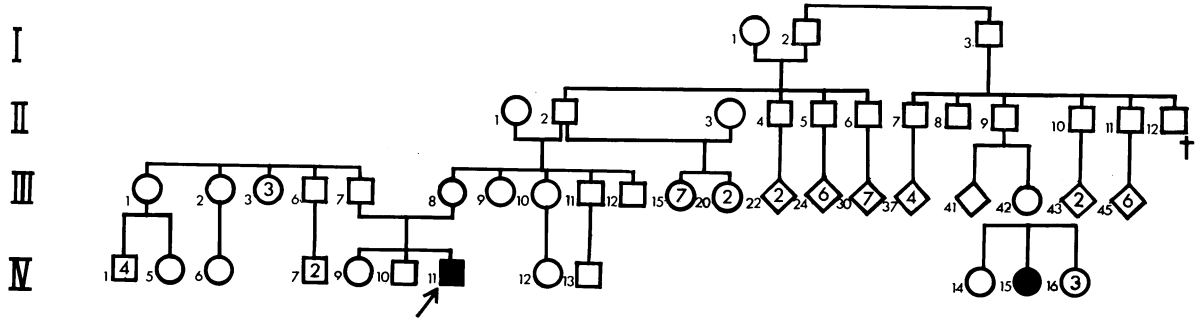
RB 801 J.M.



RB 823 M.B.



RB 838a D.J.



RB 877 M.M

REFERENCES

1. Hemmes, G. D., Untersuchung Nach dem Vorkommen von Glioma retinae bei Verwandten von mit dieser Krankheit Behafteten, Klin. Monatsbl. Augenh. 86:331, 1931.
2. Griffith, A. D., and A. Sorsby, The genetics of retinoblastoma, Brit. J. Ophth., 28:279, 1944.
3. Falls, H. F., and J. V. Neel, Genetics of retinoblastoma, A.M.A. Arch. Ophth., 46:367, 1951.
4. Vogel, F., Ueber Genetik und Mutationsrate des Retinoblastoms (glioma retinae), nebst einigen allgemeinen Bemerkungen über die Methoden zur Mutationsratenschätzung beim Menschen, Ztschr. Menschl. Vererb.-u. Konstitutionslehre, 32:308, 1954.
5. Böhringer, H. R., Statistik, Klinik und Genetik der schweizerischen Retinoblastomfälle, 1925 to 1954, Arch. Julius Klaus-Stiftg. Vererbg. forsch., 31:1, 1956.
6. Hemmes, G. D., Morbiditeit en prognose von retinoblastoma (glioma retinae), Nederl. Tijdschr. Geneesk., 11:211, 1958.
7. Macklin, M. T., Inheritance of retinoblastoma in Ohio, A.M.A. Arch. Ophth., 62:843, 1959.
8. Stevenson, A. C., and V. A. F. Martin, Occurrence of retinoblastoma in Northern Ireland, 1938 to 1956, Brit. J. Prev. & Social Med., 11:29, 1957.
9. Bech, K., and O. A. Jensen, Bilateral retinoblastoma in Denmark, 1928 to 1957, A.M.A. Acta Ophth., 39:561, 1961.
10. Mork, T., Malignant neoplasms of the eye in Norway; incidence, treatment and prognosis, Acta ophth., 39:824, 1961.
11. Francois, J., and M. T. Matton-Van Leuven, Recent data on the heredity of retinoblastoma, in (Ocular and Adnexal Tumors, new and controversial aspects), St. Louis: C. V. Mosby, 1964.
12. Verhoeff, F. H., Retinoblastoma. Report of a case in a man aged 48, A.M.A. Arch. Ophth., 2:643, 1929.
13. Rasmussen, K., Retinoblastoma in a man aged 48 years, Acta ophth., 21:210, 1944.
14. Makley, T. A., Jr., Retinoblastoma in a 52 year old man, A.M.A. Arch. Ophth., 69:325, 1963.
15. Arseni, C., and I. Opresco, An unusual case of retinoblastoma, Ann. Anat. Path., 4:129, 1959.
16. Boniuk, M., To be published in Tr. Am. Acad. Ophth.
17. Franceschetti, A., and V. Bischler, Rétinoblastome et hérédité, Arch. Julius Klaus-Stiftg. Vererbgsforsch., 21:322, 1946.
18. Macklin, M. T., A study of retinoblastoma in Ohio, Am. J. Human Genet., 12:1, 1960.
19. Vogel, F., Die eugenische Beratung beim Retinoblastom, Acta Genet. med. et gemel. 7:565, 1957.
20. Weiner, S., A. B. Reese, and G. A. Hyman, Chromosome studies in retinoblastoma, A.M.A. Arch. Ophth., 69:311, 1963.
21. Stallard, H. B., and L. S. Penrose, Chromosome deletion in a case of retinoblastoma, Ann. Human Genet., 27:171, 1963.
22. Brown, D. H., The urinary excretion of vanillylmandelic acid (VMA) and homovanillic acid (HVA) in children with retinoblastoma, Am. J. Ophth., 62:239, 1966.
23. Tsukahara, I., A histopathological study on the prognosis and radiosensitivity of retinoblastoma, A.M.A. Arch. Ophth., 63:1005, 1960.
24. Popoff, N., Personal communication.
25. Schofield, P. B., Diffuse infiltrating retinoblastoma, Brit. J. Ophth., 44:35, 1960.

26. Sakic, D., A case of retrogressed bilateral glioma retinae, Ber. deutsch. ophth. Gesellsch., 62:300, 1959.
27. Brown, D. H., The clinicopathology of retinoblastoma, Am. J. Ophth., 61:508, 1966.
28. Carbajal, U. M., Observations on retinoblastoma, Am. J. Ophth., 45:391, 1958.
29. Carbajal, U. M., Metastasis in retinoblastoma, Am. J. Ophth., 48:47, 1959.
30. Howard, G. M., Ocular effects of radiation and photocoagulation. A study of 100 globes with retinoblastoma, some of which were treated prior to enucleation, A.M.A. Arch. Ophth., 76:7, 1966.
31. Kitchin, D., To be published.
32. Pfeiffer, R. L., Roentgenographic diagnosis of retinoblastoma, A.M.A. Arch. Ophth., 15:811, 1936.
33. Kitchin, D., Personal communication.
34. Duguid, I. M., Features of ocular infestation by Toxocara, Brit. J. Ophth., 45:789, 1961.
35. Irvine, W. C., and A. R. Irvine, Jr., Nematode endophthalmitis: Toxocara canis, report of one case, Am. J. Ophth., 47:185, 1959.
36. Küchle, H. J., H. Remky, and R. Sattler, Diagnosis of gliomatous pseudouveitis, report of a case, Am. J. Ophth., 45:439, 1958.
37. Weizenblatt, S., Differential difficulties in atypical retinoblastoma, report of a case, A.M.A. Arch. Ophth., 58:699, 1957.
38. Meyer-Schwickerath, G., Light Coagulation, St. Louis: C. V. Mosby, 1960.
39. Reese, A. B., Persistent hyperplastic primary vitreous, Am. J. Ophth., 40:317, 1955.
40. Mann, I., Developmental Abnormalities of the Eye, 2nd ed., Philadelphia: J. B. Lippincott, 1957.
41. Reese, A. B., and F. C. Blodi, Retinal dysplasia, Am. J. Ophth., 33:23, 1950.
42. Reese, A. B., and B. R. Straatsma, Retinal dysplasia, Am. J. Ophth., 45(4) Part II:199, 1958.
43. Zimmerman, L. E., Personal communication.
44. Chee. P. H. Y., Radiation retinopathy, Am. J. Ophth., 66:860, 1968.
45. Cibis, P. A., and D. V. L. Brown, Retinal changes following ionizing radiation, Am. J. Ophth., 40:84, 1955.
46. Forrest, A. W., Tumors following radiation about the eye, Tr. Am. Acad. Ophth., 65:694, 1961.
47. Sagerman, R. H., J. R. Cassady, P. Tretter, and R. M. Ellsworth, Radiation-induced neoplasia following external beam therapy for children with retinoblastoma, To be published.
48. Melchers, M. J., Diathermy treatment of intraocular tumors, Utreckt: Schotonus & Jens, 1953.
49. Perera, C. A., Treatment of retinoblastoma by diathermic coagulation, Am. J. Ophth., 34:1275, 1951.
50. Dunphy, E. B., Management of intraocular malignancy, Am. J. Ophth., 44:313, 1957.
51. Stallard, H. B., Glioma retinae treated by radon seeds, Brit. M. J., 2:962, 1936.
52. Stallard, H. B., Ocular and Adnexal Tumors, the conservative treatment of retinoblastoma, St. Louis: C. V. Mosby, 1964.
53. Stallard, H. B., Doyne Memorial Lecture, the conservative treatment of retinoblastoma, Tr. Ophth. Soc. U. Kingdom, 82:473, 1962.
54. Ellsworth, R. M., Treatment of retinoblastoma, Am. J. Ophth., 66:49, 1968.
55. Wolff, J. A., Personal communication.
56. Wolff, J. A., C. B. Pratt, and A. L. Sitarz, Chemotherapy of metastatic retinoblastoma, Cancer Chemotherapy Reports, No. 16, 1962.
57. Stanford, G. B., To be published.