Retinoblastoma

By JAMES O. BISHOP, M.D.

It has been estimated that 200 new cases of retinoblastoma occur in the United States each year. This small number of cases assures that relatively few practicing pediatricians or ophthalmologists will ever encounter such a case in their practice. Despite its rarity, however, retinoblastoma is an important tumor with potential to provide fundamental insights into tumor biology in general. It is the goal of this article to outline in a necessarily simplistic fashion the current concepts about and approach to the problem of retinoblastoma, as well as to point out some of the unique features of the tumor that seem to give it special importance.

HISTOPATHOLOGY

There now appears to be fairly good agreement on the cell of origin of retinoblastoma, although the history of its descriptive pathology has been dominated by controversy. The retina is embryologically derived from the primitive medullary epithelium of the neural tube. The neural tube differentiates into ependymal cells, spongioblasts (which are the precursors of astrocytes), and germinal cells. The germinal cells differentiate further into medulloblasts (which are glial cell precursors) and neuroblasts (which are precursors of ganglion cells, bipolar cells, and photoreceptor cells).

Electron microscopy has lent strong support to a neuroblastic origin for retinoblastoma by the demonstration of organelles and other ultrastructural characteristics, both in vivo and in vitro, that bear marked similarities to normally developing retinoblasts.

The histologic picture of retinoblastoma varies but little, with main differences between tumors being degree of differentiation and amount of necrosis. Ts’o and others have demonstrated photoreceptor differentiation in about 6 per cent of retinoblastomas, the ultimate manifestation of which is the fleurette, a fleur-de-lis configuration of photoreceptorlike cells with abundant cytoplasm and long processes fanning out through a fenestrated membrane. In marked contradistinction, the typical retinoblastoma cell is uniformly small and rounded, with scant cytoplasm and deeply staining nuclei.

Increasing degrees of differentiation correlate with an improved prognosis for survival despite the fact that well-differentiated tumors are significantly less radiosensitive than their more anaplastic counterparts. This accounts for the finding that 40 per cent of eyes secondarily enucleated after failure of radiation therapy demonstrate photoreceptor differentiation, whereas only 6 per cent of eyes enucleated primarily show fleurette formation.

The spread of retinoblastoma can occur in several ways. Intraocular spread occurs by di-
rect extension into the optic nerve or choroid or by seeding into any part of the eye. The tendency toward implantation growth by seeding is great because the tumor has little stroma; consequently, it is not possible to determine with certainty in unilocular cases the exact number of de novo tumor foci. A knowledge of the number of primary tumors in unilaterally affected eyes would apparently be of extreme value in classification of the case as either sporadic or familial and would provide a much greater degree of certainty in genetic counseling than is now possible.

Choroidal invasion implies a reduced prognosis for survival, but the volume of choroid infiltrated by tumor seems to correlate better with mortality than the simple presence or absence of choroidal extension (Figure 1)*. Since extraocular extension usually occurs via the optic nerve, invasion of this structure is the single most important prognostic finding of microscopy. In one study of 300 cases there was a survival rate of 91.6 per cent with no optic-nerve invasion, 55.6 per cent survival when optic-nerve invasion failed to reach the plane of transection, and 36 per cent survival when the surgical transection passed through invaded optic nerve. From the optic nerve the tumor usually spreads in the subarachnoid space to the cranial cavity. Blood-borne metastases may also occur, occasionally many years after removal of the affected globe.

Occurrence rates in developing nations in tropical regions seem to be uniformly higher than in Western Europe or the United States. It has been estimated that there is one case per 3,300 live births in Haiti and one per 10,000 live births in Malawi and in the Bantu of South Africa. The question of case clustering in time and in space has not yet been settled, although the few epidemiologic studies to date have failed to demonstrate such clustering.

There are suggestions of a racial predilection for blacks, supported by the relatively high occurrence rates in Haiti and in Africa. The retinoblastoma mortality for blacks in the United States at the peak mortality age of two to three years is more than twice that of whites. Some, and perhaps all, of this excess mortality may be related to delay in diagnosis. However, the Malawi study suggested a particularly virulent course in blacks and a genetic study in Ohio demonstrated a higher mutation rate for retinoblastoma in blacks than in whites. There is no predilection for sex or for laterality.

**DIAGNOSIS**

Causes of leukokoria. The vast majority of retinoblastoma cases can be easily diagnosed, with about 90 per cent of patients presenting

---

* Figures 1 to 5 were prepared with the assistance of Mr. Johnny Justice, of the Department of Ophthalmology, Baylor College of Medicine. Figure 6 was provided by the Bascom Palmer Eye Institute, Miami, Florida.

Figure 1. Sagittal section of the eye showing retinoblastoma with uveal invasion.
Illostone® (erythromycin estolate)

Brief Summary
Consult the package literature for prescribing information.

WARNING

Hepatic dysfunction with or without jaundice has occurred, chiefly in adults, in association with erythromycin estolate administration. It may be accompanied by malaise, nausea, vomiting, abdominal cramps, and fever. In some instances, severe abdominal pain may simulate an abdominal surgical emergency.

If the above findings occur, discontinue Illostone promptly. Illostone is contraindicated for patients with a known history of sensitivity to this drug and for those with preexisting liver disease.

Indications: Included among the indications for this drug is streptococcal pharyngitis (Group A Beta-hemolytic) - Upper and lower respiratory tract infections and skin and soft tissue infections of mild to moderate severity.

Inj ectable penicillin G benzathine is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treating the above-mentioned conditions, penicillin G or V or erythromycin is the alternate drug of choice.

The importance of the patient’s strict adherence to the prescribed dosage regimen must be stressed when oral medication is given. A therapeutic dose should be administered for at least 10 days.

Consult the package literature for other indications.

Contraindications: Known hypersensitivity to this antibiotic.

Warnings: See Warning box above. The administration of erythromycin estolate has been associated with the infrequent occurrence of cholestatic hepatitis. Laboratory findings have been characterized by occasional hepatic function test values, peripheral eosinophilia, and leucocytosis. Symptoms may include malaise, nausea, vomiting, abdominal cramps, and fever. Jaundice may or may not be present. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in anaphylactic obstructive jaundice. Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within 48 hours after the drug is discontinued and may be more severe in sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Usage in Pregnancy — Safety of this drug for use during pregnancy has not been established.

Precautions: Caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

Surgical procedures should be performed when indicated.

Adverse Reactions: The most frequent side effects are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonresistant bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

Administration and Dosage: Adults — The usual dosage is 250 mg every 12 hours. This may be increased up to 4 or 5 mg per kg per day according to the severity of the infection.

Children — Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg per kg per day divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every 12 hours.

Streptococcal Infections — For the treatment of streptococcal pharyngitis and tonsillitis, the usual dosage range is 20 to 50 mg per kg per day in divided doses.

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Total Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg or less (less than 25 lb)</td>
<td>250 mg</td>
</tr>
<tr>
<td>11.1-18 kg (25-40 lb)</td>
<td>375 mg</td>
</tr>
<tr>
<td>18.1-25 kg (40-55 lb)</td>
<td>500 mg</td>
</tr>
<tr>
<td>25.1-36 kg (55-80 lb)</td>
<td>750 mg</td>
</tr>
<tr>
<td>36 kg or more (more than 80 lb)</td>
<td>1000 mg (adult dose)</td>
</tr>
</tbody>
</table>

In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least 10 days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg twice a day.

Consult the package literature for further dosage information.

Figure 2. Dilated pupil showing persistent hyperplastic primary vitreous (PHPV) with typical elongated ciliary process attached to the lens.

with white pupil (leukokoria), strabismus, visual loss, or glaucoma before the age of four years. However, in a small proportion of patients there may be major difficulties in making a certain diagnosis.

The first step in the evaluation of any child with strabismus must be a thorough fundus examination. All squinting children should be referred to an ophthalmologist. But because there is frequently a tendency for parents to procrastinate or ignore completely the pediatrician's recommendation to "see a specialist for a turned-in eye," the pediatrician should make every effort to obtain a good view of the fundi.

There are numerous conditions that can cause a white pupil, some of which may appear very similar to retinoblastoma. In one large series of 500 cases referred for possible retinoblastoma, 265 cases (53 per cent) had other causes of white pupil. The common cause of leukokoria in this series, other than retinoblastoma, was persistent hyperplastic primary vitreous (PHPV) (Figure 2). PHPV is a condition in which the fibrovascular tunic of the embryonic lens and the hyaloid vascular system persist and contract, ultimately resulting in degeneration of the
globe in most cases. These eyes may be difficult to distinguish from those harboring retinoblastoma, but differentiating features can usually be demonstrated.

A cause of leukokoria that is being increasingly recognized clinically is larval granuloma due to *Toxocara canis* or cysticercus (Figure 3). Especially in cases with organized vitreous abscess and hazy media, this lesion can appear very similar to retinoblastoma. In cases presenting an intraretinal or ciliary-body mass with clear media, worm tracks can frequently be seen in the fundus. Retrolental fibroplasia is obviously of diminishing differential diagnostic importance as a cause of leukokoria.

Coats' disease is an exudative retinal vasculopathy usually characterized by retinal telangiectasis, outpouring of massive amounts of subretinal and intraretinal lipid exudate, and retinal detachment, typically in males near the end of their first decade (Figure 4). A retinoblastoma growing exophytically — that is, from the posterior surface of the retina into the subretinal space — can present a clinical picture ophthalmoscopically indistinguishable from Coats' disease. Leber's miliary aneurysms and von Hippel-Lindau angiomatosis are retinal exudative vasculopathies that are usually more easily distinguishable from retinoblastoma.

The various retinal dysplasia syndromes are uncommon causes of leukokoria that are usually easily differentiated from retinoblastoma by their accompanying clinical features; however, there has been a recent, disturbing case report of a retinoblastoma occurring in a child with incontinentia pigmenti (Bloch-Sulzberger syndrome). Other differential diagnostic possibilities include organized vitreous hemorrhage or abscess, severe granulomatous uveitis, and such other intraocular tumors as astrocytic hamartoma, dictyoma, choroidal hemangioma, and intraocular extension of optic-nerve meningioma.

Diagnostic techniques. The binocular indirect ophthalmoscope used with the technique of scleral indentation is the single most important diagnostic tool in retinoblastoma. This instrument makes possible the visualization of very peripheral lesions that, by virtue of their relative inaccessibility, have in the past carried an ominous prognosis.

Echography has been shown to be more sensitive than x-ray in detecting intraocular calcification, which is highly suggestive of

---

*Figure 3.* Funduscopic view showing a nematode scar. This lesion can give a white pupillary reflex and can be difficult to distinguish from retinoblastoma, particularly in hazy media.

*Figure 4.* Funduscopic view showing typical features of Coats' disease. A similar exudation can occur in retinas overlying exophytic retinoblastoma.
retinoblastoma (Figure 5), and this technique may be very helpful in cases of opaque media in outlining tumor configuration and size. But it is not possible to differentiate retinoblastoma from organized hemorrhage echographically.

Computerized axial tomography is of particular value in preoperative assessment of orbital or metastatic involvement.18

The radioactive-phosphorus—uptake test has been highly acclaimed as a diagnostic mode in choroidal melanoma, but it probably should be avoided in children in general. Additionally, there is at least one group of retinoblastoma patients who seem to be exquisitely sensitive to radiation-induced neoplasia, particularly osteosarcoma, and any radiation that is not absolutely essential should be avoided in these children.

Cutaneous delayed hypersensitivity reactions have been demonstrated in patients with retinoblastoma who were skin-tested with a crude membrane extract of retinoblastoma tissue-culture cells; controls demonstrated no reaction.19 This finding has obvious diagnostic implications and may also indicate some hope for immunotherapy directed against a hypothetical retinoblastoma-tumor antigen.

Carcinoembryonic antigen and alphafetoprotein have been elevated in patients with retinoblastoma and have subsequently returned to normal following enucleation.20

In the occasional atypical case, study of the aqueous-humor lactic-acid dehydrogenase pattern and aqueous cytology have been of value. There is a tendency for the ratio of aqueous LDH concentration to serum LDH concentration to be greater than 1.5:1 in retinoblastoma and to be less than 1:1 in non-retinoblastoma.21 Additionally, in retinoblastoma the ratio of isoenzymes LDH2:LDH1 tends to be greater than 5:1, whereas that ratio is 1.4:1 or less in controls.22 There have been well-documented exceptions to these generalizations, and enzyme pattern determination should be viewed as an adjunctive test that can be suggestive but not diagnostic. Paracentesis probably has some small risk of tumor spread and should be reserved for particularly difficult atypical cases. There is one group of cases, however, usually in children older than four years, who frequently present with a granulomatous uveitis, in which aqueous enzymology and cytology may be most helpful. Tumor spread through scleral biopsy

There is at least one group of retinoblastoma patients who seem to be exquisitely sensitive to radiation-induced neoplasia

site has been demonstrated histologically, and it seems that vitreous aspiration should be done rarely, if ever.

A consistent histocompatibility antigen pattern in retinoblastoma patients has not yet been demonstrated.

CLASSIFICATION

It has become obvious that there are at least three discrete categories of patients with retinoblastoma, although it is not always possible to assign a particular patient to a group with certainty. There seem to be no differences in the tumors themselves; it is the persons who harbor the tumors that demonstrate fundamental differences. Every effort should

Figure 5. Funduscopic view showing typical features of retinoblastoma. The hard, sharply delineated areas probably represent calcium-DNA complexes.
be made to classify a patient with retinoblastoma into one of the following diagnostic groups:

**Sporadic retinoblastoma.** These patients are characterized by having only one primary-tumor focus. All sporadic cases have unilateral involvement, but not all unilateral cases are sporadic. It has been estimated that 60 per cent of cases are sporadic, and it is a fact that about 75 per cent of cases in the United States are unilateral.\(^{23}\) These patients tend to present at a later age than other patients, averaging around two years at age of presentation,\(^{24}\) but they may develop their tumor at any age. These individuals are phenocopies who seem to be normal in every way except for their tumor.

**Syndrome of multiple primary retinoblastomas (familial retinoblastoma).** These patients have germinal mutations\(^{26}\) for retinoblastoma that may be expressed as no primary focus, one primary focus, or several primary foci. Survivors transmit the mutation in an autosomal-dominant fashion with 80 per cent penetrance. These persons suffer from a family cancer syndrome with an increased risk of primary neoplasms involving the same organ and other organ systems and with other family members having an increased risk of neoplasia.\(^{26}\) Affected subjects tend to present at a very early age, usually younger than one year.\(^{24}\) It has been estimated that about 40 per cent of cases are familial, and approximately 25 per cent of cases in the United States are bilateral. All bilateral cases with normal karyotypes belong in this group. These children are exquisitely sensitive to radiation-induced neoplasia.\(^{26}\) Modern series, with necessarily limited follow-ups in relation to normal life expectancy, consistently demonstrate about a 10 per cent rate of subsequent primary tumors involving other organ systems. Two-thirds to three-fourths of the second malignancies occur within the field of radiation, and one-fourth to one-third occur outside of the radiation field or in nonirradiated patients.

Retinoblastoma with chromosome anomaly. Probably fewer than 5 per cent of patients with retinoblastoma have demonstrable chromosomal abnormalities. These patients usually demonstrate several congenital anomalies and a varying degree of mental retardation as well. The most common abnormality involves partial deletion of the long arm of chromosome 13; this is the only known instance in man or animal in which a specific prezygotic chromosomal aberration predisposes to a specific tumor.\(^{27}\) The risk of retinoblastoma seems to be increased by aneuploidy\(^{+}\) in general, and cases have been reported in XXY\(^{28}\) and trisomy 21,\(^{29}\) among others. It is interesting that Patau’s syndrome of retinal dysplasia is the expression of trisomy 13. It would probably be a waste of resources to karyotype every retinoblastoma patient, but all patients with associated congenital malformations or any degree of mental retardation should have chromosomal studies.

**GENETICS**

Familial retinoblastoma is transmitted in an autosomal-dominant fashion with 80 to 90 per cent penetrance. All bilateral cases should be considered familial, even if there is a negative family history. Since 10 to 15 per cent of unilateral cases represent the familial form.

\(^{+}\) Aneuploidy: any deviation from an exact multiple of the haploid number of chromosomes — e.g., fewer, as in Turner’s syndrome, or more, as in Down’s syndrome.
with reduced expressivity, the risk for a patient unilaterally affected with a negative family history to have affected children is about 5 per cent. Formulas are available to provide increasing degrees of certainty with each new bit of family history.\textsuperscript{30}

The current model for explaining the vertical transmission of retinoblastoma is Knudson's hypothesis: two mutations are required for the expression of retinoblastoma.\textsuperscript{33} If the first mutation occurs in a germ cell (prezygotically), the potential for familial retinoblastoma is determined. Both mutations occur in somatic cells in sporadic cases. The concept of delayed mutation is well established, and some clinical features of retinoblastoma can be explained by the two-hit hypothesis. The earlier age of presentation of familial cases might be related to their having been determined prezygotically. The hypothesis also explains how there can be only one tumor focus in sporadic cases, whereas there can be zero, one, or several foci in carriers of the germinal mutation. A pleiotropic effect of the germinal mutation has been proposed to account for the excess neoplasia in the familial form.\textsuperscript{31}

Knudson has raised the possibility that other cancers of childhood, such as Wilms' tumor, medulloblastoma, and neuroblastoma, might also demonstrate a prezygotically and postzygotically form.\textsuperscript{32} He believes that the high survival in retinoblastoma enables this pattern to be more clearly defined than in the other childhood tumors. Familial cases of Wilms' tumor and neuroblastoma tend to occur at an earlier age than nonfamilial cases and also have an increased tendency toward bilaterality. This suggests that lessons learned from a relatively small number of retinoblastoma patients could apply to childhood cancer in general.

The nature of the "mutation" is unknown. The finding of reverse transcriptase (RNA-directed DNA-polymerase) in retinoblastoma tissue raises the question of a viral etiology.\textsuperscript{33} Retinoblastoma phenocopies have been induced in experimental animals by viruses,\textsuperscript{34} but no viral particles have been demonstrated in retinoblastoma tissue. The finding that fibroblasts from the familial and D-deletion forms are more radiosensitive than normal fibroblasts raises the question of the possibility of a deficient DNA-repair mechanism.\textsuperscript{35}

**SPONTANEOUS REGRESSION**

The phenomenon of spontaneous regression of retinoblastoma has been well documented and proved histologically.\textsuperscript{36} Many hypotheses have been offered to explain how a virulent malignant tumor can suddenly disappear, but there is not a shred of evidence to support one over the other. Vascular compromise, immunologic response, sudden maturation similar to that seen in neuroblastoma, and reduction of tumor angiogenesis factor are some of the possibilities. At present, spontaneous regression remains another of the curious manifestations of retinoblastoma of unknown cause (Figure 6).

![Figure 6. Funduscopic view showing typical appearance of spontaneously regressed retinoblastoma.](continued)
TREATMENT

The preservation of life is, of course, the primary goal of treatment, but the maintenance of some degree of useful vision should be attempted in any case in which the probability for success is great enough to justify the risk of conserving a cancerous eye. Obviously this judgment requires extensive clinical experience as well as the exercise of a keen sense of medical ethics. Of absolute necessity is the ability to recognize treatment failures early and to enucleate hopeless eyes promptly.

Reese and Ellsworth are recognized as the most experienced authorities in the treatment of retinoblastoma, and their approach to the problem of classification and prognosis is outlined in Table 1. An examination under anesthesia is conducted, and detailed retinal baseline drawings are prepared. Each eye is then classified according to the prognostic scheme.

Most unilateral cases are far advanced at the time of presentation; consequently, enucleation is commonly performed after a thorough examination of the fellow eye and a metastatic search. Strict attention must be directed toward obtaining an optic-nerve stump about 10 mm. long. Small unilateral tumors are most commonly detected (1) if they occur in the macula and provoke strabismus or (2) by screening members of retinoblastoma families. Because of a generally good success rate with conservative (i.e., conservation of the globe) therapy in prognostic groups I to III, more and more unilateral cases are being treated. Some authorities believe that the only indication for enucleation is involvement of

---

TABLE 1

PROGNOSTIC CLASSIFICATION FOR RETINOBLASTOMAS 
(ACCORDING TO REESE43,44)

<table>
<thead>
<tr>
<th>Group</th>
<th>Prognosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Very favorable</td>
<td>a. Solitary tumor, less than 4 disc diameters in size, at or behind the equator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Multiple tumors, none over four disc diameters in size, all at or behind the equator</td>
</tr>
<tr>
<td>II</td>
<td>Favorable</td>
<td>a. Solitary tumors, 4 to 10 disc diameters in size, at or behind the equator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Multiple tumors, 4 to 10 disc diameters in size, behind the equator</td>
</tr>
<tr>
<td>III</td>
<td>Doubtful</td>
<td>a. Any lesion anterior to the equator</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Solitary tumors larger than 10 disc diameters behind the equator</td>
</tr>
<tr>
<td>IV</td>
<td>Unfavorable</td>
<td>a. Multiple tumors, some larger than 10 disc diameters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Any lesion extending anteriorly to the ora serrata</td>
</tr>
<tr>
<td>V</td>
<td>Very unfavorable</td>
<td>a. Massive tumors involving over half the retina</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Vitreous seeding</td>
</tr>
</tbody>
</table>

---

*Dr. Bishop is Clinical Instructor, Department of Ophthalmology, Baylor College of Medicine, and attending physician at Memorial Hospital, Houston.*
the optic nerve and that all cases that can be seen to be free of optic-nerve involvement should be conservatively treated.37

In bilateral cases the presenting eye is usually enucleated because of massive involvement, and the second eye is usually treated. If favorable tumors are found in both eyes, they are both treated. If both eyes have relatively advanced symmetrical involvement, they are both treated. Frequently, asymmetry will develop after radiotherapy, and the possibility of salvaging one of the eyes exists. By the use of this technique, both eyes are conserved in about one-fourth of cases, one eye is conserved in about half of the cases, and both eyes are lost in about one-fourth of the cases. Only occasionally are both eyes primarily enucleated, but in the case of bilateral far-advanced disease, this seems to be the only reasonable thing to do.

In group V intraocular cases, Ellsworth38 is using a protocol of ocular irradiation in combination with systemic vincristine and cyclophosphamide. Because of the need for intracarotid injection and subsequent severe complications, triethylenemelamine (TEM), the first widely used chemotherapeutic agent for retinoblastoma, is being replaced by more effective and safer drugs. In cases in which there are suspected micrometastases,39 such as in optic-nerve invasion, massive choroidal involvement, epibulbar growth, or involvement of the scleral emissaries, vincristine and cyclophosphamide are used prophylactically for 12 to 15 months.

If there is microscopic involvement of the cut end of the optic nerve, the orbit is irradiated. In the case of gross optic-nerve involvement or central nervous system disease, orbital and whole-brain irradiation and intrathecal methotrexate are given. In orbital recurrences, an excisional biopsy is performed and orbital irradiation is delivered together with the chemotherapeutic regimen of vincristine, cyclophosphamide, and Adriamycin. These same agents are being used palliatively in metastatic disease. Orbital exenteration* never was shown to be effective in orbital recurrence and has been discontinued, at least until the effectiveness of the chemotherapeutic approach has been determined.

**CONSERVATIVE TREATMENT MODALITIES**

Radiation therapy. With the exception of the more differentiated tumors, retinoblastomas are extremely sensitive to radiation. Because of the diffuse nature of many retinoblastomas, Reese38 considers the entire retina to be at risk and utilizes external-beam radiation as the cornerstone of treatment. However, the increased recognition of the hazard of radio- genic neoplasia in the survivors will lead to the increased utilization of photocoagulation and cryotherapy in the future.

Desirable characteristics of external-beam supravoltage irradiation are a knife-sharp beam, enabling exclusion of the lens through a temporal portal, and an isodose curve that delivers maximum energy to the plane of the tumor and very little to skin and developing bone. A total dose of 3,500 to 4,500 rads fractionated into 400-rad doses given three times weekly seems to give optimal results, with freedom from radiation complications in about 75 per cent of patients.38 Corneal necrosis, radiation glaucoma, and radiation cataract can usually be avoided by use of a temporal portal, and the main complication is then retinal vascular necrosis. The incidence of radiation-induced second primary tumors has been estimated to be about 1 per cent at that dosage level.40

---

* Removal of the entire contents of the orbit.
Photocoagulation is being increasingly used to treat small tumors up to 6 disc diameters initially or small recurrent tumors after diffuse irradiation. The goal of treatment is to inter-

rupt the retinal tumor circulation. Some restraint in the intensity of photoapplications must be urged because repeated applications to large unfavorable tumors can cause disruption of the lamina vitrea, massive choroidal invasion, scleral necrosis, and epibulbar extension.41

Cryotherapy is a treatment mode that is complementary to photocoagulation since it can be used on similar, but more anteriorly located, lesions. It can also be very useful in final obliteration of tumors that have been partially treated by photocoagulation.

Radioactive explants* can be useful for recurrences too large to attack with cryotherapy or photocoagulation or for initial treatment of a single tumor up to about 12 mm. in diameter. The two types in most common use are cobalt plaques, which are gamma emitters, and ruthenium plaques, which are beta emitters. Eighteen out of 22 eyes treated primarily with ruthenium plaques in a recent series were conserved.42 Case selection is crucial.

TREATMENT RESULTS

The current survival rate in England and in the United States is in the range of 86 to 90 per cent.24,38 This is mainly attributable to early diagnosis. The mortality in the developing nations sometimes approaches 100 per cent. The cure rates in several large series using the modalities already discussed are in the range of 70 to 80 per cent of treated eyes' retaining some degree of useful vision. In reading the literature one must be constantly alert to the distinction between survival rate and cure rate (rate of conservation of affected eyes).

It has been demonstrated that children with retinoblastoma fare better in referral centers with a retinoblastoma protocol and an organized team approach than they do in hospitals lacking these features.44 Additionally, the relative rarity of retinoblastoma presents a serious problem in its study, and the potential to learn from many cases will be wasted unless all patients are referred to established treatment centers. It should be obvious that without the studies done on large series of cases by Reese and others we could not have achieved our present understanding of the tumor.

continued
The amount of excess mortality engendered by conservative therapy has not yet been conclusively determined. The survival rate among therapeutic failures (children with enucleations because of uncontrolled or recurrent tumor growth or radiation complications) seems to be as good as in those enucleated primarily. However, this is a very difficult and complex question and more data are needed.

**SUMMARY**

Retinoblastoma is a radiosensitive malignancy of neuroblastic origin that primarily affects young children. Its relatively low incidence belies its potential importance in the understanding of tumor biology in general. A case is made for referral of all retinoblastoma patients to centers with retinoblastoma protocols.

---

**BIBLIOGRAPHY**