ADVANCED COATS' DISEASE

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INTRODUCTION

IN 1908, GEORGE COATS DESCRIBED A SERIES OF PATIENTS WITH A UNIQUE ocular disorder characterized by massive intraretinal and subretinal exudation.[1] Although numerous studies during the past eight decades have expanded our knowledge of this disorder, Coats' classic treatise remains the finest description of its clinical and pathologic characteristics. The advanced form of Coats' disease, defined in this study as an ocular condition characterized by total exudative retinal detachment secondary to leakage from congenital retinal telangiectasias, has remained a diagnostic and therapeutic challenge. If left untreated, advanced Coats' disease progresses naturally to the development of rubeosis iridis and painful neovascular glaucoma. The disease may be extremely difficult to differentiate from exophytic retinoblastoma, inasmuch as both conditions may present in children with the triad of total retinal detachment, subretinal mass or exudation, and abnormal retinal vessels. Differentiation is important for two major reasons. First, a secure diagnosis avoids unnecesary enucleation in the benign Coats' disease, permitting the ophthalmologist to safely explore alternative means of ocular salvage. More importantly, patients harboring retinoblastoma do not incur delays in diagnosis and thus have a better prognosis for ocular salvage and overall survival.

The main purpose of this study is to define the clinical and auxiliary diagnostic features that permit an accurate and rapid distinction between advanced Coats' disease and exophytic retinoblastoma. The literature on this disease is briefly reviewed, and the clinical findings and disease progression of children with advanced Coats' disease are analyzed.

HISTORICAL REVIEW

The literature on Coats' disease encompasses more than 100 manuscripts published in the past eight decades. This review is limited to highlights of literature pertinent to the present study. The reader is referred to the exhaustive landmark reviews of the literature on Coats' disease by Woods and Duke[2] and by Campbell[3] for additional details.

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RECOGNITION

In his classic paper published in 1908,[1] Coats described an ocular condition characterized by the presence in the fundus of large masses of white or yellow exudation, sometimes accompanied by retinal vascular abnormalities. Coats personally studied six cases both clinically and histologically; two were children aged 7 and 8 years, and four were young adults aged 26 to 37 years. From these detailed studies, augmented by information drawn from the published literature, he defined three classes of retinal disease presenting with massive exudation in the fundus:

1. Without gross vascular disease.
2. With gross vascular disease.
3. With large arteriovenous communications.

He pointed out that ". . . with regard to Groups 1 and 2, the points of similarity are so numerous that one can scarcely believe the pathological basis to be different."

In a subsequent paper, published in 1912,[4] Coats amended his original classification and combined groups 1 and 2 to form a single clinical entity—exudative retinitis—subsequently known as Coats' disease. He eliminated group 3 from his former classification after von Hippel[5] demonstrated that the formation of an arteriovenous anastomosis was associated with the development of a retinal angiomatosis, which constituted a distinct condition known as angiomatosis retinae.

Coinciding with the publication of this second paper, Leber[6] reported a form of retinal disorder characterized by the presence of multiple aneurysms, which he thought should be included in classification group 2 as described by Coats in 1908. Today, most ophthalmologists accept that Leber's miliary aneurysms correspond to a stage of Coats' disease in which telangiectasis and aneurysm formation are evident, but without extensive exudation.[3,7-9]

CLINICAL CHARACTERISTICS AND DISEASE PROGRESSION

As described by Coats,[1] this condition is initially painless and develops slowly and insidiously. Often, it is not discovered until well advanced. The cases described by Coats in 1908 were of end-stage disease and, although new formation has been added, many of the features that he described have been confirmed as being typical of the disease.[3,8,10-12] Coats[1,4] summarized the characteristics of the disorder as follows:

1. It most frequently occurs in young males.
2. It usually presents unilaterally.
3. It is congenital but nonfamilial and not associated with any systemic disease.

4. The retinal vascular anomalies, which may be difficult to visualize ophthalmoscopically, include irregularities in the caliber of the smaller vessels with the formation of telangiectatic aneurysms, capillary drop-out, and the development of arteriovenous shunt vessels, hemorrhage, perivasculitis, and vascular sheathing.
5. Exudation is a prominent feature. Intraretinal accumulations often involve the macula, and large deposits are generally found in the posterior pole of the fundus, penetrating the subretinal space and lying beneath the retinal vessels. The mass of exudate (thought by Coats to originate from a retinal hemorrhage) contains cholesterol.
6. Intraretinal and subretinal infiltration by "ghost," "foam," or "balloon" cells representing lipid-laden macrophages is associated with the exudative process.
7. There is slow progression to retinal detachment, cataract, glaucoma, and phthisis bulbi.

More recent clinical data have confirmed that the disease occurs predominantly in infant or juvenile males and is almost always unilateral.[10,13] Of the 51 patients studied by Morales,[10] the average age at first examination was 8 years (range, 1 to 34 years), and in 78% of the cases the disease was unilateral. In cases where the condition occurs bilaterally, development in the two eyes is asynchronous.[9]

Several large studies[8,12,14-19] have provided additional information about the early development and progression of the disorder. After reviewing these works, Sigelman[20] modified a classification of the clinical progression of Coats' disease by Morales[10] into five major stages: (1) retinal telangiectasis; (2) focal intraretinal exudates; (3) subretinal mass with partial retinal detachment; (4) total retinal detachment; and (5) chronic retinal detachment with subretinal membrane, uveitis, glaucoma, and cataract.

The ophthalmoscopic appearance of the disorder varies according to its stage of progression. Telangiectases and other vascular abnormalities develop in the retinal capillary network. In their earliest stages, these lesions may be difficult to visualize ophthalmoscopically, but fluorescein angiography can be used to demonstrate their presence.[17,18] Affected vessels show irregular enlargement and distortion, and there are associated microaneurysms (Leber's miliary aneurysms) on terminal vessels.[21-23] Microaneurysms are commonly found surrounding areas of capillary drop-out and are often centrally orientated.[24] Partial or total retinal vein occlusion may occur, and arteriovenous communications develop. Intraretinal hemorrhage sometimes results from rupture of the dilated vessels,[21] and fundus fluorescein angiography reveals that the telangiectases

leak dye.[13] Leakage is particularly profuse from microaneurysms situated in the peripheral retina, giving a typical "light-bulb" appearance.[20]

Vascular abnormalities and leakage lead to edema and the accumulation of exudates. The exudates tend to accumulate preferentially in the outer retina, in the region of the macula, forming a macular star. The abnormal vascular elements responsible for exudation may surround the macula, be situated close to it, or be situated within the peripheral retina. Once the macula is involved, visual acuity is rapidly affected. Hence, such cases tend to be diagnosed relatively early in the course of the disease. Subretinal accumulations of exudate also generally develop in the posterior pole of the eye, taking the form of yellowish-white mounds and broad sheets of lipid material with cholesterol as the chief component.[25] Retinal blood vessels overlying patches of exudate gradually become masked and may undergo gliotic sheathing.[11,16] Furthermore, as the mass of exudate increases and retinal detachment occurs, retinal vessels become obscured. Long-standing subretinal exudates may show superficial crystalline deposits. Proliferated retinal pigment epithelium may be found attached to the retina and within the subretinal space. These pigment epithelial cells may be associated with subretinal fibrous proliferation and resultant retinal folds.[12]

Vascular abnormalities and the accumulation of exudate commonly occur in the sector temporal to the fundus, predominantly in the superior quadrant, the macular, and the foveolar areas.[24] If the exudate involves a full quadrant of the retina, a partial serous retinal detachment almost always ensues. This detachment can be expected to increase in extent as the vascular and exudative components of the disorder progress, until there is a total retinal detachment overlying a yellow-green subretinal mass. The secondary complications of uveitis, glaucoma, and cataract may follow.[10,13] The choroid and sclera are usually unaffected by the disorder and the vitreous generally remains clear, at least until the retina is totally detached. After detachment, some evidence of late neovascularization and vitreous hemorrhage may be seen. Interestingly, in some patients, the condition may spontaneously regress before neovascular complications arise.[3,21,26]

ETIOLOGY AND PATHOGENESIS

Coats originally believed that retinal hemorrhage was the primary lesion in this disorder and suggested the term "external hemorrhagic retinitis."[1] He stated that "the presence of cholesterin" crystals in a tissue was indicative of a preceding hemorrhage. In his 1912 paper, Coats reported that although the primary feature of the disease was hemorrhage in the

outer retinal layers, and exudative and inflammatory feature was also present, and he suggested the term "external exudative retinitis." In 1915, Leber[27] questioned this premise and suggested that the hemorrhage was secondary. Marshall and Michaelson[28] had the opportunity to evaluate four early cases and concluded that "haemorrhages played a very minor role in the process." Further evidence to support this idea was presented by Manschot and de Bruijn[12] as well as other authors.[15,29]

Coats speculated that the disorder represented "an unknown form of vascular disease, possibly founded on a congenital vulnerability of the vessel wall."[1] Subsequent investigators have confirmed this view and provided detailed information on the pathogenesis of the disorder,[8,12,16,21] although the exact nature of the primary lesion remains to be defined. Conversely, as exemplified by Imre,[9] another school of thought exists that regards chronic inflammation as the basis of Coats' disease[6,7] and regards the vascular changes as secondary.

In 1934, Junius[30] suggested the walls of small arterioles were affected by minute physicochemical changes. In his 1955 Gifford lecture, Algernon Reese[8] described finding a periodic acid-Schiff (PAS)-positive thickening of vascular basement membranes. Reese stated that "the basic change in this disease is the formation of this polysaccharide under the endothelium leading to atresia and even occlusion of vessel lumina thereby occasioning vascular ectasia and the formation of collateral channels."

Wise[14] thought that the vascular abnormalities arose as a response to local retinal hypoxia. Imre[9] suggested the possibility that underlying endocrine disturbance was causative. Duke and Woods[25] refuted Reese's earlier findings and reported that the "deposition of a PAS-positive mucopolysaccharide in the retinal arterioles and telangiectases play no role in the pathogenesis of the disease." They suggested that the intermediate action of an acid mucopolysaccharide enter "into a combination with the lipoproteins of the blood plasma, thus forming a new acid-mucopolysaccharide-lipoprotein complex. The resulting hydrolysis of this complex would free the cholesterol for deposition in the external retina and subretinal space, while the fatty acids are extravasated into the subretinal space." Other attempts to define the cause of the disease and establish a new classification system served only to confuse and complicate Coats' original scheme. As noted above, Leber[6] suggested that an inflammatory process was a major factor in the development of the disorder. Duke-Elder[31] reinstated angiomatosis retinae as one of the categories of Coats' disease, distinguished various types of retinitis, and added an exudative choroiditis to the classification listing. The inclusion of these various inflammatory conditions proved particularly misleading. More recent

studies have confirmed Coats' original view that the retinal changes are not predominantly inflammatory in nature.[3,12,16,25,32,33] Few additional insights into the underlying cause of Coats' disease have been proposed, and the etiology of this disease remains controversial.

Histologic and electron microscopic studies[12,16,19,21,34,35] have demonstrated the characteristics of the early vascular changes. These include thickening and hyalinization of the vessel walls in some areas and thinning, with loss of the endothelium and other elements, elsewhere. As would be predicted, the thinning is associated with vascular dilatation and the formation of telangiectases and aneurysms.

Copious leakage from the areas of telangiectases results in thickening of the retina, with intraretinal and subretinal accumulation of fluid and exudates, and the appearance of cysts. These effects lead to the disorganization and degeneration of the neural retina, with gliosis and invasion by phagocytic cells ("ghost" cells or lipoidal macrophages). These "ghost cells" apparently originate predominantly from retinal pigment epithelial cells.[35,36] However, some "subretinal macrophages may be histiocytes that have migrated from the retina."[12] Cells of the retinal pigment epithelium and glial cells from the retina form a subretinal fibrous membrane. This membrane is attached to the external surface of the neural retina and may lead to a local retinal detachment early in the progression of the disease. A more extensive retinal detachment is almost invariably associated with subretinal accumulations of cholesterol-laden material, which may be substantial, forming mounds and sheets and containing cholesterol clefts. These accumulations lie between the retina and the retinal pigment epithelium, and the latter may show local areas of proliferation. Chang[19] observed retinal pigment epithelial abnormalities in 46 of 62 eyes (74.2%), including "exuberant proliferation and fibrous metaplasia of the retinal pigment epithelium" in the submacular space in 13 of 62 cases (21%). Although hemorrhages may occur, Coats' suggestion that aggregates of cholesterol represent a late stage in the organization of a subretinal hemorrhage has not been substantiated.[29]

The results of histologic and ultrastructural studies have thus confirmed that abnormalities of the retinal vessels are fundamental in the development of Coats' disease. Tripathi and Ashton[16] further postulated that pathologic changes are initiated by a functional or structural breakdown in the blood-retinal barrier (ie, the vessel wall), and that this breakdown precedes the observed cellular disorganization and formation of telangiectases, aneurysms, and their sequelae.

This sequence represents the accepted pattern characteristic of Coats' disease as it occurs in juvenile patients. Some clinicians report having

adult patients (over 30 years of age at disease onset)[3,11,25,33] with ocular disease features identical to those occurring in juveniles. Whether the precipitating factor for ocular change is the same, and whether the adult form of the disorder should be designated as Coats' disease, has been questioned.[12] Many of the adult patients investigated so far have also shown hyperlipidemia with elevated levels of serum cholesterol (not present in juvenile patients) and, frequently, a history of uveitis.[15,25]

DIFFERENTIAL DIAGNOSIS

For Coats' disease, accurate diagnosis is critical. Considerable difficulties arise because, in its advanced stage, the disease simulates a number of other conditions, most notably the highly malignant intraocular tumor of infancy and childhood, retinoblastoma. Howard and Ellsworth[37] reported that 10 of 254 cases (3.9%) initially diagnosed as retinoblastoma were subsequently discovered to be Coats' disease. Moreover, a striking number of cases included in published clinical and histopathologic reports of Coats' disease had been referred, or the eye enucleated, because retinoblastoma was suspected.[12,13,38,39] Chang[19] reviewed 62 cases of histologically confirmed Coats' disease submitted to the Armed Forces Institute of Pathology from 1958 through 1980, reported that "Coats' disease was the primary clinical diagnosis in only 13 of 62 cases analyzed. The remaining cases were misdiagnosed as retinoblastoma in 36 (58%) and retinal detachment in 13 (21%)."

Retinoblastoma is the most common primary malignant tumor of infancy and childhood. The average age at diagnosis is 18 months, and the majority of cases have become clinically manifest by 3 years of age. Unlike Coats' disease, there is no sexual predilection and, although often first detected unilaterally, both eyes are involved in approximately one third of patients. Some cases show a familial history, since this is an autosomal dominant disorder in patients with the germinal mutation. In the majority of retinoblastoma cases, a clearly discernible intraocular mass can be viewed ophthalmoscopically. This pinkish, highly vascular mass may be single or multiple and show the characteristic findings of cottage-cheese calcification or tumor seeding. The diagnosis is more difficult when the retinoblastoma presents in an exophytic form with the tumor mass totally underlying a nonrhegmatogenous retinal detachment. Telangiectatic retinal blood vessels are not considered characteristic of retinoblastoma, although a Coats'-like reaction in the retina blood vessels has been noted in some retinoblastoma patients. Therefore, when retinoblastoma presents with nonrhegmatogenous detachment, telangiectatic vessels, and subretinal particles, it may be impossible to clinically distinguish from advanced Coats' disease.

Delay or error in distinguishing between Coats' disease and retinoblastoma carries severe implications for the patient. Misdiagnosing Coats' disease as retinoblastoma can lead to the enucleation of a potentially salvageable eye. Conversely, misdiagnosing a case of retinoblastoma as Coats' disease is likely to delay the appropriate therapeutic intervention, thus increasing the possibility of extraocular tumor spread and death. Additionally, if subretinal drainage is performed in a retinoblastoma patient misdiagnosed as having Coats' disease, it is possible to seed cancer cells into the orbit, accelerating extraocular extension.

The advanced stages of Coats' disease must be differentiated from other pediatric conditions that present with leukocoria or strabismus and are characterized by a nonrhegmatogenous retinal detachment with extensive subretinal exudation. Although such a misdiagnosis may affect ocular survival, it fortunately does not affect the mortality since these diseases are generally benign.

The major exception to this statement is angiomatosis retinae. This phakomatosis is associated with an autosomal dominant inheritance pattern, visceral and central nervous system hemangioblastomas, visceral cysts and tumors, including renal cell carcinoma, and pheochromocytoma. Von Hippel-Lindau "angiomatosis retinae" can usually be distinguished from Coats' disease, because in early stages, the ophthalmoscopic picture is markedly different. In angiomatosis retinae, an afferent feeder arteriole and an efferent draining venule are found entering and leaving a discrete yellow or reddish balloon-like mass. Although advanced cases of angiomatosis retinae and Coats' disease may be indistinguishable on ophthalmoscopic grounds alone, several inherent clinical and familial characteristics are valuable in differentiation. Descriptions of the distinguishing features of these two entities have been published previously.[8,31] In brief, although Coats' disease is typically a unilateral condition in males, angiomatosis retinae is bilateral in 30% to 50% of patients and affects both sexes equally. Patients with advanced Coats' disease are usually diagnosed in the first decade of life and have negative family histories, while those with angiomatosis retinae typically become symptomatic in the second or third decades of life and may have a family history of this disorder. Thus, since the disease does not usually manifest itself as a massive retinal detachment in childhood, and our patient base was exclusively pediatric, we were not confronted with this possible diagnostic dilemma.

The following conditions may present with a nonrhegmatogenous retinal detachment: exophytic retinoblastoma, *Toxocara* endophthalmitis, persistent hyperplastic primary vitreous, retrolental fibroplasia, angioma-

tosis retinae (exudative phase), and organized subretinal hemorrhage. Generally, the diagnosis can be made confidently on the basis of clinical examination and case history. However, Haik and co-workers[40] recently reported that, in about 20% of cases presenting with leukocoria, the diagnosis could not be established using standard clinical techniques. In these instances, the auxiliary diagnostic techniques of ultrasonography, computed tomography, and magnetic resonance imaging were employed to achieve greater diagnostic accuracy.

TREATMENT

Because the etiology and pathogenesis of Coats' disease has been a constant source of confusion and debate, many therapeutic modalities have been utilized. McGrand[41] noted, "Medical therapy with antibiotics, vitamins and corticosteroids has been given with no consistent benefit." Guyton and McGovern[42] first reported success with diathermy coagulation for Coats' disease in 1943. In 1956, Reese[8] presented two patients with Coats' disease who responded poorly to radiation therapy and also proposed that diathermy might be an effective treatment modality. Brini[43] suggested the use of either diathermy or photocoagulation in 1957. In 1960, Meyer-Schwickerath[44] reported failure of diathermy in four patients but promising results with photocoagulation in two others. Successful photocoagulation results in patients with Coats' disease were described during the next decade by Lemmingson,[45] Paufique and Charleuk,[46] and others.[41,47-49] In 1965, Morales[10] presented the Columbia-Presbyterian experience in treating 13 Coats' disease patients with diathermy and/or photocoagulation. He reported that fewer than half of a group of untreated patients (10 of 22) showed definite progression of the disease during a 5-year follow-up. On the other hand, of nine patients with established Coats' disease who underwent photocoagulation, one showed progression from partial to total retinal detachment (within 2 years); and two—who when treated had large exudates but no retinal detachment—showed no change ophthalmoscopically during 2 years. The remaining patients showed "chorioretinal scarring" in place of the abnormal vasculature, indicating a halt in the development of the disorder. Morales concluded, "The early results in the group treated by photocoagulation are encouraging. However, since Coats' disease proved to be nonprogressive in a high percentage of cases during a follow-up period of approximately 5 years, final evaluation of the benefit derived from photocoagulation must await a longer follow-up evaluation."

The use of photocoagulation at an early stage in the development of Coats' disease affords the best prospects for treatment.[3,23,32,50] This form

of treatment is most effective if applied when the neural retina and retinal pigment epithelium are in contact, before the formation of a subretinal fibrous membrane and the deposition of exudates or retinal detachment have taken place. Photocoagulation is used to eliminate defective retinal blood vessels, particularly telangiectases and aneurysms, and so arrests the exudative process. The treatment is less likely to be effective if more than two quadrants of the retina show vascular abnormalities.[3,10,24]

Elimination of defective vessels not only prevents further leakage but is followed by the resorption of already-formed exudates[13,22,24,32,41]; however, recurrences have been reported between 2 and 5 years later, linked with the appearance of new vascular abnormalities.[10,50] Thus, a long follow-up of treated patients is required. Although treatment may interrupt the clinical progression of the disease and the associated decline in vision, few clinicians report any subsequent improvement in visual acuity.[3,13,50]

Tarkkanen and Laatikainen[18] found cryotherapy more effective than photocoagulation "in the more advanced cases and in the far periphery." Photocoagulation or cryotherapy alone is usually ineffective once the retina becomes detached. With regard to the advanced form of the disease, Morales[10] summarized the prevailing pessimism and stated, "No case in the present series with a total detachment of the retina was subjected to any means of treatment, and it is unlikely that any means of therapy presently at our disposal would improve such a case."

As Silador and associates[51] pointed out, "In the past, relatively few children with advanced Coats' disease with bullous retinal detachment received any treatment." They were not treated because retinoblastoma could not be completely ruled out; or in other cases; where a secure diagnosis was established, therapy was withheld because of fear that intervention would accelerate rather than retard loss of the eye.[32]

The drainage of subretinal exudative fluid and/or the placement of a scleral buckle may be used to help restore the relationship between the neural retina and retinal pigment epithelium in advanced cases,[3,20,22,24,51,52] even if fibrosis prevents their complete reattachment. These surgical procedures may facilitate the treatment of abnormal vessels by photocoagulation or cryotherapy and inhibit further accumulation of exudates or, at the least, prevent progression to phthisis bulbi.[50,51] Sophisticated vitreoretinal procedures involving intraocular infusion, subretinal drainage, and cryotherapy have been successfully utilized to preserve comfortable, cosmetically acceptable eyes. Silador and co-workers[51] reported their conclusions as follows: "Our technique of intraocular infusion, drainage of subretinal fluid, and cryotherapy appears to be better than no

treatment in terms of length of preservation of such eyes as cosmetically acceptable, pain free organs." The role of additional procedures, such as vitrectomy, retinectomy, subretinal membrane excision, and intraocular injection of gas, silicone, hyaluronic acid, or perfluorocarbons to assist in repositioning the retina, has not been fully explored. Kremer and associates,[53] using such advanced vitreoretinal procedures on two patients with advanced Coats' disease, were plagued by postoperative complications and disappointing results. Schepens[52] regarded all operations as useless in the final stage of Coats' disease and reported, "Retinal vessels proliferate under the unpigmented epithelium of the pars plana ciliaris and form visible anastomoses with the vasculature of the ciliary processes. At this point, closure of the retinal arteries supplying the proliferating vessels simply leads to dilatation of the ciliary feeder vessels. The latter cannot be reached by photocoagulation because of their peripheral location and the haze of the media. The vitreous is hazy and vascularized, and much of the peripheral retina is hidden under whitish exudates." Treatment of the final stages of Coats' disease is limited to the symptomatic relief of severe ocular inflammation or painful glaucoma.

Finally, as pointed out by Campbell,[3] untreated Coats' disease does not invariably lead to intractable glaucoma with loss of the globe. In 1914, Friedenwald[54] described a patient with widespread superficial telangiectasia. Friedenwald and Friedenwald subsequently reported in 1929[55] that all vessels had become attenuated and all exudate had disappeared. Reese[8] reported two additional cases of spontaneous regression in his 1955 Gifford lecture. Campbell[3] presented additional cases of spontaneous regression in Coats' disease and remarked, "Long term follow-up shows that many cases, even those quite advanced, may regress spontaneously." Deutsch and co-workers[26] reported on three adult patients in whom spontaneous regression of Coats' disease occurred. They speculated that "perhaps large areas of abnormal vessels autoinfarcted, thus causing ablation of telangiectasia, thrombosis, and collapse of retinal vessel walls."

CURRENT PATIENT SERIES

MATERIALS AND METHODS

A detailed retrospective study of the clinical and diagnostic findings in 156 patients seen between 1955 and 1990 was performed. Seventy-five were found to meet the criteria of advanced Coats' disease. In each case a detailed review of the family history, present illness, and ocular and systemic findings were conducted. All patients underwent a detailed

ophthalmologic examination while under anesthesia. The diagnosis of advanced Coats' disease was established by histopathologic evaluation of the enucleated eye in 51 cases. In the other cases a secure diagnosis could be established on classical ophthalmoscopic findings supplemented by ultrasonography, computed tomography, magnetic resonance imaging, intraocular aspiration, response to therapy, and long-term clinical follow-up. The ophthalmologic findings were consistent with grade IV (total detachment of the retina of a yellow or dark green color) or grade V (grade IV changes progressing to secondary complications such as iridocyclitis, glaucoma, or cataract) of the Morales[10] classification in all patients.

To provide a framework for comparison of the diagnostic criteria used, data are presented from 104 patients with histologically proven exophytic retinoblastoma, examined during the same period as those with advanced Coats' disease. This comparison was carried out because, in the diagnosis of Coats' disease, exophytic retinoblastoma represents not only the most common simulating condition but also the most dangerous.

Follow-up data to help illuminate the natural course of advanced Coats' disease were obtained by periodic examination of the patient or from information provided by the referring ophthalmologist.

CLINICAL CHARACTERISTICS

Age

The patients' age at initial diagnosis ranged from 1 month to 9 years (Fig 1). Of the 75 patients, 30 (40%) presented before age 2 years. The mean was 3.03 years.

Sex and Race

Of the 75 patients, 62 (82.7%) were males and 13 (17.3%) were females. Sixty-five were white, eight were black, and two were Oriental.

Family, Prenatal History, and Delivery

No similar ocular histories of pediatric retinal disease were elicited from the family members of affected children. One patient's mother was exposed to rubella in the first trimester of pregnancy. Another patient's mother suffered from toxemia in pregnancy. Of the group, 68 patients were delivered vaginally and 4 by cesarean section at term without significant complications. The other three patients were premature vaginal deliveries (2 weeks, 2 weeks, and 4 weeks). Birth weights were generally normal and ranged from 4 pounds 11 ounces to 10 pounds 9 ounces (mean, 7 pounds 2 ounces).

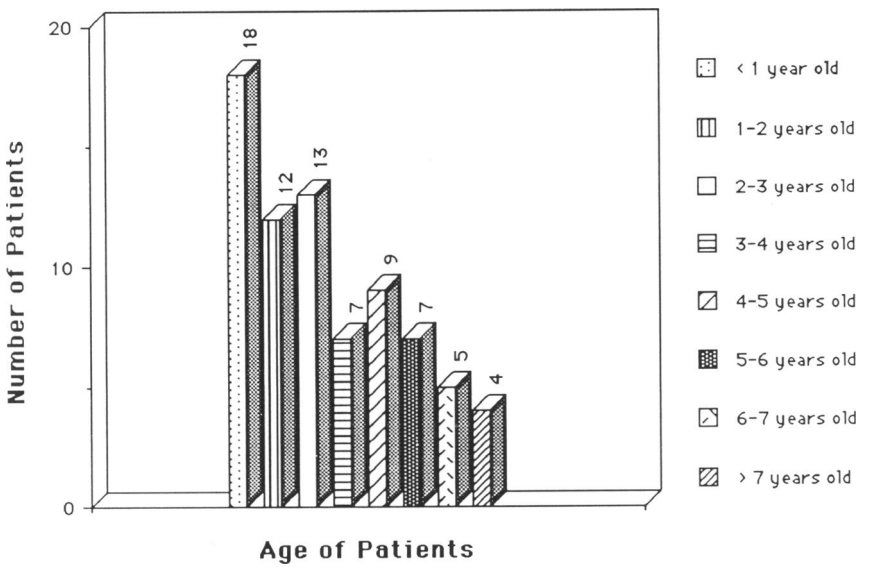


FIGURE 1
Age at initial presentation of Coats' disease.

Postnatal History and Associated Physical Findings

Three patients received limited oxygen in the immediate postnatal period (4 days, 7 days, and 28 days). Physical examinations were unremarkable except that one patient was found to have trisomy 8 mosaic. Blood lipid and cholesterol tests were performed in 27 patients and found to be normal in all.

Presenting Signs and Symptoms

Strabismus and leukocoria were the most common presenting signs, accounting for 51 of 75 patients (68%) (Fig 2). The next most common presentations were the presence of a red painful eye or abnormality of iris color. Rarer presentations are summarized in Table I.

Referring Diagnosis

The major diagnostic possibilities entertained by referring physicians included retinoblastoma in 36 patients (48%), Coats' disease in 15 patients (20%), retinal detachment in 8 patients (10.7%), *Toxocara canis* infection in 6 patients (8%), angiomatosis retinae in 4 patients (5.3%), glaucoma in 3

patients (4%), persistent hyperplastic primary vitreous in 1 patient (1.3%), and retinal dysplasia in 1 patient (1.3%). The diagnosis was unknown in one patient (1.3%).

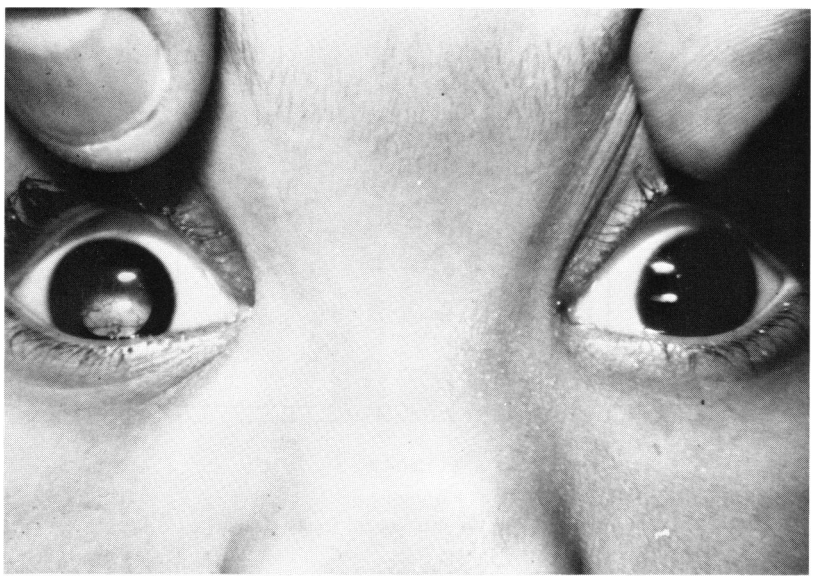


FIGURE 2
Four-year-old boy with right leukocoria secondary to advanced Coats' disease.

CLINICAL FINDINGS ON PRESENTATION

Eye Involved

The right eye was involved in 42 children (56%), and the left eye was involved in 31 cases (41.3%). Two cases (2.7%) were bilateral.

Bilaterality

Two patients had bilateral disease; however, the retinal vascular disorder in the patient's second eye was limited to less than one quadrant and, although the yellowish exudate was present, the retinas were not detached.

TABLE I: PRESENTING SIGNS AND SYMPTOMS
(n = 75)

SIGN/SYMPTOM	NO. OF PATIENTS	%
Strabismus	27	36
Leukocoria	24	32
Glaucoma/inflammation	6	8
Heterochromia	6	8
Poor visual acuity	4	5.3
Routine examination	3	4
Microphthalmos	2	2.7
Anisocoria	1	1.3
Blepharoptosis	1	1.3
Unknown	1	1.3

Status of Fellow Eye

The fellow eye was normal in all cases, except for the two patients with bilateral Coats' disease.

External Examination

A variable strabismus (exotropia, 17 patients [22.7%]; esotropia, 15 patients [20%]) was detectable in 32 patients (42.7%), and, as mentioned above, was the primary presenting sign in 27 children (36%). Periocular edema or erythema was noted on the involved side in nine (12%) patients with concomitant glaucoma and intraocular inflammation.

OPHTHALMIC FINDINGS

Anterior Segment

On initial examination, 18 of 75 patients (24%) had anterior segment abnormalities. The most significant findings were present in nine patients with neovascular glaucoma (intraocular pressure range, 27 to 62; average, 37). Corneal edema and perilimbal injection was present in all. Shallowing of the anterior chamber was present in four of these patients and a totally flat anterior chamber was found in another. In four of these patients, the affected eye was buphthalmic; corneal diameters were 0.75 mm, 1.0 mm, 1.0 mm, and 1.5 mm greater than the normal fellow eye. In three of the patients with neovascular glaucoma, heterochromia was noted, with the eye involved with advanced Coats' disease being darker in two patients and lighter in one.

The anterior segment disorders in the other nine patients included rubeosis iridis without glaucoma in four patients, mild microphthalmia in

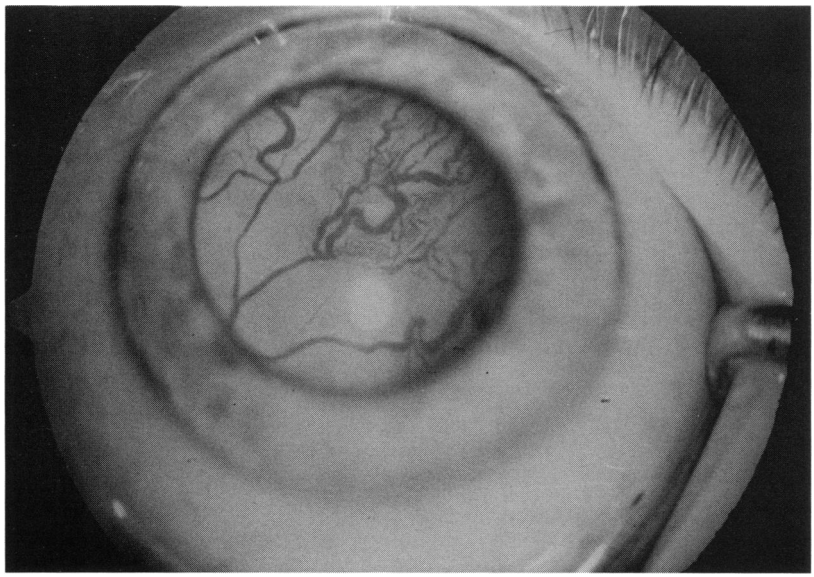


FIGURE 3
Total retinal detachment secondary to exudation from dilated, tortuous telangiectases.

three patients (one with prominent ciliary processes), and aqueous cells and flare associated with posterior synechiae in two patients.

Vitreous Cavity

The vitreous cavity was present and ophthalmoscopically clear in 65 patients. In five others, a mild cellular reaction or vitreous hemorrhage was noted. In the remaining five patients, there was no residual vitreous cavity since the retinal bullae were in contact with each other and the posterior lens capsule.

Retinal Detachment

A total retinal detachment was evident on examination in all of the patients. The configuration of the retinal detachment varied from shallow to highly bullous with the retinal bullae adherent to the posterior lens capsule in the most advanced cases. Although difficult to evaluate because the leaves of the retinal detachment were often convoluted, intraretinal and subretinal gliosis were noted in approximately 20% of patients.

Retinal Vascular Abnormalities

Abnormal retinal vessels (Fig 3) were ophthalmoscopically visible in 58 of

75 patients (77.3%). These were detected in all four quadrants in 5 patients, in three quadrants in 7 patients, in two quadrants in 29 patients, and one quadrant in 17 patients. In 5 of the 17 patients with quadratic vascular abnormalities, the abnormal retinal vessels were only seen on careful ophthalmoscopy with indentation (Fig 4A and B). In 17 patients, abnormal vessels were not detectable ophthalmoscopically.

The abnormal retinal vessels were found to involve the posterior pole only rarely, and the majority of abnormal vessels were found to involve the equator and more peripheral part of the retina. Abnormal vessels were distributed throughout all four quadrants of the globe, but at a slightly higher incidence in the inferior temporal periphery. The retinal vascular abnormalities were noted to vary greatly on ophthalmoscopy, portable biomicroscopy, and fundus photography. In some patients, only focal tufts of telangiectasis were seen, while in others massive sheaves of vessels formed a "sea-fan" configuration. In the most subtle cases, the retinal vessels were mildly enlarged in caliber and slightly irregular in configuration, while in others sausage-like vascular beading or large saccular outpouchings were noted. In the most dramatic cases, bizarre configurations of vessels with "light-bulb" dilatations, massive arteriovenous shunting, perivascular hemorrhage, and massive exudation with vascular sheathing and obscuration were noted.

Subretinal Deposits, Mass, or Hemorrhage

Subretinal abnormalities were visible in 50 of the 75 patients (66.7%). The clinical impression of cholesterol crystals was commonly noted, as was that of hemorrhage, solid mass, or mounds and calcific deposits (Table II). Many patients simultaneously had multiple subretinal abnormalities.

TABLE II: CLINICAL IMPRESSION OF SUBRETINAL DEPOSITS, MASS, OR MATERIALS (n = 75)

CLINICAL IMPRESSION	NO. OF PATIENTS	%
Cholesterol	50	53.3
Hemorrhage	18	24
Mass or mound	15	20
Calcium	15	20
Granuloma	5	6.7
Pigmented mass	4	5.3

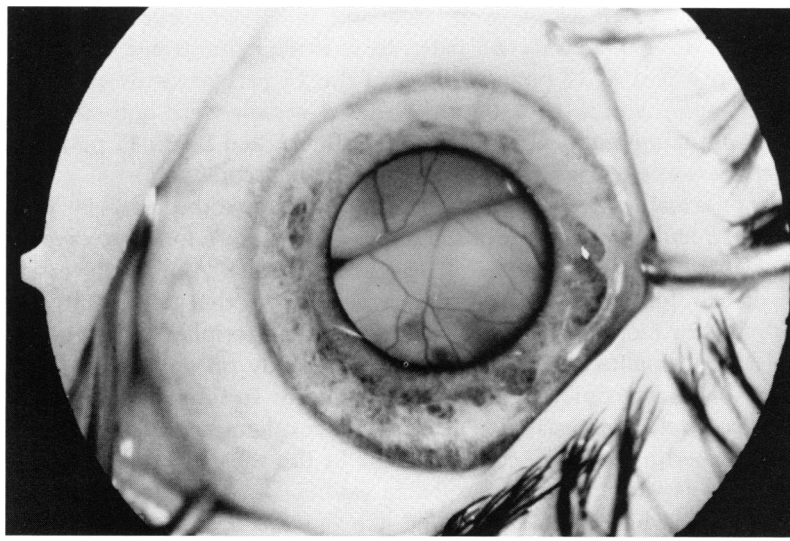
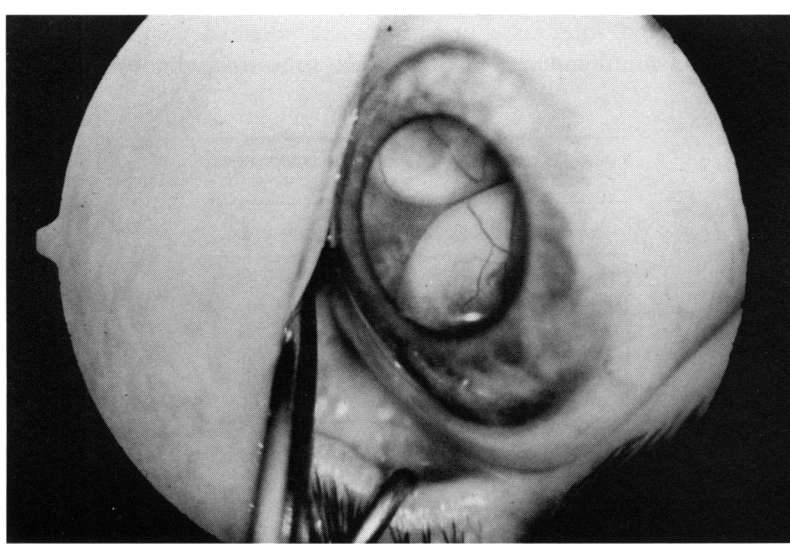


FIGURE 4

A: Total bullous retinal detachment in a patient with Coats' disease. No retinal vascular anomaly is visible, and two small pigmented regions are noted inferiorly. B: On scleral indentation, a segment of diffuse telangiectases is seen.



Retinal Color on Initial Presentation

Abnormality of retinal color was noted in 43 of 75 patients (57.3%). In 34 patients the retina was bright yellow or yellow-green, and in 9 patients the retina was noted to be dark green or grayish.

Clinical Impression

The constellation of clinical findings at the time of our evaluation resulted in a preliminary diagnosis of Coats' disease in 29 patients and of retinoblastoma in 7. In five patients, various retinal abnormalities unassociated with Coats' disease and retinoblastoma were suggested. Thus, in 34 patients, although the possibility of Coats' disease was strongly suspected, retinoblastoma could not be ruled out (Table III).

TABLE III: CLINICAL DIAGNOSIS AT PRESENTATION (n = 75)

DIAGNOSIS	NO. OF PATIENTS	%
Coats'/retinoblastoma	34	45.3
Coats'	29	38.7
Retinoblastoma	7	9.3
Congenital retinoschisis	1	1.3
Angiomatosis retinae	1	1.3
Retinal dysplasia	1	1.3
Persistent hyperplastic primary vitreous	1	1.3
Traumatic retinal detachment	1	1.3

Long-Term Follow-Up

Follow-up information was available on 67 of 75 patients. Information on the remaining patients was unavailable despite intensive efforts because the referring physicians had retired or died, inactive medical records were destroyed, and lastly, some patients did not return to their referring physician. Data are summarized in Table IV.

TABLE IV: LONG-TERM FOLLOW-UP (n = 67)

Primary enucleation		34
Coats' disease/rule out retinoblastoma	18	
Misdiagnosed as retinoblastoma	7	
Coats' disease with neovascular glaucoma	9	
Observation		25
Neovascular glaucoma—enucleation	14	
Neovascular glaucoma—phthisical	4	
Stable persistent detachment with normal intraocular pressures	3	
Spontaneous regression	2	
Phthisical (without previous glaucoma)	2	
Xenon arc photocoagulation therapy		3
Neovascular glaucoma—enucleation	2	
Normal pressure—total detachment	1	
Argon laser photocoagulation therapy		2
Neovascular glaucoma—enucleation	1	
Neovascular glaucoma—phthisical	1	
Vitreoretinal surgery		3
Stable intraocular pressure—retina attached	2	
Phthisis		
Lost to follow-up		8

MANAGEMENT

Enucleation was performed as primary therapy in 34 patients (45.3%). Seven of these patients had been misdiagnosed as harboring exophytic retinoblastoma. In nine patients, a secure diagnosis of advanced Coats' disease was made; however, the patients' eyes were enucleated because of painful neovascular glaucoma. In 18 other patients, advanced Coats' disease was the most likely diagnosis, but retinoblastoma could not be completely ruled out. Since these eyes were felt to have minimal or no visual potential and represented possible malignancy, enucleation was also performed. It should be noted that the majority of patients in this group was seen prior to routine utilization of sophisticated diagnostic modalities such as ultrasonography, computed tomography, and magnetic resonance imaging.

Of the remaining 41 patients, 8 were lost to follow-up. Therefore, information is available on 33 patients to provide insights into the natural history and response to therapy. Each of these cases was followed for a minimum of 5 years, or until enucleation of the affected eye. Of these patients, 25 were observed, because the treating physicians believed that the benefits of available surgery did not justify the risks associated with

prolonged anesthesia and complicated surgery in eyes with little visual potential.

Eighteen of these patients developed neovascular glaucoma during the period of observation, and 14 were secondarily enucleated for this complication. The other four patients' globes eventually became phthisical. Two of these had been treated before the onset of phthisis, with topical cycloplegics and corticosteroids to minimize symptoms related to glaucoma and intraocular inflammation.

Five patients retained comfortable globes with normal intraocular pressures. Three of these had persistent total exudative detachments, while two had undergone spontaneous regression with retinal reattachment. Two patients became quietly phthisical without documented episodes of ocular pain, inflammation, or glaucoma.

Therapeutic intervention was attempted in eight patients. Aggressive xenon arc photocoagulation was carried out in three patients in an attempt to destroy the abnormally permeable vessels. Two of these patients experienced disease progression and developed neovascular glaucoma that required enucleation to alleviate pain. The third patient retained a comfortable eye with normal pressure but a chronic detachment.

Two patients were treated repeatedly with argon laser photocoagulation delivered by indirect ophthalmoscopy, combined with cryotherapy. One developed florid rubeosis iridis and painful glaucoma within 6 months, resulting in enucleation; the other became phthisical.

Lastly, three patients underwent vitreoretinal surgery including subretinal drainage with simultaneous intraocular infusion followed by cryotherapy and photocoagulation. Two of these eyes were preserved in a comfortable state with attached retinas and normal intraocular tensions, with light perception vision in one. The third patient's eye treated with such a procedure became phthisical.

DIAGNOSTIC TESTING

Our patient series spans 35 years, dating from 1955, and therefore encompasses cases that pre-date the introduction of sophisticated diagnostic techniques.

The three major noninvasive imaging modalities discussed—ultrasonography, computed tomography, and magnetic resonance imaging—have all contributed greatly to the characterization of Coats' disease and its differentiation from simulating conditions. Ultrasonography was the first practical technique in the early 1970s; it was followed by computed tomography in the mid 1970s and magnetic resonance imaging in the mid 1980s. Their potential for increasing diagnostic morphologic information

was quickly recognized and applied, but because of their fairly recent development, only patients in the latter period of the series could be studied.

Ultrasonography

We examined 53 patients with combined B- and A-scan ultrasonography. A contact technique was used, applying the transducer directly to the closed lids by means of a coupling gel (methylcellulose). In isolated instances, a small water chamber stand-off was used in conjunction with a light weight Barraquer lid speculum to improve imaging of the anterior segment by eliminating attenuation by the eyelid. The initial ultrasound instrument in the early stages of evaluation was an Ocuscan 400 (Sonometrics Systems, Inc); later, a Coopervision Ultrascan digital system and a Sonomed B-2000/3000 were also employed. All studies were performed with a 10 MHz transducer. The clinical impressions were obtained during real-time examination, and the findings were documented by Polaroid photographs.

Studies were conducted to assess the following aspects of each eye: the presence of retinal detachment, the presence of vitreal or subretinal masses; and the configuration and density of any such masses. When possible, spontaneous and voluntary movement associated with intraocular pathology was evaluated, but most of the patients were examined under light general anesthesia, and voluntary eye movements were not obtained.

In all 16 patients with advanced Coats' disease, total retinal detachment was identified ultrasonically. In eight cases, the subretinal space was sonolucent or contained only low-amplitude, diffuse echoes and the detachment showed a range of patterns, from classically V-shaped (Fig 5) to highly convoluted (Fig 6). The retina was of uniform thickness in early stages of detachment, but showed progressive signs of thickening, cystic degeneration, and organization. In two patients, the V-shaped pattern (of insertion at the optic disc and extension to the ora serrata) was seen but was outlined by densely packed subretinal echoes, producing the appearance of a solid detachment (Fig 7).

Six patients demonstrated the initial pattern of a globe filled with low- or moderate-amplitude echoes, raising the suspicion of a large intraocular mass, but reducing the sensitivity or gain of the system clarified the pattern. At lower gain, the retinal detachment was seen, but was commonly constricted centrally and convoluted (Fig 8). The original pattern of an echo-filled globe thus emerged as dense subretinal echoes. Difficulty in outlining the detachment was due to both alignment (the stalk of the detachment is parallel to the examining sound beam) and an insufficient

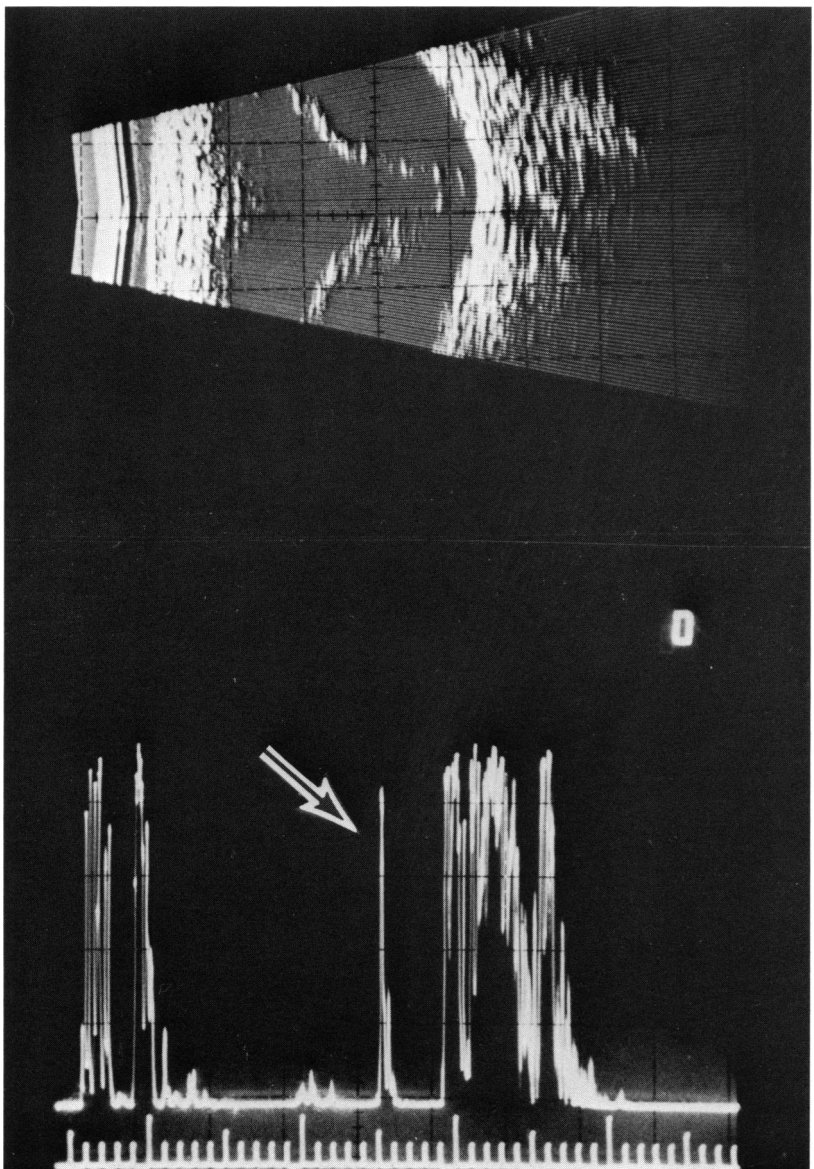


FIGURE 5

B- and A-scan ultrasonogram of a patient with Coats' disease. B-scan (top) shows a retinal detachment extending from optic nerve head to ora serrata with a sonolucent or acoustically clear subretinal space. Accompanying A-scan (bottom) shows a high-amplitude echo (*arrow*) from retina and no echo response from subretinal area.

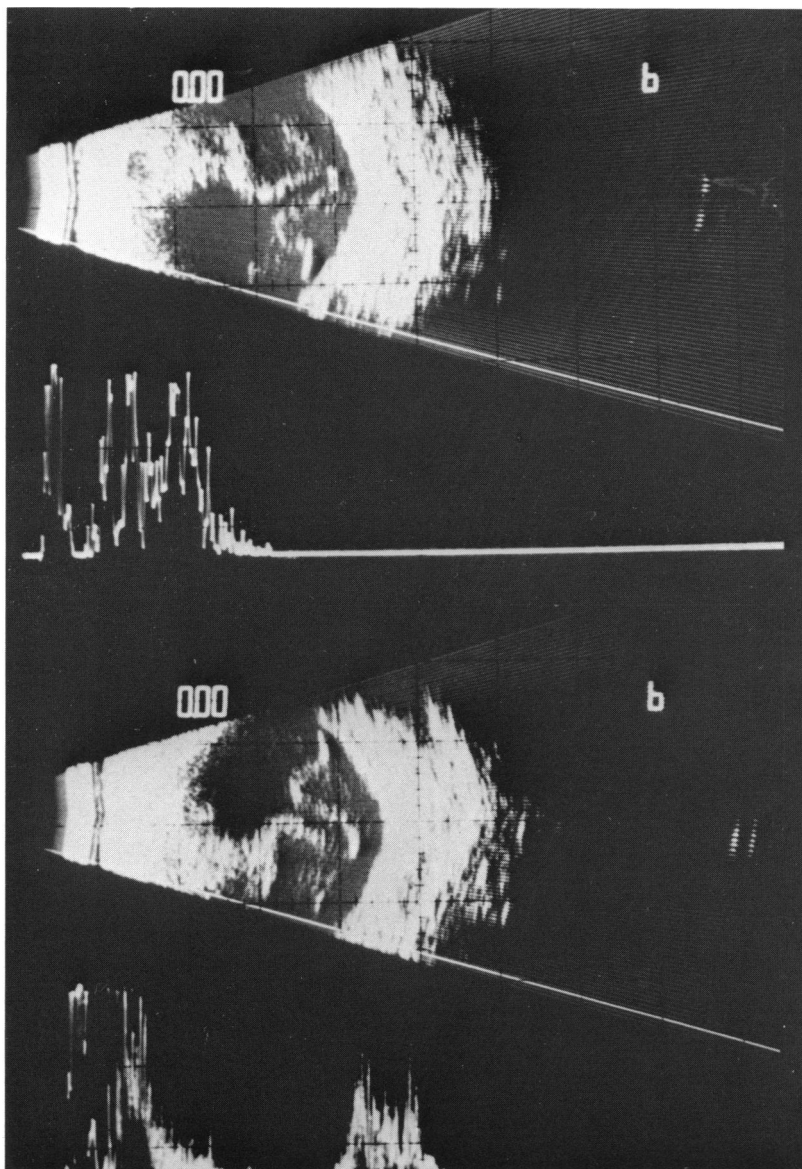


FIGURE 6
B-scan ultrasonogram of a patient with Coats' disease. Retinal detachment is thickened and highly convoluted.

acoustic impedance mismatch (an irregular or atrophied retina will not have a high-amplitude surface, and thus will be difficult to separate from organized subretinal material). Also, the bullae of the retina are contracted anteriorly, so the vitreous compartment is extremely small, and the subretinal space occupies most of the globe.

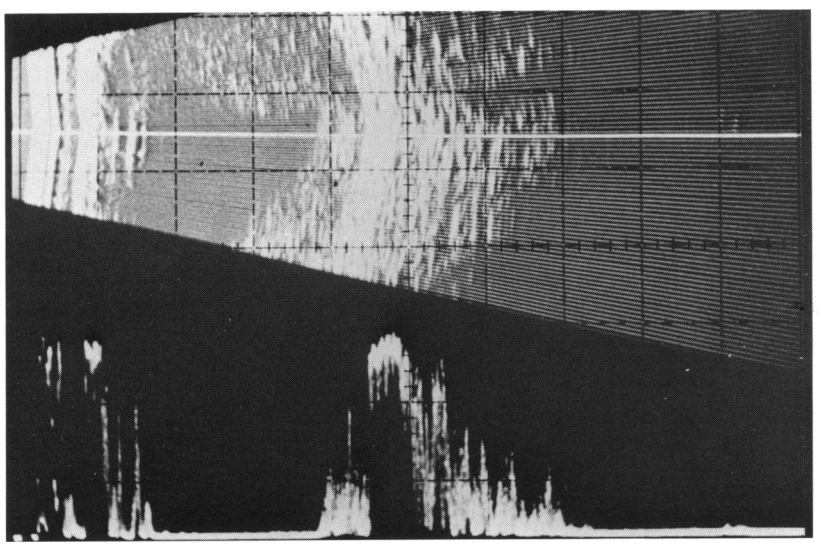


FIGURE 7
B-scan ultrasonogram of a patient with Coats' disease. Detachment is outlined by subretinal echoes.

The presence or absence of a mass was ascertained by lowering the sensitivity, or gain, of the system to identify high-density echoes. On the Ocuscan, sensitivity was measured by introducing ever-increasing levels of attenuation (measured in decibels [db]). Discrete masses were not identified in any of the 16 patients with Coats' disease. The density of the diffuse subretinal echoes ranged from 0 db to 21 db.

We studied 46 eyes (37 patients, 9 bilateral presentations) with retinoblastoma to provide comparative information. A distinct retinal detachment was seen in three patients, but clear separation of retina from intraocular mass could not be seen in the remainder. An isolated intraocular mass was immediately seen in 29 eyes (Fig 9). In the other 17, the globe appeared filled with dense intraocular echoes, which, when sensitivity was lowered, revealed a high-amplitude mass outline (Fig 10).

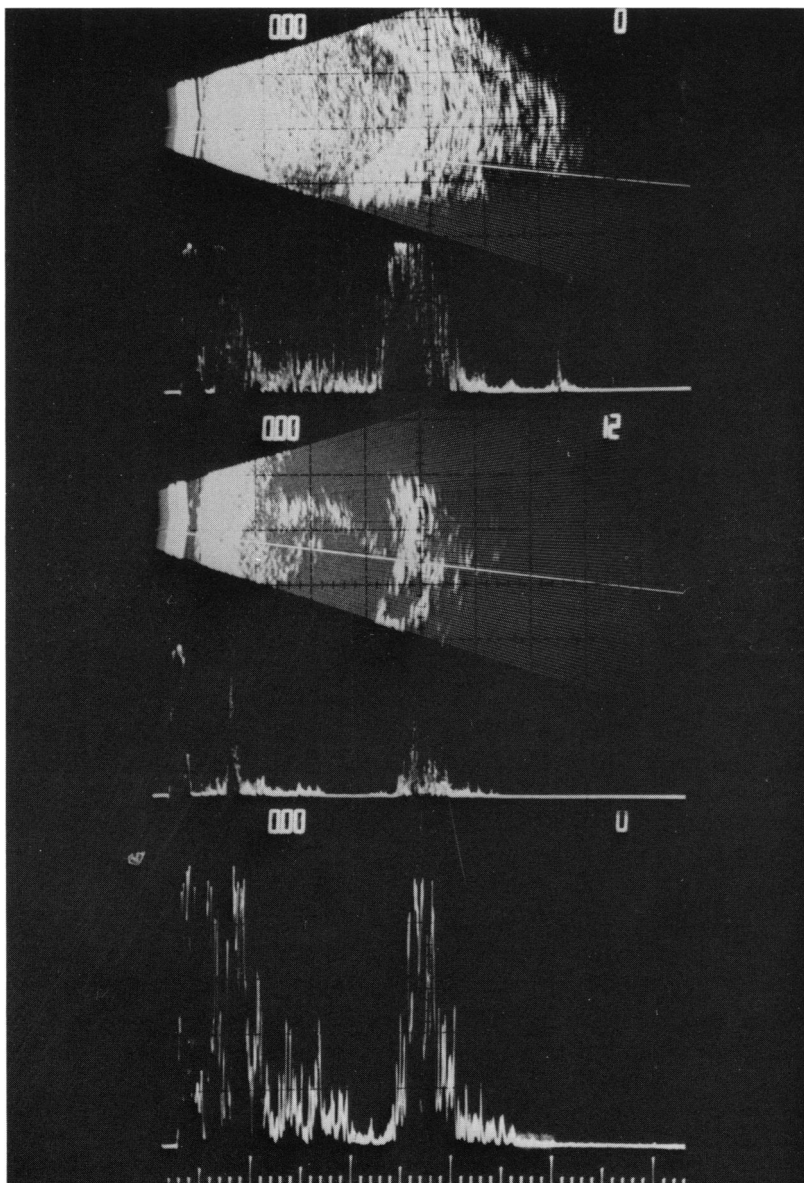


FIGURE 8
B- and A-scan ultrasonograms of a patient with Coats' disease. At full gain (top), the pattern of retinal detachment is obscured by dense intraocular echoes. At lowered sensitivity settings (middle), convoluted detachment is evident.

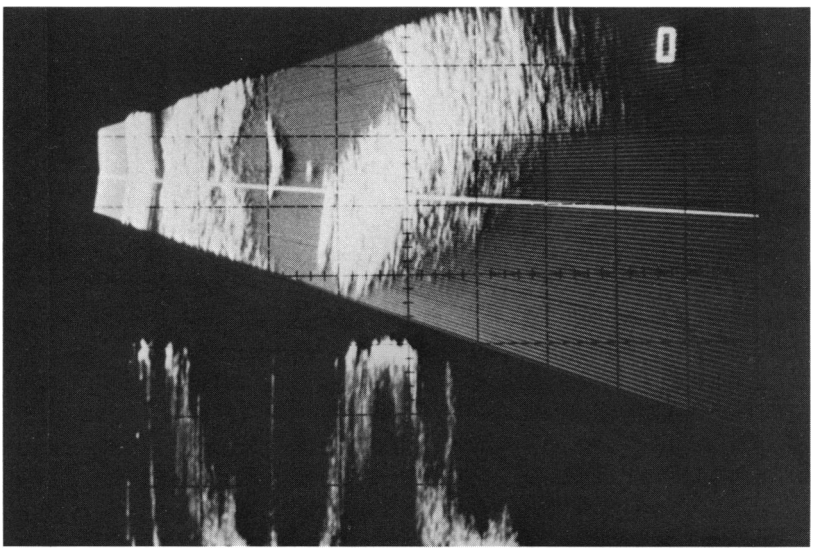


FIGURE 9
B- and A-scan ultrasonogram of patient with exophytic retinoblastoma. Tumor mass is well circumscribed, occupying temporal hemisphere of globe and extremely reflective on both gray scale of B-scan and amplitude of A-scan. Path of A-scan is indicated by bright vector on B-scan.

In addition, 12 eyes demonstrated "shadowing," or absence of normal echogenic structures produced by sound absorption through a dense acoustic structure (Fig 11). This artificial defect of the posterior globe or orbital structures is indicative of a highly reflective structure within the globe, in these instances, a calcified lesion.

The masses identified showed marked persistence at lowered gain settings, with a range of 23 db to 46 db. Comparative attenuation data from both Coats' disease and retinoblastoma patients are presented in Fig 12.

When kinetic evaluation was available, the Coats' disease patients showed movement and after-movement of subretinal material, while the retinoblastoma patients demonstrated no shifting of echoes representing either soft tissue or calcified portions of the mass.

Plain Radiography

Plain film radiographic studies of the orbit and skull (A-P, Waters, Caldwell, and lateral) were studied in nine patients with advanced Coats' disease during the period before computed tomography. Exposure of the

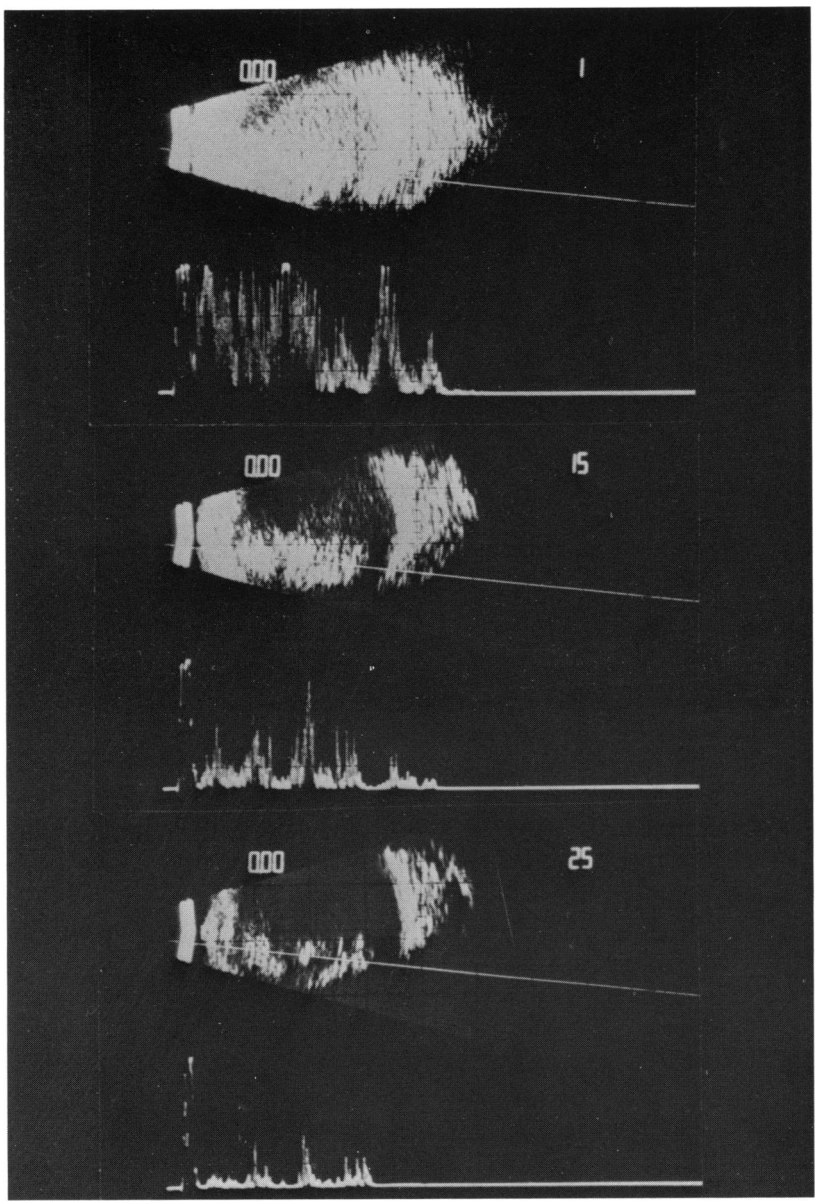


FIGURE 10

B- and A-scan ultrasonograms of a patient with exophytic retinoblastoma. Levels of attenuation introduced are indicated by number in the upper-right corner of each scan. At full sensitivity (top), globe appears filled with high-amplitude echoes. Decrease in sensitivity or increase in attenuation (middle and bottom) causes echoes from soft-tissue portion of mass to be suppressed, leaving only echoes from calcific portions visible.

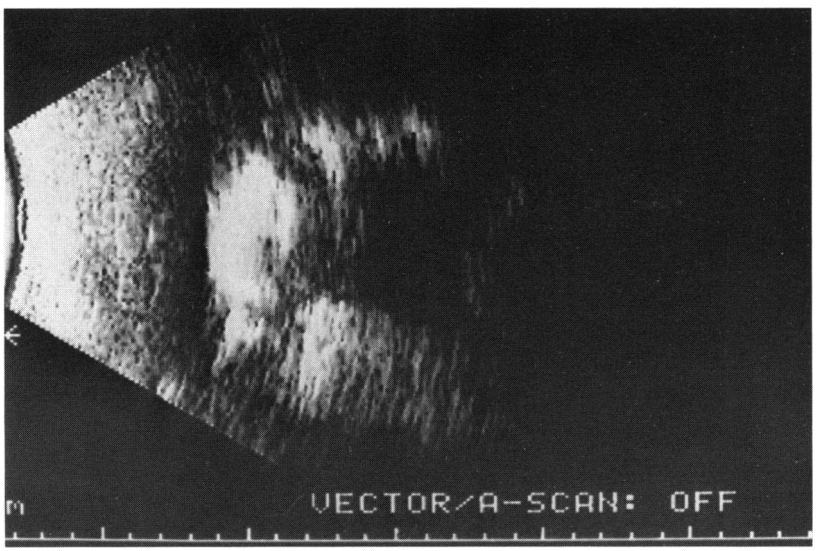


FIGURE 11
B-scan ultrasonogram of a patient with exophytic retinoblastoma demonstrating shadowing. Large tumor mass occupying central portion of globe is highly reflective (bright on B-scan) and produces an artifactual defect of posterior globe wall and subsequent orbital fat.

radiographic film was closely monitored to permit detection of subtle intraorbital abnormalities. No radiographic abnormalities were detected. Fifteen patients were exophytic retinoblastoma were evaluated with plain radiography in a similar fashion, and flocculent intraocular calcifications were detected in nine patients.

Computed Tomography

Nineteen patients with advanced Coats' disease and 54 eyes in 50 patients with exophytic retinoblastoma were evaluated by high-resolution computed tomography (General Electric 8800, 9800, or Picker 1200 SX).

Patients were sedated with chloral hydrate (25 mg/kg body weight) or with intramuscular injection of a combination of demerol 2 mg/kg, phenergan 1 mg/kg, and thorazine 1 mg/kg. Although there was some variation in scanning sequences, a specific examination routine was followed when possible. Contiguous precontrast scans of 2-mm thickness were obtained in the axial plane throughout the orbits. Following intravenous injection of iodinated contrast material (hypaque meglumine diatrizoate 60% 2 ml/kg), repeat axial scanning was performed through the orbits at 2-mm intervals and through the brain at 5-mm intervals. Image reformatting

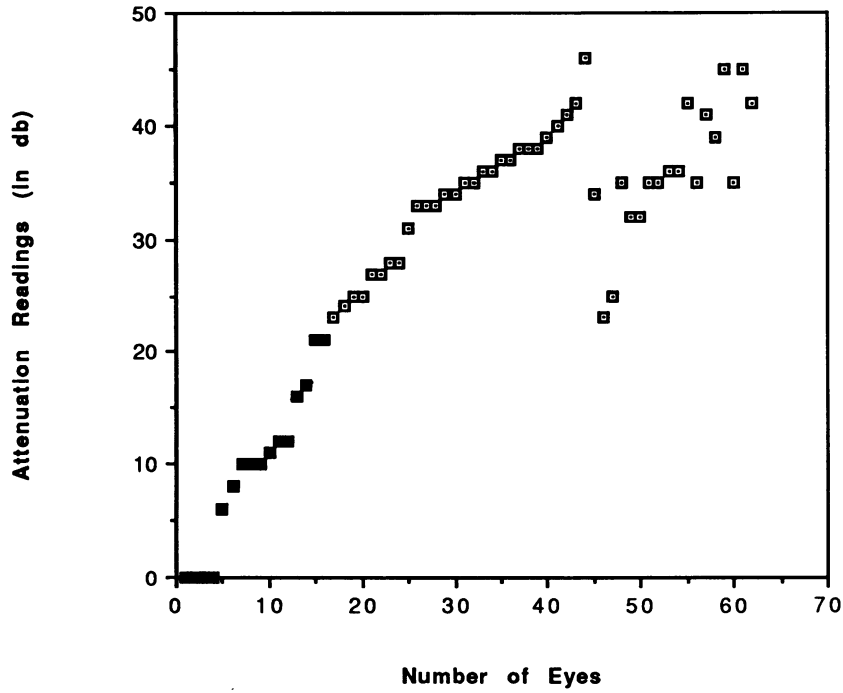


FIGURE 12
Maximum acoustic attenuation readings in Coats' disease (■) and retinoblastoma (⊡). Sixty-two eyes were examined.

into sagittal and coronal planes was routinely performed to permit multidimensional visualization of the intraocular pathology without having to place the sedated child in an uncomfortable or airway-compromising position.

The resultant study of each patient was carefully evaluated to assess the following characteristics: globe size and contour, intraocular morphology (detection of retinal detachment, subretinal mass or density, the homogeneity or heterogeneity of the subretinal material and residual vitreous), radiographic density, the degree and pattern of intraocular contrast enhancement detected, and the presence of associated optic nerve, orbital, or intracranial abnormalities.

Globe Size and Contour—The axial length of both eyes in each patient was measured either electronically on the computed tomographic monitor or directly from the radiographic film using calipers and appropriate scale of reference. Comparison was made to published standards[56,57] and the fellow eye when normal.

In 15 patients with advanced Coats' disease the globe was of normal size and contour. Two patients had slightly enlarged globes (1.0 mm and 1.5 mm larger than the normal fellow eye), and two others were microphthalmic (1.0 mm and 3.0 mm shorter than the normal fellow eye).

In the exophytic retinoblastoma patients, 48 eyes were of normal size and contour; however, in six other cases, buphthalmus (1.0 mm, 1.0 mm, 1.5 mm, 2.0 mm, 2.0 mm, and 2.5 mm larger than normal) was detected.

Intraocular Morphology—The soft-tissue morphology was evaluated by reviewing the axial, coronal, and sagittal images so that a three-dimensional sketch of the intraocular pathology was created. Adjusting gray scale and density levels facilitated the depiction of intraocular anatomical details.

In 14 patients with Coats' disease, a distinct pattern of retinal detachment was visualized with attachments at the optic nerve and ora serrata (Fig 13). The detachment was of varying size and configuration. The extent of detachment could be approximated by evaluating serial axial slices, as well as sagittal and coronal reconstructions. The retinal detachment was estimated to involve less than 25% of the intraocular volume in two patients, 25% to 50% in three patients, 50% to 75T in five patients, and 75% to 90% in the remaining four patients.

In the two patients with minimal (< 25%) involvement, shallow, flat, curvilinear retinal elevations were noted. In the more advanced patients (25% to 75% involvement) a butterfly pattern of bullous retinal elevation was observed. In the most advanced cases with radiographically detectable detachments the retinal bullae were highly elevated, often convoluted, and only a minimal residual vitreous cavity was seen.

In the second group of five patients, a retinal detachment could not be seen radiographically, even though it was known to exist from previous ophthalmoscopic evaluation. The globe appeared normal with the exception of an increased density to the intraocular cavity (Fig 14).

The impression of a distinct circumscribed or nodular intraocular mass was not observed in any of the Coats' disease patients. However, a diffuse homogeneous accumulation of radiographically dense material was routinely visualized.

In the 54 eyes with exophytic retinoblastoma, a radiographically detectable retinal detachment was seen in only nine cases. The contour of the retinal detachment was rarely seen in all views and generally was not as distinct as in the Coats' disease patients. In the remaining 45 patients, a retinal detachment was not visible, and one could not distinguish the residual vitreous from the subretinal space.

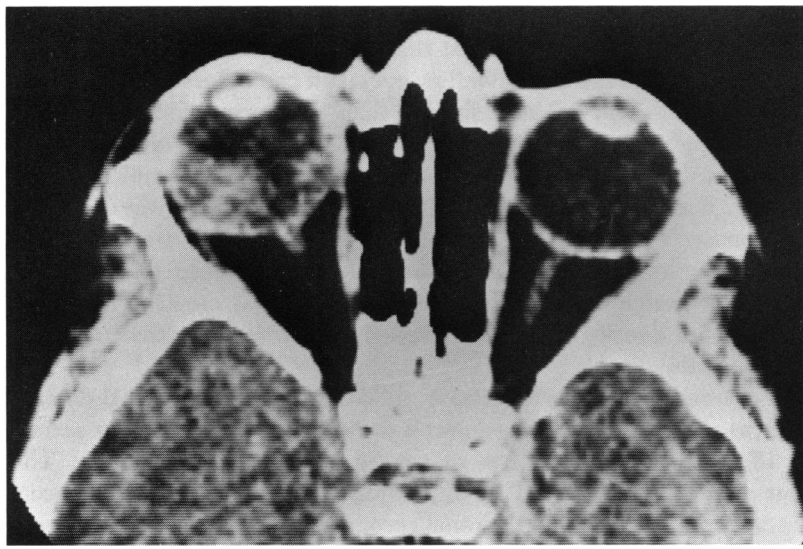


FIGURE 13
Axial computed tomogram of a patient with Coats' disease demonstrating a total retinal detachment with moderate subretinal densities.

The impression of an intraocular mass was seen in all the exophytic retinoblastoma patients. In some this was a distinct nodule confined to a quadrant of the globe (Fig 15), and in others the density appeared to involve the entire globe (Fig 16). The subretinal mass was heterogeneous in 51 eyes and homogeneous in 3.

Intraocular Density—The radiographic density was determined by direct measurement of x-ray attenuation within the region of interest. A cursor box, 5 × 5 mm rectangle or free-form trace, was placed encompassing the lesion, and at least five computer-generated averages of radiographic density were obtained and averaged. The radiographic density was measured according to the New Hounsfield Scale, a system of measurement named in honor of Godfrey Hounsfield, who received the Nobel Prize for his pioneering research that led to the first computed tomographic scanners.[58] This scale grades radiographic density using air (−1000 Hounsfield units [HU]), water (0 HU), and dense bone (+1000 HU) as reference standards.

The subretinal density in advanced Coats' disease measured between 15 and 72 HU, while the residual vitreous cavity ranged from 6 to 24 HU

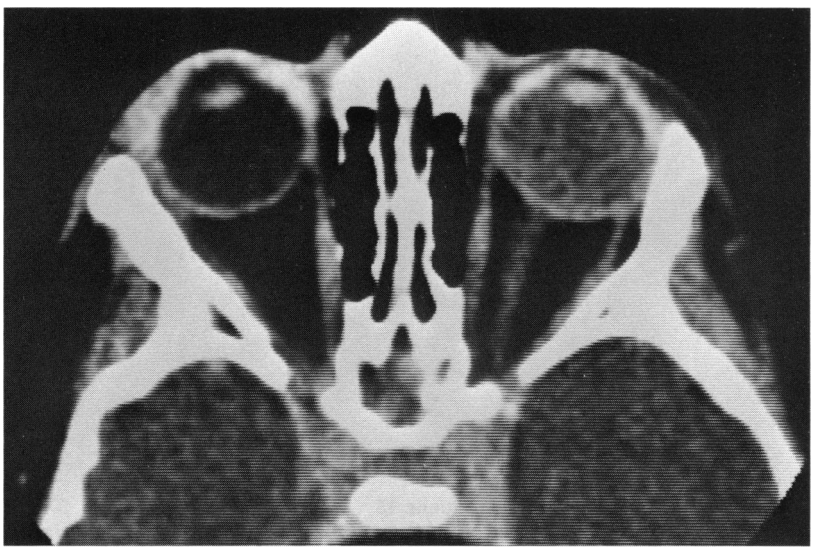


FIGURE 14
Contrast-enhanced axial computed tomogram of a patient with Coats' disease. Left globe shows a moderate increase of intraocular density with no retinal detachment apparent.

(Fig 17). Subretinal densities were quantified in 49 of the exophytic retinoblastoma patients. Subretinal density measurements varied considerably and ranged from 20 to 538 HU (Fig 18). Densities of over 125 HU consistent with calcification were detected in 47 patients, with most demonstrating extensive calcification, although in several patients only trace calcifications were detected in the periphery of the tumor mass. Thus, calcification was a characteristic feature of exophytic retinoblastoma, being observed in 47 of 49 patients.

Enhancement—Noncontrast and contrast-enhanced computed tomographic studies were available in 11 patients with advanced Coats' disease and 33 patients with exophytic retinoblastoma. No enhancement of the subretinal space was observed in any of the Coats' disease patients (Fig 19), whereas all of the retinoblastoma patients demonstrated enhancement (Fig 20), including the two patients without radiographically detectable calcification (Fig 21). In eight patients with advanced Coats' disease and 10 patients with exophytic retinoblastoma, Hounsfield densities in the subretinal space were measured (Table V).

Associated Optic Nerve, Orbital, or Intracranial Abnormalities—No

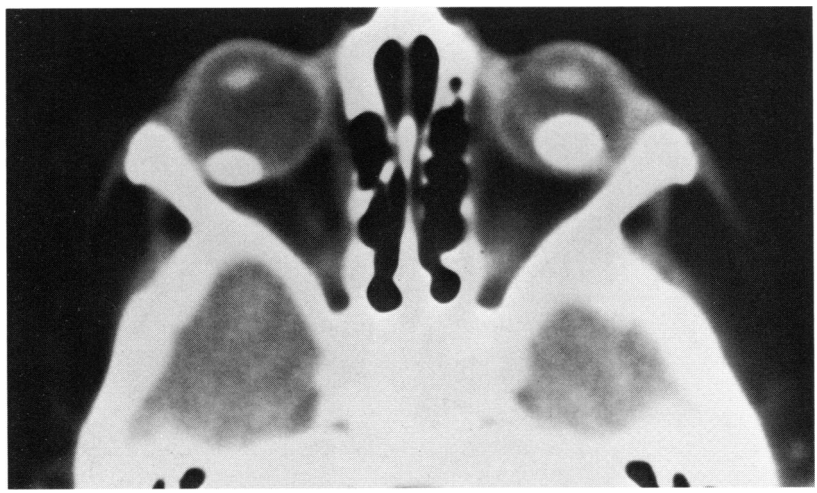


FIGURE 15
Axial computed tomogram of a patient with bilateral retinoblastoma. Ophthalmoscopically, right eye was an endophytic mass. Exophytic mass in left eye appears as an extremely high density (bone density) isolated mass. Retinal detachment is not seen well radiographically.

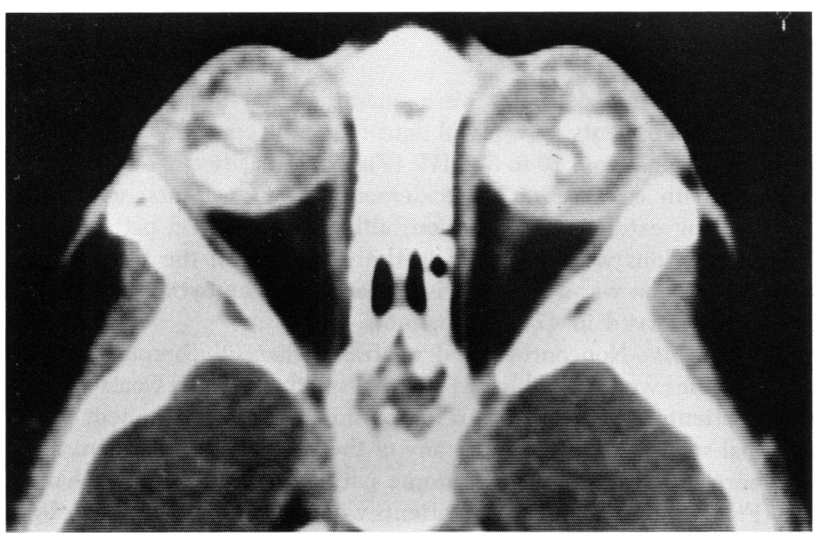


FIGURE 16
Axial computed tomogram of a patient with bilateral exophytic retinoblastoma. Both globes are filled with moderate- to high-density masses. Disparate density levels correspond to areas of soft-tissue mass and calcifications.

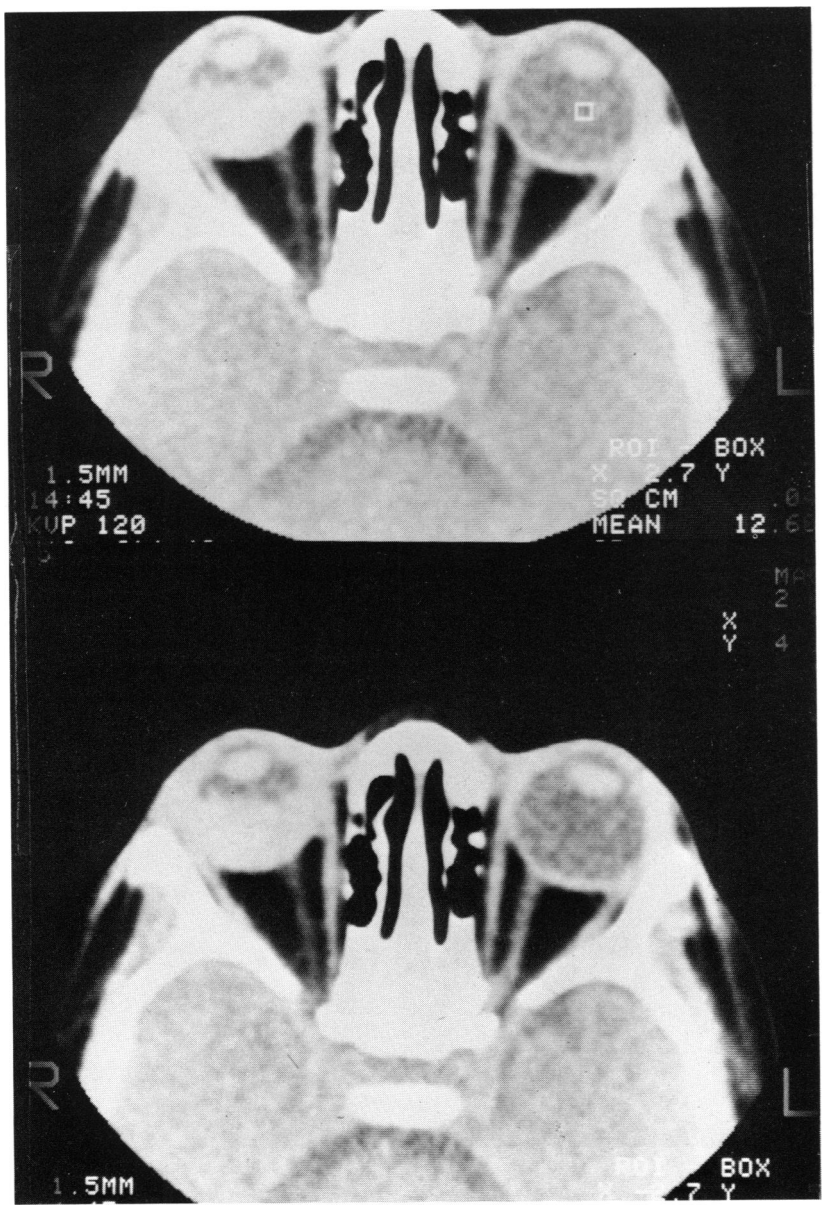


FIGURE 17
Axial computed tomograms of a patient with Coats' disease, demonstrating density measurement. Vitreous in normal fellow eye (top) measured 12 HU, while subretinal exudate in the diseased eye (bottom) measured 47 HU.

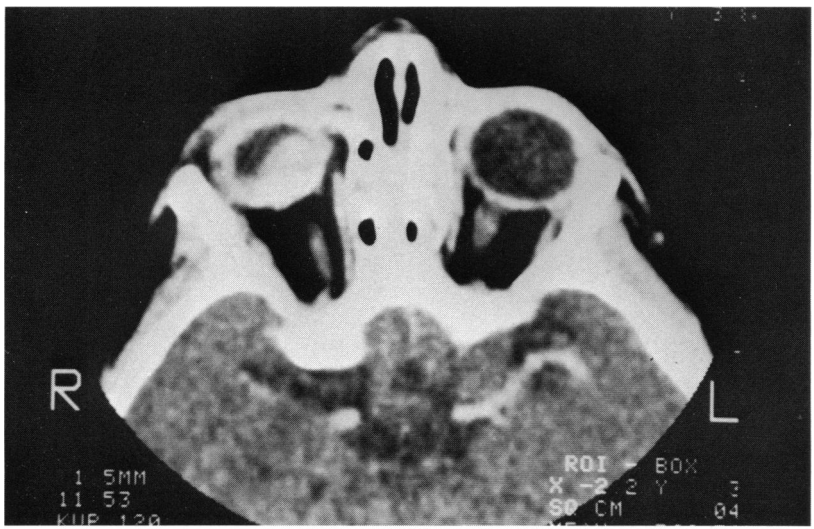


FIGURE 18
Contrast-enhanced axial computed tomogram of a patient with exophytic retinoblastoma Cursor blends into the bright calcified portion of tumor, which measured 566 HU.

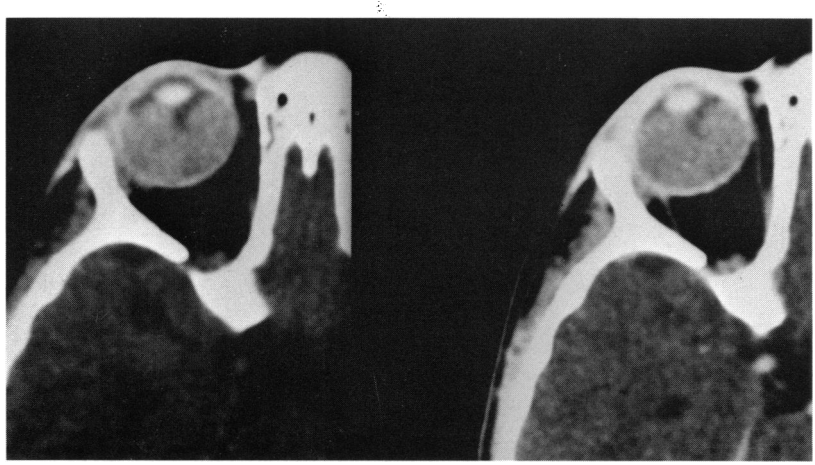


FIGURE 19
Axial computed tomograms of a patient with Coats' disease. A total retinal detachment with minimal vitreous cavity is shown well on the nonenhanced scan (left). No increase in subretinal density is noted after contrast enhancement (right), although enhancement of carotid and basilar arteries is seen.

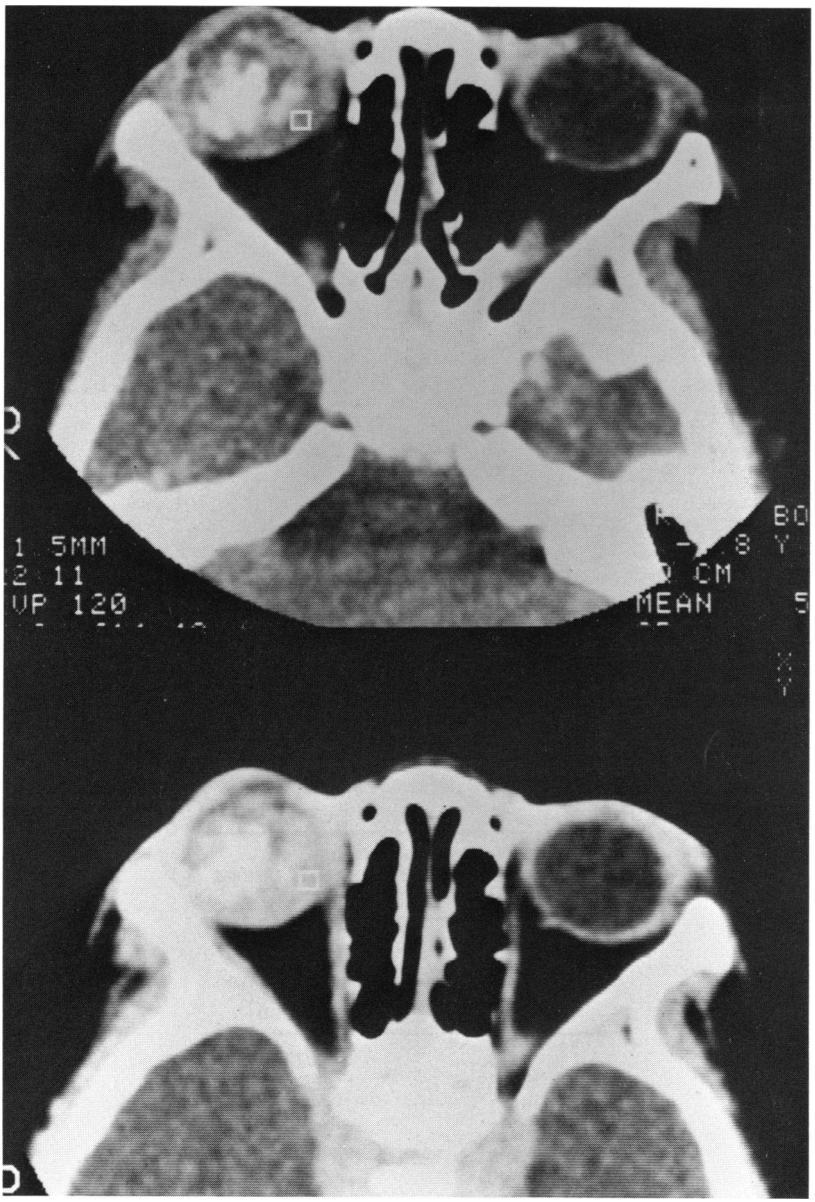


FIGURE 20
Axial computed tomograms of a patient with unilateral retinoblastoma. Soft-tissue components of tumor are seen to increase dramatically following contrast enhancements.

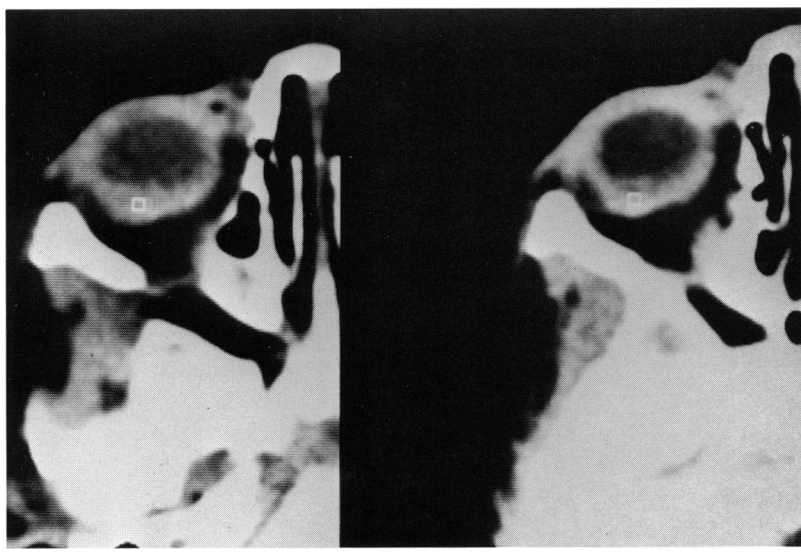


FIGURE 21
Axial computed tomogram of a patient with diffuse, noncalcified retinoblastoma. Distinct enhancement is seen after introduction of contrast material (right). Cursor placed in subretinal space increases from 64 to 80 HU in contrasted study.

evidence of optic nerve enlargement, orbital, or intracranial tumors were detected in either patient group.

TABLE V: COMPUTED TOMOGRAPHY—EFFECT OF ENHANCEMENT IN COATS' DISEASE AND RETINOBLASTOMA

COATS' NONENHANCED/ ENHANCED	RETINOBLASTOMA (NONCALCIFIED PORTIONS OF SUBRETINAL MASS) NONENHANCED/ ENHANCED
72/73	64/75
65/63	56/64*
40/41	65/78
47/47	67/73
52/54	99/112
44/40	45/57
67/69	64/80*
42/43	66/79
	60/66
	95/117

*Noncalcific exophytic retinoblastoma.

Magnetic Resonance Imaging

Magnetic resonance (MR) studies were performed with a 0.5 Tesla (Technicare) or a 1.5 Tesla (Signa-General Electric) superconducting unit on 9 patients with Coats' disease and 13 patients with exophytic retinoblastoma. All patients were sedated using the same protocol described for computed tomography (CT). Orbital surface coils were utilized, when available, to provide higher spatial resolution by increasing the MR signal and decreasing background noise. All images were obtained with a 256 × 128 matrix, 18-cm field of view, and two excitations. Slice thickness was 3 mm to 5 mm, with an interslice gap of 0 mm to 2 mm. Examination planes included axial, coronal, and oblique sagittal views. A routine spin-echo examination included T_1-weighted, long TR (time of repetition, 2000 to 300 msec) multiecho scanning sequences. Proton-density-weighted images used a TR of 2000 msec and a time of echo of 20 to 30 msec.

Morphology and Intensity—MR imaged was available for the evaluation of nine patients with advanced Coats' disease. The retinal detachment was demonstrated on both T_1- and T_2-weighted sequences in five patients and was not seen on both in the remaining four. The subretinal fluid was internally homogenous in both T_1 and T_2 sequences on all nine. The subretinal fluid was of moderate intensity relative to vitreous in the normal eye on T_1-weighted sequences (Fig 22) in seven patients and markedly hyperintense in one patient. A very high intensity was noted on the T_2-weighted studies on all nine (Fig 23), and was clearly contrasted from the residual vitreous in all patients with visualized detachments. In three patients, the retina was in direct contact with the posterior lens capsule, and no residual vitreous could be seen on MR studies. In these patients, the globes were homogenous, with moderate intensity on T_1-weighted studies and high intensity on T_2-weighted studies. The last patient studied had progressed to phthisis, and study showed a microphthalmic eye with mixed internal intensities, including two hypointense areas on all sequences (Fig 24), indicating possibly calcific foci.

In our 13 patients with exophytic retinoblastoma, a retinal detachment was visible in only 5. In all patients, an intraocular mass was visible. This was typically heterogenous with marked variation in intensity on both T_1- and T_2-weighted sequences. Hypointense foci consistent with calcium (Fig 25) were seen on both T_1- and T_2-weighted images within the mass in 11 of 13 patients. The main mass was of moderate intensity relative to normal vitreous on T_1-weighted (Fig 26) and hypointense on T_2-weighted sequences (Fig 27). In five patients, hyperintense areas were seen adjacent to the hypointense mass on T_2-weighted sequences. Histologically, these hyperintense areas corresponded to subretinal fluid and/or hemorrhage.

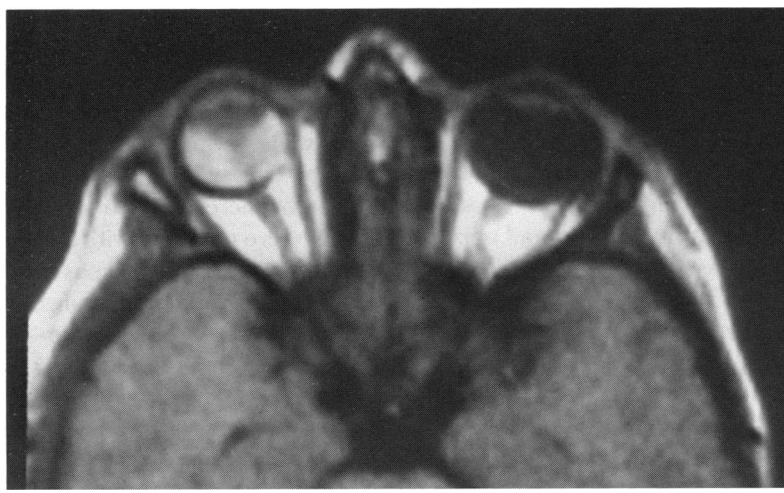


FIGURE 22
T_1-weighted (500/30) image shows a butterfly retinal detachment. Thickened retinal leaves (*arrow*) can be followed to their attachment at optic nerve head. Subretinal fluid is moderately hyperintense relative to vitreous.

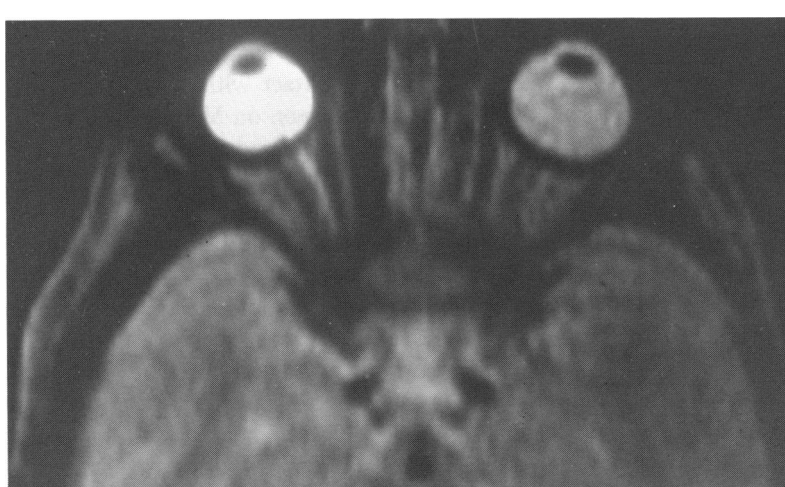


FIGURE 23
T_2-weighted (2000/3.96) image. Anterior chamber, residual vitreous, and subretinal fluid are indistinct and hyperintense in this sequence.

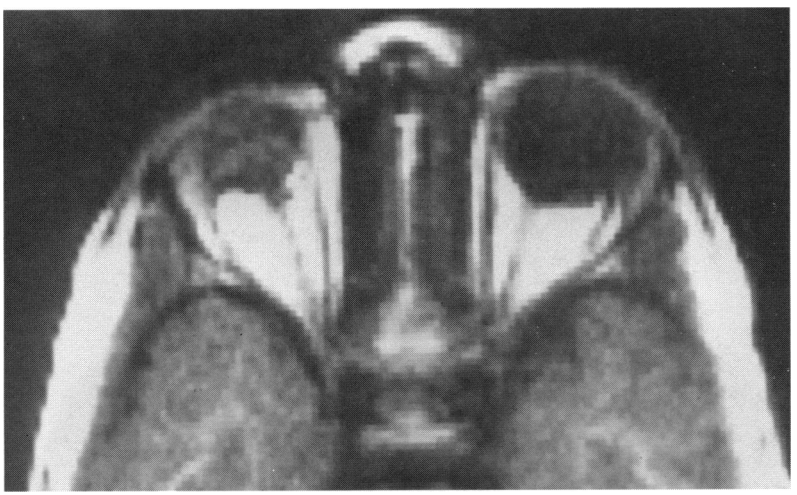


FIGURE 24
T_1-weighted image shows moderate hyperintensity within phthisical globe. Intensity is slightly heterogeneous. Lens is disrupted, and there are no distinctive planes of normal tissues.

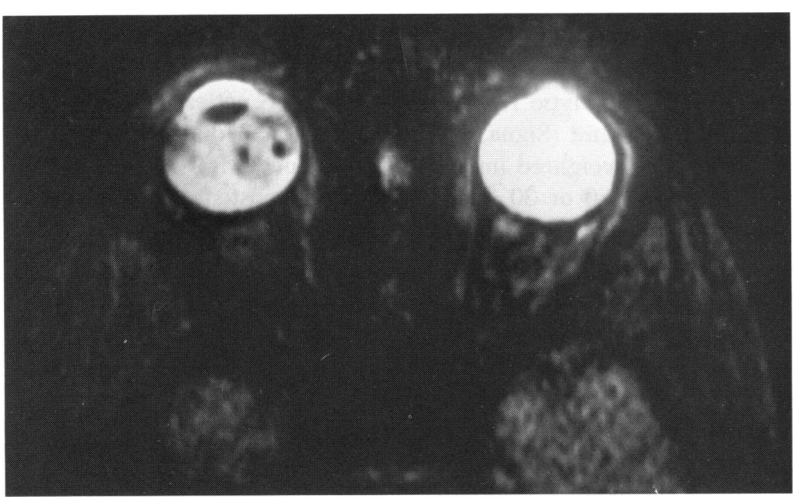


FIGURE 25
T_2-weighted (2000/90) axial MR image of a patient with unilateral retinoblastoma in right eye. Several discrete hypointense foci are outlined by moderate intensity of surrounding soft-tissue mass.

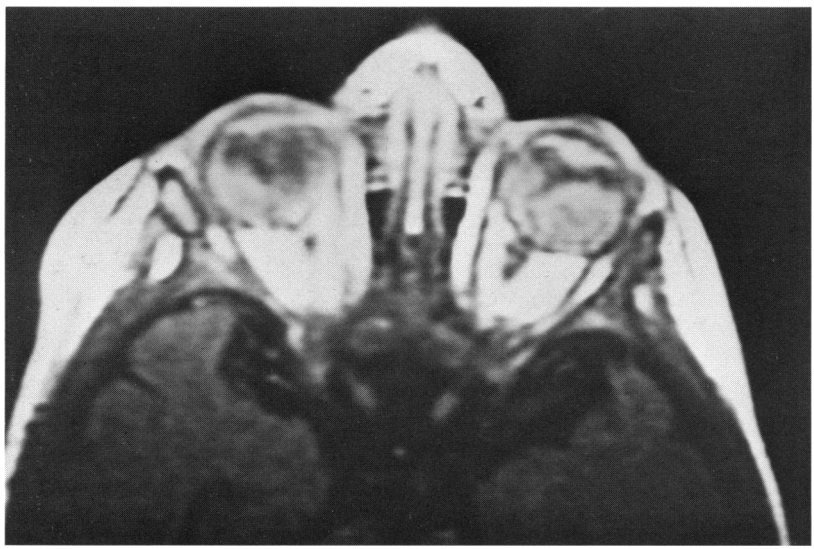


FIGURE 26
T_1-weighted (500/30) axial MR image of patient with bilateral retinoblastoma. Ophthalmoscopically, right eye showed an endophytic mass. Left eye demonstrates a mass of moderate intensity as compared to vitreous.

Contrast-to-noise Ratios and Gadolinium-DTPA Contrast—Gadolinium DTPA contrast was injected intravenously at a dose of 0.1 mmol/kg of body weight in one patient with advanced Coats' disease and in five patients with exophytic retinoblastoma. These patients were examined with 1.5 T MR unit (Signa, GE) with a 12.5-cm diameter receive-only surface coil. T_1-weighted images were obtained with TR 500 or 600 and echo time (TE) 20 or 30 for both pre- and postcontrast examinations. Proton-density-weighted (TR/TE = 2000/20) and T_2-weighted (TR/TE = 2000/70) images were also obtained. Examination planes for T_1-weighted images were axial, coronal, and oblique sagittal, and for proton-density-weighted and T_2-weighted imaged were axial only. Imaging parameters were 256 × 128 or 256 × 192 matrix; 1, 1.5, or 2 numbers of excitation; 8 cm field of view; 3-mm slice thickness; and 1.5 mm slice gap. The same imaging parameters were used for pre- and postcontrast T_1-weighted images. Contrast-to-noice ratios (CNR) were calculated according to the following formula:

$$\text{CNR} = \frac{\text{SI(tumor)} - \text{SI(vitreous)}}{\text{SD (noise)}}$$

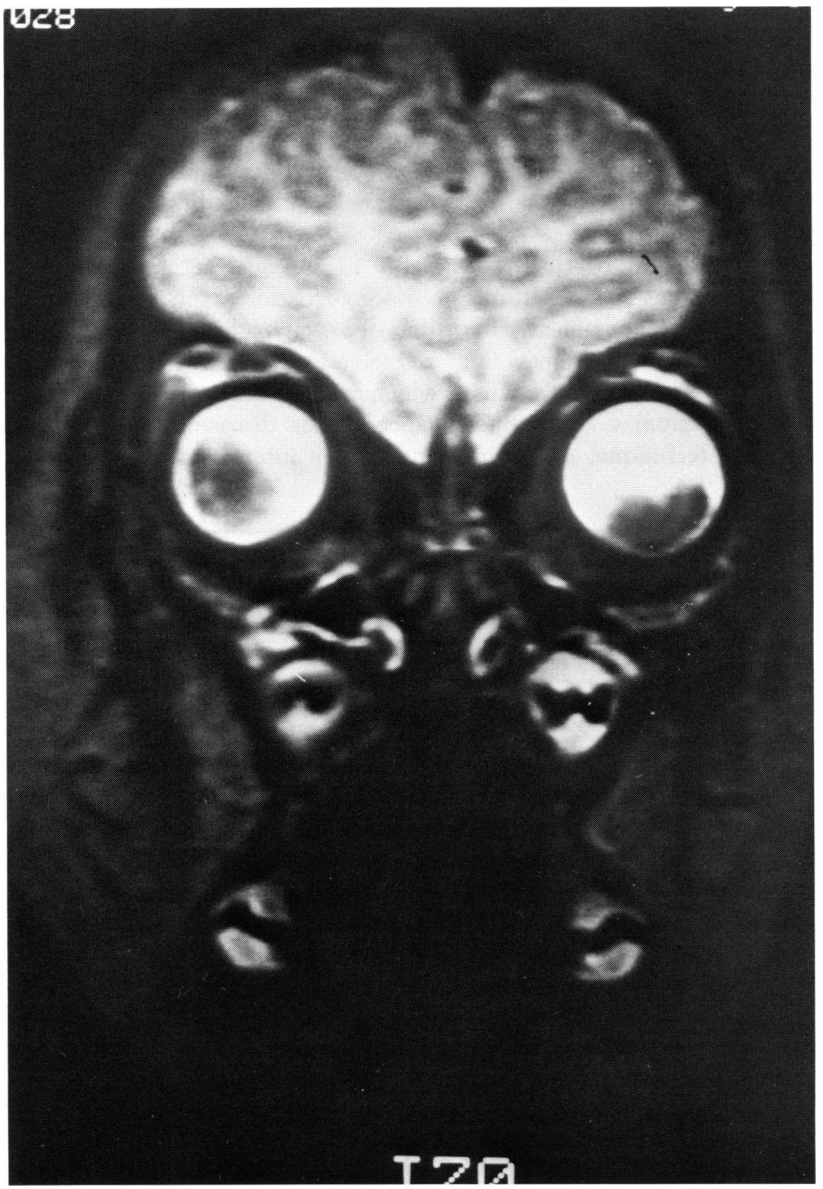


FIGURE 27
T_2-weighted (2000/90) coronal MR image of same patient shown in Fig 25, showing main tumor mass as hypointense compared to vitreous.

In this equation, signal intensities (SI) were measured on the computer from a region of interest (ROI) cursor of 4.0 mm^2. The ROI cursor was placed over a region of maximal intensity within the tumor mass and multiple readings were averaged for each final SI (tumor) value. The SI (vitreous) was an average of multiple readings taken from the ROI cursor in the residual vitreous of the affected eye or the normal fellow eye. The SD (noise) was measured within the field of view, but outside of the patient.

CNR calculations are listed in Table VI. Because retinoblastomas are inhomogeneous as a result of calcification, SI differs among tumors and within a tumor, particularly in proton-density-weighted and T_2-weighted images. The soft tissue mass in all retinoblastoma lesions showed increased SI and CNR by contrast material, which made calcification more apparent in retinoblastomas. In our one advanced Coats' disease patient evaluated with this technique, a moderate increase in intensity was measured.

TABLE VI: CNR MEASUREMENTS

PATIENT	PRECONTRAST T_1-WEIGHTED	POSTCONTRAST T_1-WEIGHTED	PROTON-DENSITY-WEIGHTED	T_2-WEIGHTED
1	20.0	52.9	—	—
2	22.5	106.7	87.5	52.7
3	1.5	30.6	27.3	40.0
4	7.4	34.7	4.1	22.5
5	11.7	34.0	9.6	19.2
Coats' disease				
6	18.8	36.7	6.6	10.8

Aqueous Humor Enzyme Analysis

Lactic Acid Dehydrogenase—Aqueous lactic acid dehydrogenase (LDH) levels were determined in 10 patients with advanced Coats' disease and in 16 patients with exophytic retinoblastoma. Anterior chamber cells were not visible by portable slit-lamp examination in any of these patients prior to surgery. The anterior chamber paracentesis (0.1 to 0.2 ml) was performed translimbally with a 25- or 27-gauge needle in all 11 children with advanced Coats' disease and in 7 children with exophytic retinoblastoma under anesthesia. In the other nine exophytic retinoblastoma patients, the aqueous was removed immediately after enucleation. Minimal red blood cell contamination occurred during the paracentesis in five patients (2 Coats', 3 retinoblastoma); however, the aqueous specimens remained colorless.

Serum LDH was analyzed in 9 of 10 advanced Coats' disease patients, and in 11 of 16 exophytic retinoblastoma patients. One patient with advanced Coats' disease underwent anterior chamber paracentesis on two separate occasions, separated by 6 weeks. Analysis was performed on unfrozen aqueous and serum specimens within 2 hours. Serum samples were centrifuged to prevent hemolysis. Total LDH levels were measured by means of a biochromatic analyzer and expressed in international units per liter (IU/l). An IU is the amount of activity of 1 ml of enzyme/min/l. The aqueous-to-serum LDH ratio was determined for each patient (Table VII). LDH isoenzyme levels were determined in three patients with advanced Coats' disease and in five with exophytic retinoblastoma (Tables VIII and IX). The isoenzymes were separated using cellulose acetate, agarose gel, and acrylamide gel electrophoresis, and then measured fluorometrically. The isoenzymes are designated by a number that is related to electrophoretic mobility. The most anodic and fastest moving fraction is designated LD_1 and the most cathodic and slowest moving fraction is LD_5.

TABLE VII: AQUEOUS HUMOR LDH LEVELS (IU)

	AQUEOUS	SERUM	AQUEOUS HUMOR SERUM
Advanced Coats' disease	0	95	0
	24	157	0.153
	49	NA*	NA
	50-175	169-152	0.296-1.151
	73	122	0.598
	80†	106	0.755
	86	221	0.389
	114†	230	0.496
	705	167	4.222
	1021	148	6.899
Exophytic retinoblastoma	46	NA	NA
	88	215	0.409
	90†	158	0.570
	120	143	0.839
	163	209	0.780
	255	NA	NA
	288	194	1.485
	305	NA	NA
	358	98	3.653
	415	NA	NA
	470	207	2.271
	600†	120	5
	615†	165	3.727
	728	NA	NA
	990	185	5.351
	1024	156	6.564

*NA, not available.
†Minimal red blood cell contamination.

TABLE VIII: AQUEOUS ISOENZYME PATTERNS IN ADVANCED COATS' DISEASE

TOTAL LDH	LD_1 (%)	LD_2 (%)	LD_3 (%)	LD_4 (%)	LD_5 (%)	LD_5/LD_1 RATIO (%)
73	18	23	22	20	17	94.4
87	24	21	17	18	20	83.3
114	21	30	22	13	14	66.7

TABLE IX: AQUEOUS ISOENZYME PATTERNS IN EXOPHYTIC RETINOBLASTOMA

TOTAL LDH	LD_1 (%)	LD_2 (%)	LD_3 (%)	LD_4 (%)	LD_5 (%)	LD_5/LD_1 RATIO (%)
120	23	28	25	12	12	52.2
288	13	16	21	24	26	200
305	20	25	28	13	14	70
470	14	13	15	21	37	264
600	18	19	17	22	24	133

Neuron-Specific Enolase—An aqueous specimen was obtained by anterior chamber paracentesis in one patient with advanced Coats' disease. Neuron-specific enolase was not detectable by radioimmunoassay utilizing the technique of Parma and associates.[59]

PATHOLOGY

Cytopathology

Cytopathologic analysis of subretinal aspirates was performed on eight patients with advanced Coats' disease and 19 patients with exophytic retinoblastoma. In the Coats' disease patients, a controlled fine-needle biopsy specimen was obtained while the patient was under general anesthesia. All retinoblastoma samples were aspirated from freshly enucleated eyes. A small fluid sample was aspirated through a 5/8 inch, 25-gauge needle in a region of bullous retinal elevation. The plunger was released to eliminate all negative pressure before the needle was withdrawn. The self-sealing scleral entrance tract was treated with cryotherapy in three freeze-thaw cycles to destroy any cells that may have been entrapped.

A single drop of fresh subretinal fluid was placed on several glass slides and coverslips and evaluated with light and polarizing microscopy for cells, crystals, and deposits. Additional fluid samples were examined with various preparations including Giemsa, Papanicolaou, modified Wright, and Sudan Red stains.

In all cases, evaluation of fresh preparations in Coats' disease revealed multiple large (40 to 100 μ) oval or round histiocytes (Fig 28). These cells

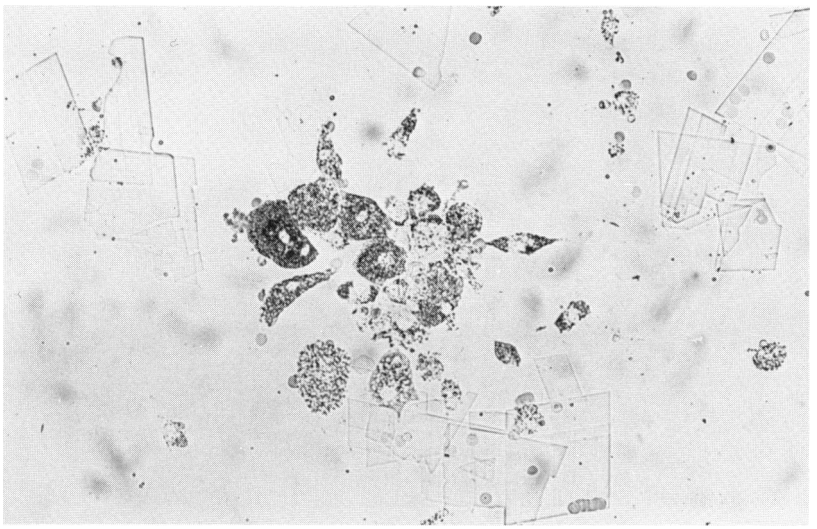


FIGURE 28
Unstained preparation of subretinal aspirate from patient with Coats' disease, revealing large oval histiocytes with intracytoplasmic pigment granules.

contained single or multiple eccentric nuclei, prominent football-shaped intracytoplasmic pigment granules, and clear vacuoles scattered throughout the cytoplasm. Multiple flat, colorless, crystalline plates with a corner notch or jagged edge consistent with cholesterol were seen routinely (Fig 29). The crystals were birefringent when evaluated under polarized light (Fig 30). Occasionally, partially phagocytized crystals were seen within the histiocytic cells (Fig 31). Single or clumped red cells were scattered in three of eight specimens. A summary of the cytopathologic findings in Coats' disease is presented in Table X.

TABLE X: CYTOPATHOLOGIC FINDINGS IN COATS' DISEASE

Fresh preparations
Multiple flat, colorless, crystalline plates with a corner notch or jagged edge
Crystals birefringent under polarizing light
Partially phagocytized crystal within macrophages
Large, round, or oval histiocytes with both pigment granules and clear vacuoles scattered throughout the cytoplasm
Single or clumped red blood cells, and inflammatory cells
Stained preparations
Large (40 to 100 μ) oval-to-round histiocytes (single or clumped)
Single or multiple eccentric nuclei
Large round or elliptical intracytoplasmic pigment granules
Foamy vacuolated cytoplasm on Giemsa, Papanicolaou, and modified Wright stain; the vacuoles stain for fat with Sudan Red
No crystals visible (dissolved by alcohol or xylol)
Occasional single or stacked red blood cells, and inflammatory cells

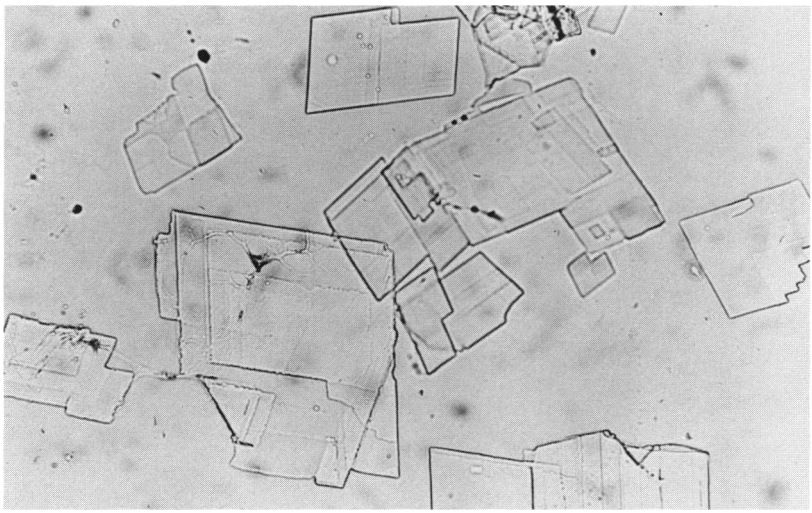


FIGURE 29
Fresh subretinal aspirate from patient with Coats' disease, depicting rectangular crystals with right-angled corners and straight edges.

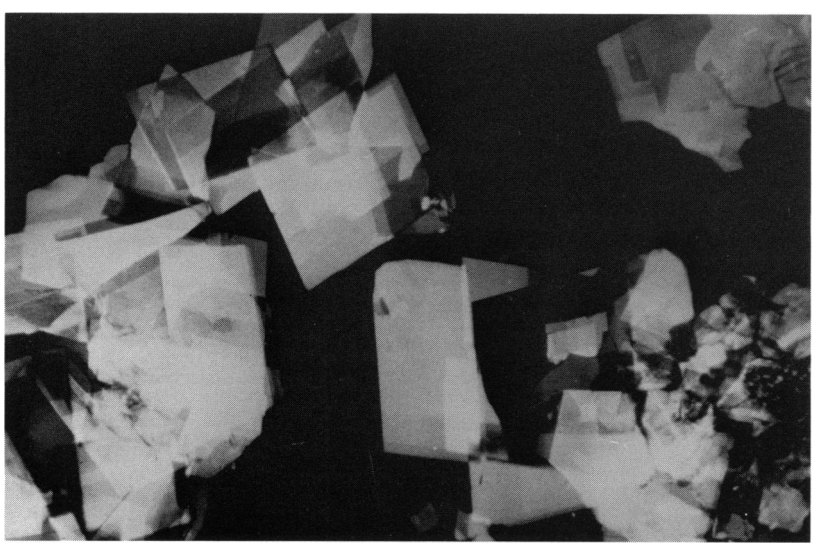


FIGURE 30
Same specimen as shown in Fig 28 examined under polarized light, revealing birefringence.

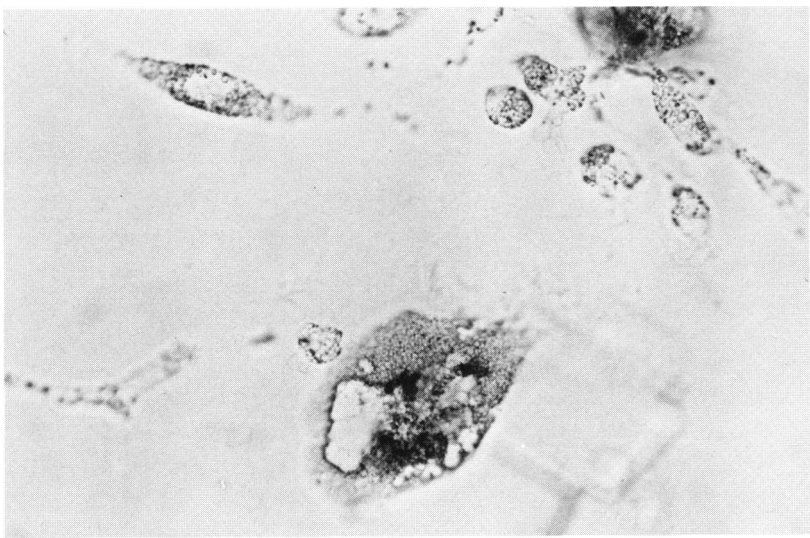


FIGURE 31
Fresh preparation of subretinal fluid demonstrating partially phagocytized cholesterol crystals.

When stained preparations were evaluated in Coats' disease patients the following additional findings were noted: (1) the foamy vacuolated cytoplasm of the pigment-laden histiocytes (Fig 32), stained for lipid with Sudan Red. (2) No crystals were visible; they presumably were dissolved by the alcohol or xylol used in preparation.

Unstained specimens from all eyes harboring retinoblastoma revealed clumps of small (10 to 12 μ) round undifferentiated cells (Fig 33). Non-polarizing amorphous crystalline material and granular or small cuboidal, calcified deposits were detected (Fig 34 A and B). Large pigment-laden histiocytes were rarely noted, but when seen, were always in a field with numerous tumor cells (Fig 35). Cholesterol crystals could not be detected in any specimens from patients with retinoblastoma.

In stained preparations, the small cells had round hyperchromatic nuclei, which at times were molded or indented and had scant or indistinct cytoplasm (Fig 36). Cells tended to clump together; however, rosette formation was never encountered. Necrotic and fragmented cells were often present as were occasional inflammatory cells and red blood cells. Deeply basophilic material consistent with calcium was frequently noted. Occasionally, pigment-laden macrophages or lymphocytes were detected,

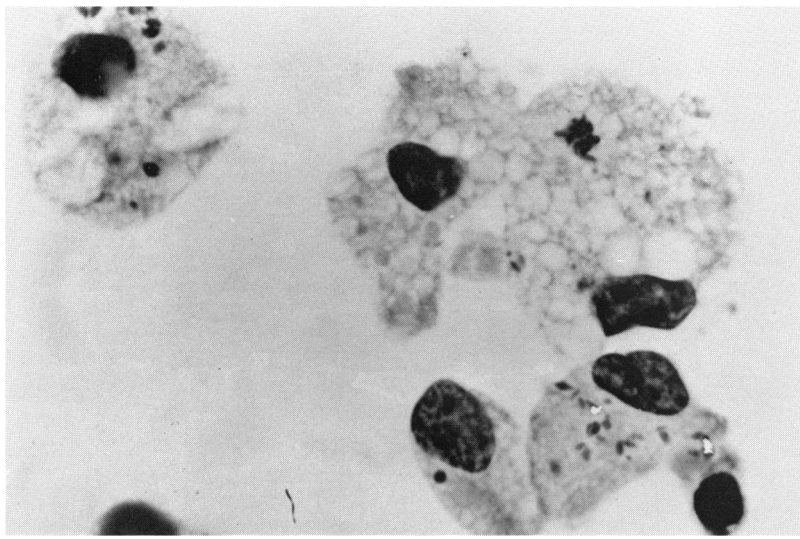


FIGURE 32
Giemsa stain of subretinal aspirate of patient with Coats' disease demonstrating a cluster of histiocytes with vacuolated cytoplasm and elliptical pigment granules.

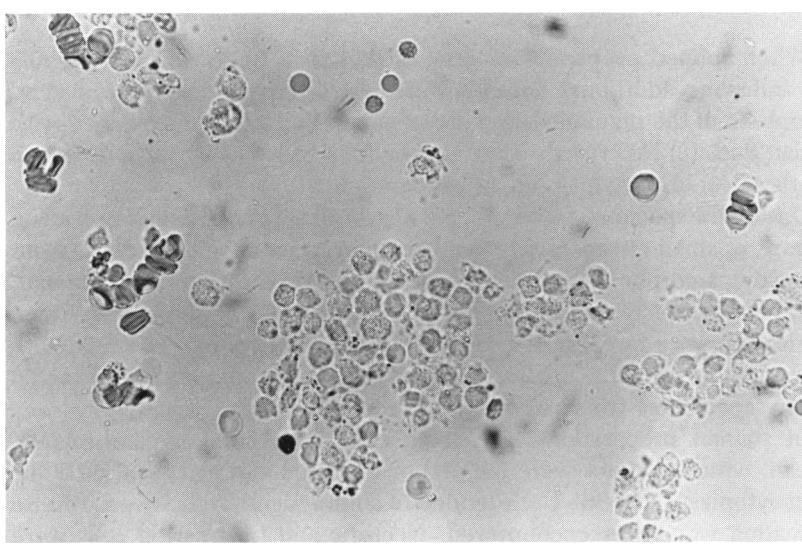


FIGURE 33
Unstained preparation of subretinal fluid from enucleated eye of a patient with exophytic retinoblastoma. Clusters of small, round undifferentiated cells are seen.

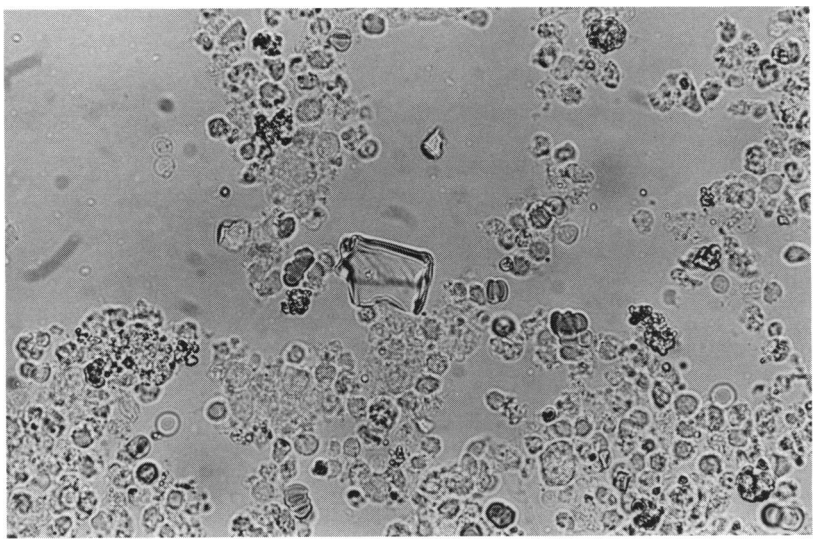
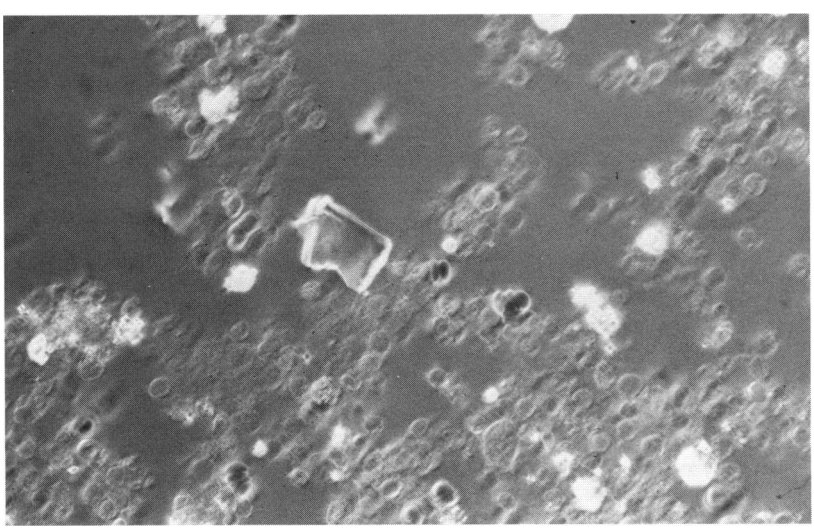


FIGURE 34

A: Unstained preparation of subretinal fluid from enucleated eye of a patient with exophytic retinoblastoma. Amorphous crystals are seen in a field of small undifferentiated cells. B: Under polarizing light, no birefringence is seen.



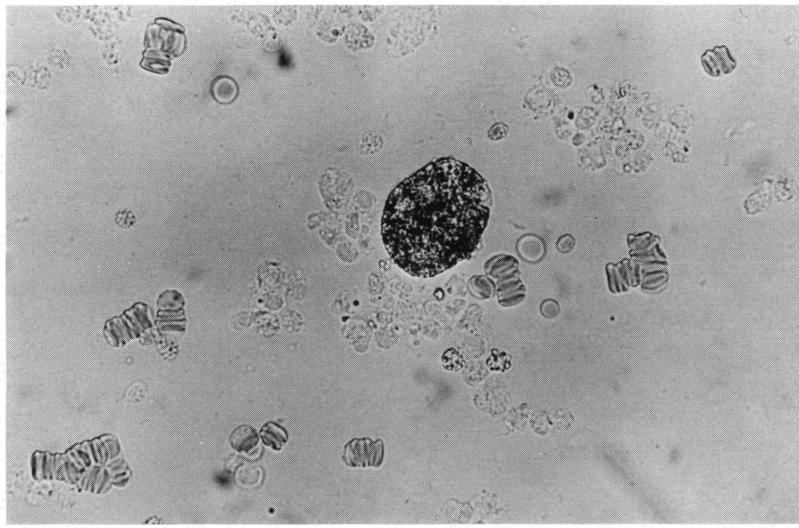


FIGURE 35
Unstained preparation of subretinal fluid from enucleated eye of a patient with exophytic retinoblastoma. A large pigment-laden histiocyte is seen within a field of small undifferentiated cells and clumps of red blood cells.

but always within or adjacent to a field of tumor cells. Table XI presents an outline of cytopathologic findings in retinoblastoma.

TABLE XI: CYTOPATHOLOGIC FINDINGS IN RETINOBLASTOMA

Fresh preparations
Clumps of small (10 to 12 μ) round undifferentiated cells
Amorphous crystalline material with small cuboidal calcified deposits (nonpolarizing)
Red blood cells, inflammatory cells, rarely pigment-laden macrophages
Stained preparations
Small undifferentiated cells with hyperchromatic round nuclei and scant or indistinct cytoplasm (some necrotic)
Nuclear indentation or molding commonly detected
Tendency to clump; rosette formation never encountered
Nuclei twice as large as nuclei of small lymphocyte
Rare cases show large benign histiocytes with ingested debris and large pigment granules
Some scattered inflammatory cells and red blood cells
Blue-black calcifications, amorphous or cuboidal

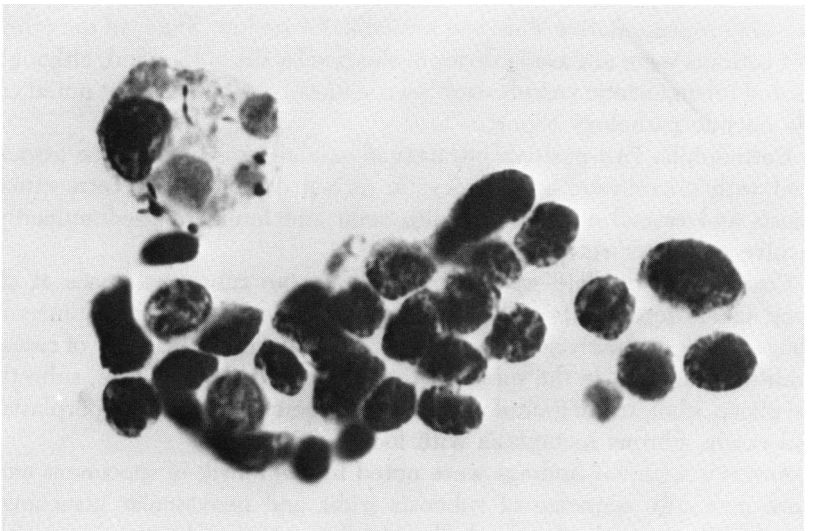


FIGURE 36
Wright stain of subretinal aspirate from enucleated eye of a patient with exophytic retinoblastoma. A cluster of small, round cells with hyperchromatic and scanty cytoplasm is seen, as well as a large pigment-containing macrophage.

Histopathology

Fifty-one of the 67 patients with long-term follow-up were enucleated. In 34 cases, pathologic material was available for review. In all of these cases, at least one representative slide stained with hematoxylin and eosin was available. In most multiple sections, representative slides were available, and PAS were employed. In the remaining 17 cases, an outside laboratory report was available, confirming the diagnosis of advanced Coats' disease. Microscopic evaluation revealed a spectrum of findings similar to the published literature. In each case, a total retinal detachment was present; in some cases, fixed folds were present, and in others, massive retinal gliosis and disorganization. Telangiectatic retinal vessels were found in portions of the peripheral retina in all but four globes. The endothelial cells of the ectatic vascular channels were often thin. PAS-positive material was commonly present within vessel walls, which varied greatly in width. Some vessels were partially thrombosed, while perivasculitis and cholesterol sheathing was noted in others.

In two of the four patients where vascular abnormalities were not seen,

only one representative slide was available for review. Slides of the other two patients were not available for evaluation by the author and, although dilated telangiectatic vessels were seen clinically, they were not noted on the outside pathology report.

Eosinophilic PAS-positive intraretinal exudate was found to be associated with microcystic or macrocystic retinal degeneration. Intraretinal gliosis and retinal atrophy was also seen and found to predominantly involve the outer retinal layers.

Eosinophilic exudate was also present in the subretinal space at all eyes. Cholesterol clefts and pigment-laden or vacuolated foamy macrophages were routinely seen, and were abundant in the majority of cases. Additional findings in the subretinal space included hemorrhage, subretinal gliosis, cholesterol granulomas, retinal pigment epithelial hyperplasia, and rarely, fibrous metaplasia with focal calcifications.

Anterior segment findings were noted in one fourth of specimens and were generally sequelae of rubeosis iridis and neovascular glaucoma. Microcystic corneal edema, shallow or flat anterior chamber, iris neovascular membranes, ectropion uveae, anterior and posterior synechiae with iris bombé, or atrophy were commonly noted in this group.

DISCUSSION

CLINICAL CHARACTERISTICS

Age

In previous reports, the age of patients with Coats' disease has varied considerably. In Coats' original paper,[1] two of his six patients were aged 7 and 8 years, and the other four were in the third and fourth decades of life. In a series of 47 patients presented by Campbell,[3] the youngest patient was 3 1/2 years old and the oldest was 59. Only eight of these patients were 10 years of age or younger. In the study by Morales[10] of 51 patients, the average age at presentation was 8 years of age, the youngest was 1, and the oldest was 34. In clinical series by Ridley[60] and Silador,[51] the average ages were 10 years and 28.4 months, respectively. In the largest clinicopathologic series reported to date, by Chang,[19] 51 of 62 patients underwent enucleation before 6 years of age.

It is not surprising that our patient population is extremely young (3 years of age) since our referral base is predominantly pediatric. Also, it appears that the advanced form of Coats' disease may progress quite rapidly in infants, leading to diagnosis early in life. Spitznas[32] speculates that juvenile Coats' disease may be diagnosed at a more advanced stage

because of two possibilities: (1) children are less concerned about visual changes than adults, and (2) "the disease may be more severe and faster progressing in the young, whereas vasoactivity decreases with increasing age."

The average age at the time of diagnosis for retinoblastoma patients is 18 months[61] versus 3 years for our patients with advanced Coats' disease. There was however, significant overlap between the age distributions. Our youngest patient with advanced Coats' disease was seen at 1 month of age and is the earliest reported in the literature.

Sex and Race

Of the 75 patients, 62 (82.7%) were male. This predilection among males is similar to previous reports.[3,19,24,32 51,60] To date, none of the reports, including the present one, elucidates the reason for male predilection. No racial pattern of involvement was noted.

Family, Prenatal History, and Delivery

As in most previous reports, no family history of Coats' disease or other pediatric retinal vascular disorders was obtained from our patients' relatives. The one notable exception in the literature is Campbell's description of retinal telangiectasia as a familial disorder in three families. In retinoblastoma, a family history is obtainable in as many as 8% of patients,[61] and may be a critical clue in establishing the proper diagnosis. No significant prenatal or delivery patterns were noted.

Postnatal History and Associated Physical Findings

Although three patients received oxygen in the neonatal period, it was not thought to be contributory since in two patients it was for 1 week or less, and the fellow eye in these three children was free of vascular disease.

Numerous associations between Coats' disease and other ocular, systemic, or genetic disorders have been documented in the medical literature (Table XII). The most striking correlation, that between Coats' disease and retinitis pigmentosa, has been reported in over 40 cases. The relationship between these diseases has been examined in detail by Khan and associates.[62] These authors came to the reasonable conclusion that the exudative response associated with retinitis pigmentosa may be due to a Coats-like vascular response but different from the classic form described by Coats. They stated that "this appears to be an entity distinct and separate from classic Coats' disease with regard to retinal location, patient age, gender, bilaterality, familial association, and association with retinitis pigmentosa." It is unclear whether or not the other associations noted in Table XII result from a similar nonspecific vascular degeneration or

incidental associations, or are true syndromes. None of the patients in our study had any of the aforementioned associated disorders. Our findings coincide with those of Coats[1]: "In almost all instances, physical examination of the patient has revealed no other disease." One of our patients was found to have a trisomy 8 mosaic, a previously unreported finding. Twenty-seven of our patients underwent blood lipid and cholesterol laboratory evaluations, which were within normal limits in all cases. These findings are consistent with Duke and Woods' findings: "In the juvenile cases the plasma lipids are consistently within normal limits."[25]

TABLE XII: ASSOCIATIONS WITH COATS' DISEASE

ASSOCIATION	REFERENCE
Retinitis pigmentosa	62-75
Senior-Loken syndrome	76
Thalassemia minor and retinitis pigmentosa	62, 71
Turner's syndrome	77
Deletion of 13 q 12.1	78
Pericentric inversion of chromosome 3	79
Hair and nail defects and intracranial calcifications	80
Infantile cataracts and ketotic hypoglycemia	81
Ichthyosis hystix (epidermal nevus syndrome)	82
Postrenal transplant	83
Muscular dystrophy	84, 85
Sturge-Weber syndrome	86
Toxoplasmosis	87, 88
Retinal gliosis	89, 90
Morning glory optic disc anomaly	91
Cornelia de Lange syndrome	92
Trisomy 8 mosaic	

In most retinoblastoma patients we have evaluated, the initial systemic evaluation is unremarkable. In approximately 5% of retinoblastoma patients, a segmental deletion of the q 14 band on chromosome 13 may be detected, and, rarely, some of these patients have psychomotor retardation and skeletal retardation and skeletal abnormalities. Retinoblastoma patients with the germinal mutation are susceptible to pinealoblastomas and secondary primary malignancies, which typically occur later in life.

Presenting Signs and Symptoms

The presenting signs and symptoms in our Coats' disease patients are similar to the findings in two large series of retinoblastoma patients reported by Howard and Ellsworth,[37] and Shields.[93] The major differences noted relate to the incidence of strabismus and leukocoria as presenting signs. In the Coats' disease patients, strabismus was the most common presenting sign, occurring in 36% of patients (Fig 37). Strabismus was the presenting sign in 22% of Howard and Ellsworth's retinoblastoma patients and in 24% of Shields' retinoblastoma patients. Leukocoria occurred in 32% of the Coats' disease patients, compared with 61% of Howard and Ellsworth's patients and 63% of Shields' patients. The remaining patients in all three series had surprisingly similar presenting signs and symptoms.

Referring Diagnosis

The referring physicians correctly diagnosed Coats' disease in only 20% of patients. In almost one half the cases, the referring physician had diagnosed retinoblastoma and referred the patient for confirmation and/or therapy.

CLINICAL FINDINGS AT PRESENTATION

Most of our patients had dramatic signs or symptoms reflecting the advanced stage of the disorder on presentation.

Eye Involved

In the present series the right eye was most commonly involved (56%). Coats[1] reported: "The right eye has more often been affected than the left (11 to 6)." This also coincides with Harris'[13] "interesting observation" of right eye involvement in 18 of his 23 cases (78%), and with Chisholm,[23] who found "the right eye to be three times more frequently affected than the left" (16 patients). About equal distribution was noted by Chang[19] (29 OD, 28 OS) and by Egerer[24] (19 OD, 19 OS). We are unable to provide insights into these interesting observations.

Bilaterality

Our findings of only a small number of bilateral cases is similar to the majority of the literature. In contrast, Campbell[3] found that 10 of his 47 patients had bilateral disease. Our patients were considerably younger and had more advanced disease than those in Campbell's series, and may thus represent a distinct subset less prone to bilateral involvement.

Retinoblastoma is bilateral in approximately 30% of cases. The disease is usually asymmetric, and on funduscopic evaluation of the less involved

eye, a diagnosis of retinoblastoma can usually be established.

Status of the Fellow Eye

The fellow eye was normal in all but the two patients with bilateral Coats' disease. Long-term follow-up was available on only one of these children. This child was initially seen at the age of 5 years. At this time, the right eye was recorded to have abnormal retinal telangiectasis involving approximately one third of the retina. Marked cholesterol exudation was noted in the macula. In the more advanced left eye, a total exudative detachment was noted, and retinal telangiectasia were visible over one fourth of the surface. Photocoagulation was carried out by the referring physician, and 5 years following therapy, the right eye was stable with 20/200 vision and no ophthalmoscopic evidence of active telangiectatic

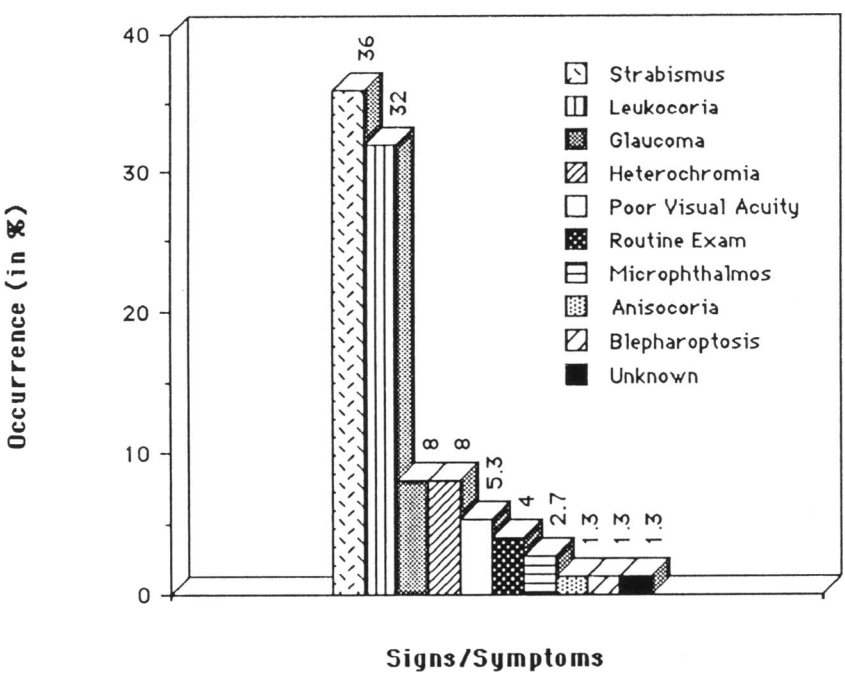


FIGURE 37
Presenting signs and symptoms in Coats' disease.

vessels or exudation. A complete retinal detachment persisted in the left eye, but the child was free of pain.

External Examination

A variable strabismus was detectable in 42.7% of patients with advanced Coats' disease. This high incidence of sensory strabismus indicates that in these patients, the retina has been detached for a significant period (weeks to months). Ellsworth[61] has noted a sensory strabismus in 20% of retinoblastoma patients.

Periocular edema, erythema, and pain were generally associated with glaucoma and/or uveitis. Similar findings are noted in patients with retinoblastoma.

OPHTHALMIC FINDINGS

Anterior Segment

Anterior segment abnormalities were found in 24% of patients on our initial evaluation and were most commonly sequelae of anterior segment neovascularization, or chronic inflammation. Rubeosis iridis was present in 11 of 75 patients (14.7%) and was considered an extremely poor prognostic sign for ocular survival. Cataractous changes in the lens were not noted on initial presentation, but were found to occur later in grossly disorganized phthisical eyes. Cataracts are also extremely rare in retinoblastoma, except as a late complication of intraocular inflammation or hemorrhage.[61]

Vitreous Cavity

The vitreous cavity was typically clear in advanced Coats' disease patients, although both hemorrhage and inflammatory debris were occasionally seen (6.7%). Tumor seeds are quite characteristic of retinoblastoma and in endophytic tumors are often seen and almost pathognomonic.[61] Unfortunately, in exophytic retinoblastoma tumor seeds are confined within the subretinal space and are not easily seen. When visible, they are sometimes difficult to distinguish from the subretinal deposits in advanced Coats' disease.

Retinal Detachment

Only patients with total retinal detachment are included in this study. In the majority of patients, a highly elevated bullous detachment was present; in several, however, only a shallow elevation was observed. Retinal movement was minimal and appeared to be damped by the thick subretinal exudate.

Retinal Vascular Abnormalities

Ophthalmoscopically visible retinal vascular abnormalities were seen in 77.3% of patients (Fig 38). In most patients, these were easily detectable; however, in some patients, the vascular abnormality was only seen following detailed indentation ophthalmoscopy, and visualization was hampered by overlying hemorrhage, inflammatory debris, intraretinal exudation, or retinal involutions. With the exception of two cases, retinal vascular abnormalities were seen on ophthalmoscopic or pathologic evaluation in all eyes with advanced Coats' disease. In the two cases without visible vessels, only a single slide was available for review, and vessels may have been detectable on review of stepped sections of the globe. It should be noted that, although less prominent than those seen in Coats' disease, in several instances, dilated tortuous vessels are seen in retinoblastoma patients (Fig 39). Jaffee and associates[94] have reported a patient with a total retinal detachment, retinal telangiectasis, and yellow subretinal exudation that eventually was diagnosed with retinoblastoma. They stated "Rather than true Coats' disease, however, this proved to be a 'Coats' reaction' to the retinoblastoma."

Subretinal Deposits, Mass, or Hemorrhage

The finding most characteristic for Coats' disease was that of scintillating cholesterol crystals, intra- or subretinal deposits, mass, and hemorrhage (Fig 40). However, subretinal deposits were often clinically indistinguishable from those seen in patients with exophytic retinoblastoma. Two findings were particularly striking: (1) in 20% of patients, a yellowish or whitish-yellow subretinal mass or mound was noted (Fig 41); and (2) in 20% of patients, granular subretinal deposits were seen (Fig 42), simulating the deoxyribonucleic acid-calcium complex found in patients with retinoblastoma. Subretinal hemorrhage was a relatively common finding, occurring in 24% of patients. Ellsworth[61] has stated that subretinal hemorrhage is much rarer in retinoblastoma, being seen in only 5% of patients.

One of the rarer clinical findings is retinal pigment epithelium hypertrophy (Fig 43). Although this feature is commonly observed in advanced Coats' disease, it is extremely rare in exophytic retinoblastoma. Typically, in retinoblastoma there is massive tumor underlying the retina, with obvious foci of cottage cheese calcification (Fig 44). Rarely, there will be a large exudative detachment with only a small, focal tumor mass with minimally detectable calcification (Fig 45), a pattern more easily confused with Coats' disease.

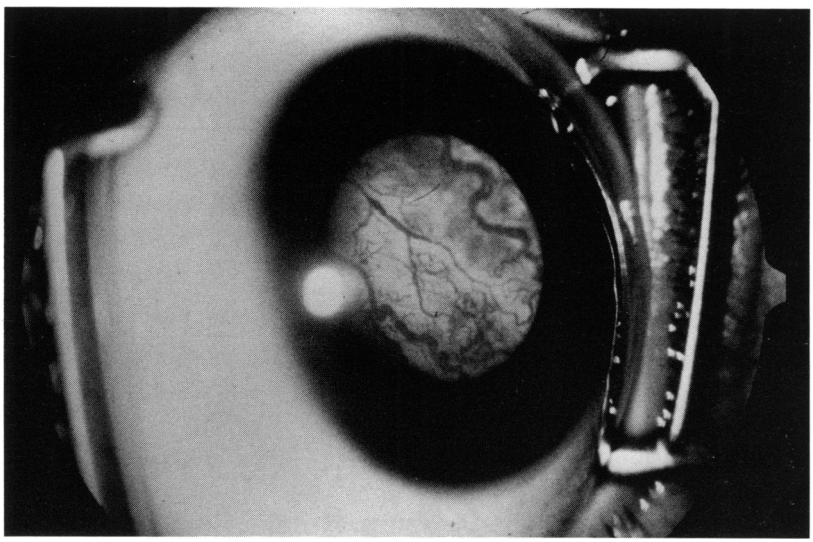


FIGURE 38
Three-year-old with advanced Coats' disease, demonstrating sheaves of retinal telangiectasia and marked variation in vascular caliber.

FIGURE 39
Solid retinal detachment in a patient with exophytic retinoblastoma. Prominent dilated retinal telangiectasias are visible.

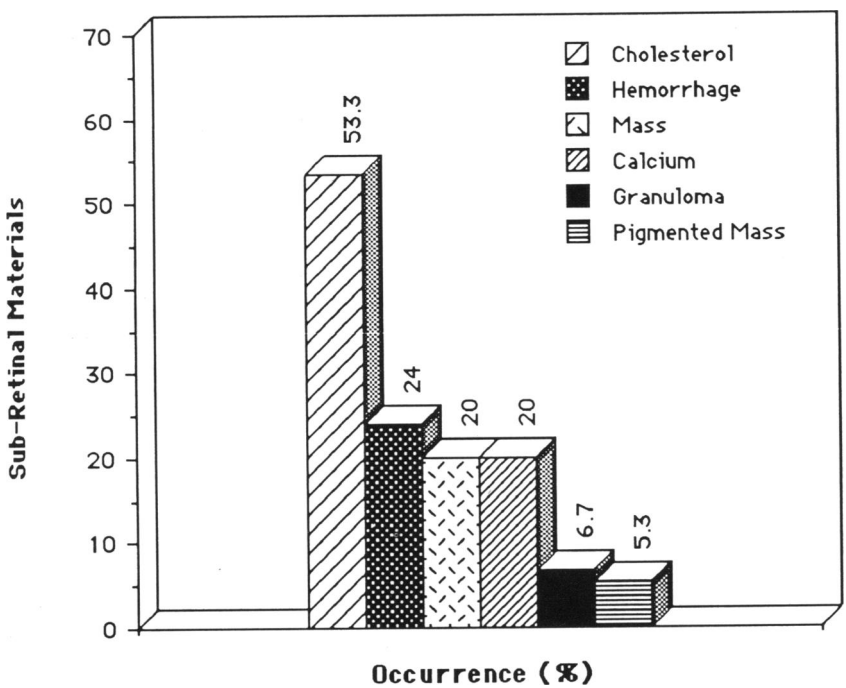


FIGURE 40
Clinical impressions of subretinal materials in Coats' disease.

Retinal Color

The characteristic bright yellow or yellow-green color described by Reese[8] was seen in 34 of 75 patients (45.3%). Nine patients demonstrated a darker yellowish-green or gray coloration to the retina, the result of hemorrhage intermixed with the subretinal exudate. Old, organized subretinal hemorrhage gave a very dark or bluish-gray hue to some of these nine patients.

Clinical Impression

A secure diagnosis of advanced Coats' disease could be made on ophthalmoscopic grounds in 29 of 75 patients (38.7%). These patients had classic exudative detachments and telangiectatic vasculature with no subretinal mass visible. In 34 of 75 patients (45.3%), Coats' disease was considered

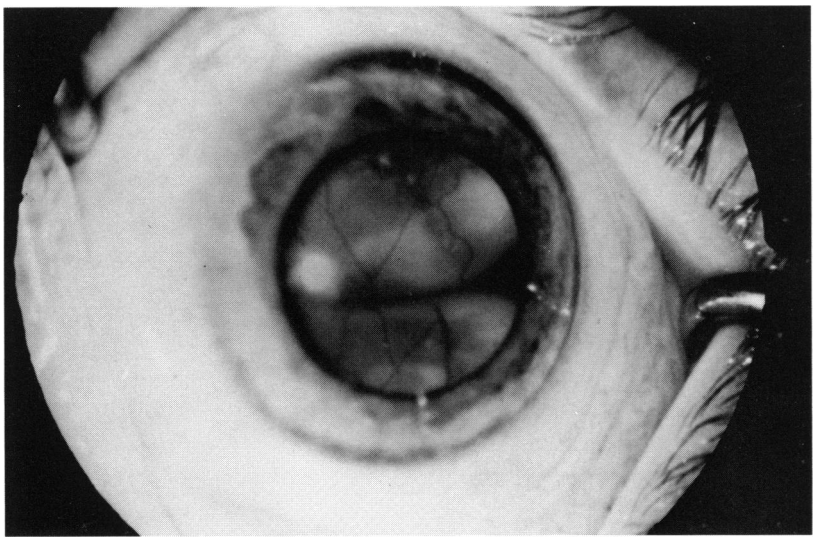


FIGURE 41
Total retinal detachment with yellowish subretinal mounds in a patient with Coats' disease.

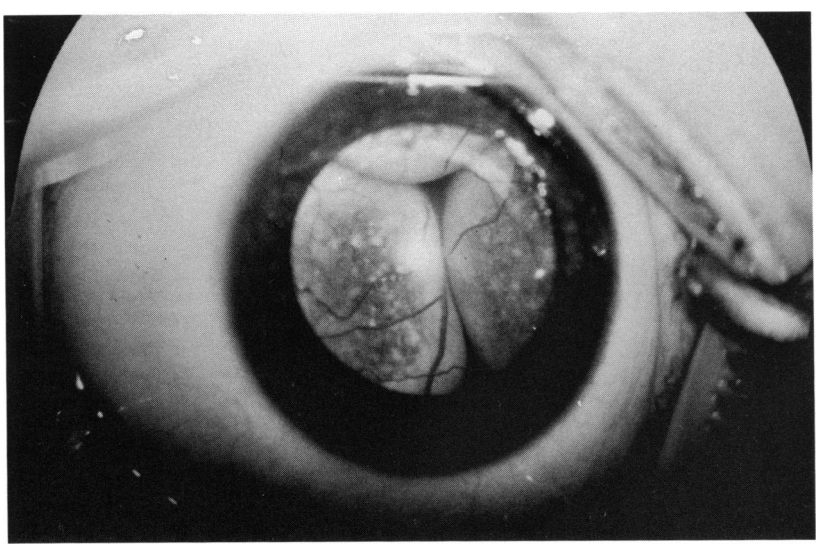


FIGURE 42
Subretinal granular deposits indistinguishable from calcium in a patient with Coats' disease.

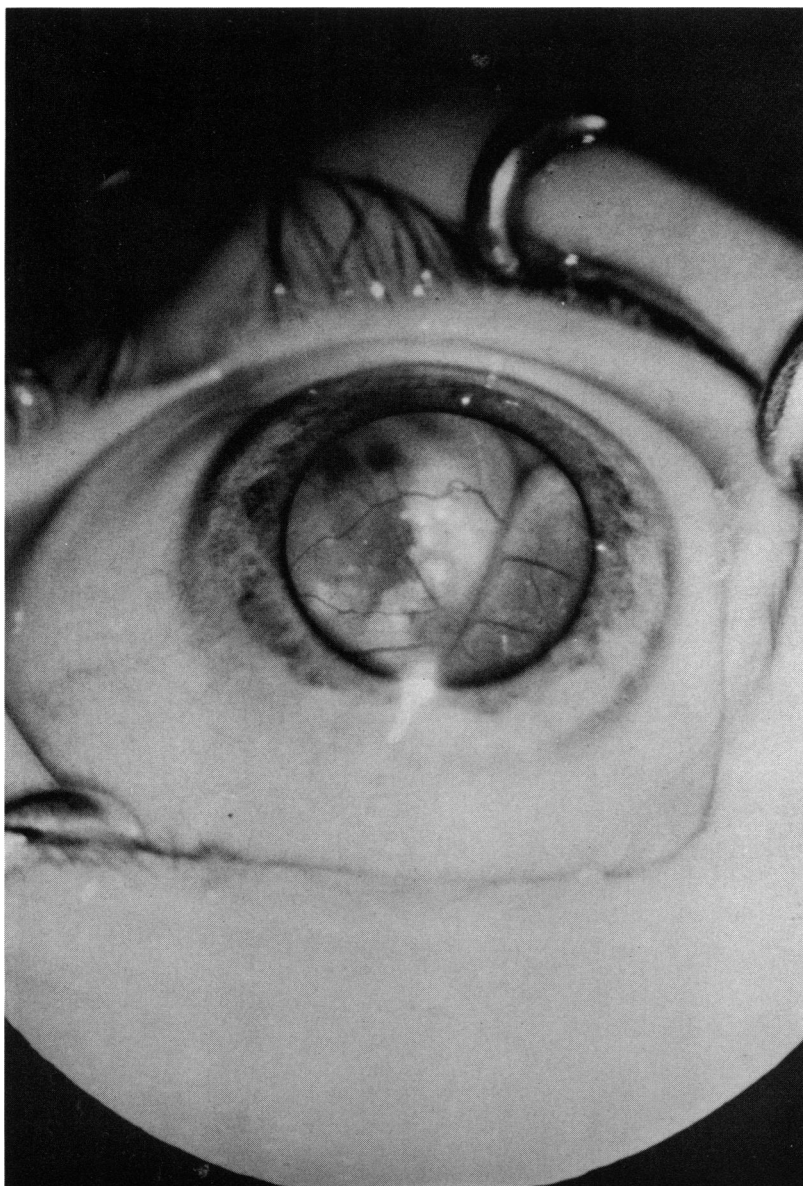


FIGURE 43
Total bullous retinal detachment with subretinal deposits and focal areas of retinal pigment epithelial hypertrophy in a patient with Coats' disease.

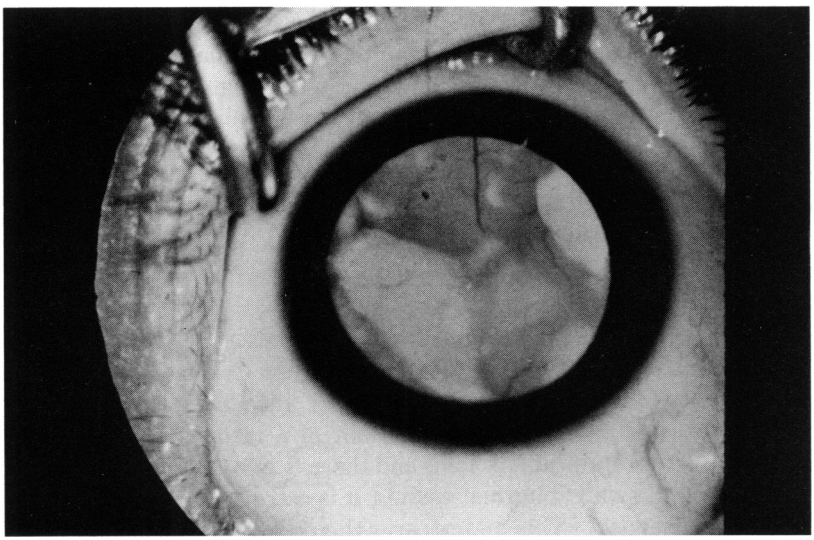


FIGURE 44
Total retinal detachment in a patient with exophytic retinoblastoma. Large areas of calcification are dispersed in the solid subretinal mass.

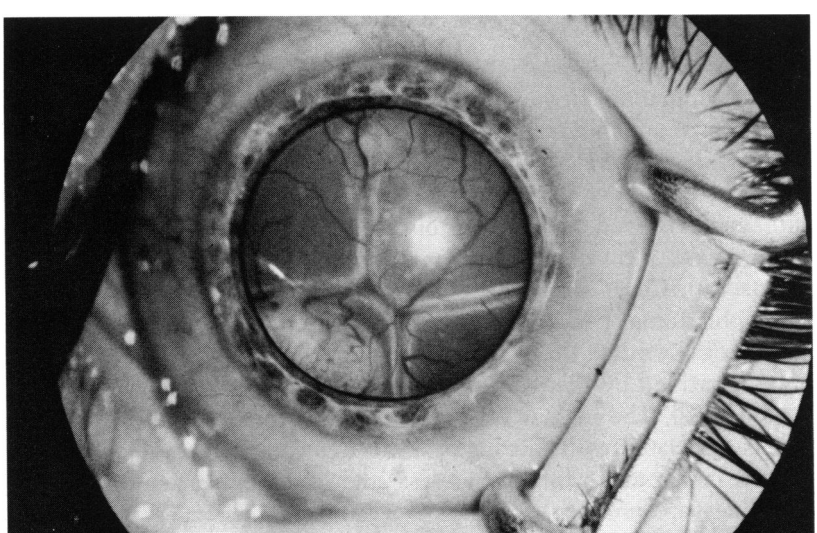


FIGURE 45
Patient with exophytic retinoblastoma. Massive exudative detachment accompanies a small peripheral mass.

the most likely diagnosis, but retinoblastoma could not be ruled out by clinical examination alone. Seven patients were misdiagnosed as having retinoblastoma and five others as having various benign retinal conditions (Table III). The high rate of misdiagnosis or inability to make a firm diagnosis by ophthalmoscopy underscores how closely this condition can simulate exophytic retinoblastoma. This observation is interesting in that two or more ophthalmologists experienced in the differential diagnosis of retinoblastoma examined each patient. In a large retrospective clinicopathologic report by Chang,[19] only 13 of 62 of the cases were correctly diagnosed prior to enucleation. Thirty-six (48%) of the eyes affected with Coats' disease had been removed after misdiagnosis as retinoblastoma. In Ellsworth's classic treatise[61] on the management of retinoblastoma, he states, "In the far advanced stage of either retinoblastoma or Coats' disease, when there is a 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." This underscores the difficulty of diagnosis, even in experienced hands and emphasizes the necessity of ancillary diagnostic studies to differentiate these conditions.

DIAGNOSTIC TESTING

Ultrasonography

Ultrasound is the diagnostic technique most easily incorporated into a clinical examination. In our series of cases, every patient was evaluated in the course of a single comprehensive ophthalmologic examination conducted under general anesthesia. Such clinical assessability, combined with a vast amount of diagnostic information immediately available to the ophthalmologist and an absence of any biologic tissue hazards to the patient, make ultrasound an essential component of the evaluation of patients with Coats' disease.

Retinoblastoma, because of its lethal potential, is the most important lesion to differentiate from Coats' disease. In most cases, retinoblastoma can be identified by the presence of a solid mass, generally arising from the globe wall. The mass is highly reflective on both A- and B-scan, and artifacts associated with this highly reflective composition (shadowing of posterior ocular and orbital structures, and in some instances, reduplication echoes) are commonly seen.[95-100] The calcium particles that produce the high reflectivity will also produce isolated, persistent foci on lowered sensitivity (or gain) settings.

The contrast in the ultrasonographic appearance of Coats' disease and retinoblastoma was striking and dramatic. The clearest distinction was

between those patients with a total retinal detachment with no to low subretinal echoes and those with an isolated, high-amplitude mass.

Even in those patients who appeared similar on initial examination, presenting with a globe totally filled with low-to-moderate amplitude echoes, a distinction was achieved by lowering the sensitivity of the system.

In Coats' disease, there was no persistence of subretinal echoes,[101] whereas in almost all cases of retinoblastoma, the echoes representing areas of soft tissue mass, hemorrhage, or necrosis dropped out, leaving the more densely calcified portions of the mass isolated. These masses showed marked resistance to increased attenuation.

Additionally, no evidence of posterior ocular or orbital shadowing was seen in the Coats' disease patients, whereas 12 of 16 eyes (75%) harboring retinoblastoma demonstrated this acoustic feature.

Although shadowing is extremely helpful in the acoustic differentiation of retinoblastoma from Coats' disease, it limits the ability of the examiner to evaluate extraocular extension, particularly if the area of shadowing encompasses and distorts the outline of the optic nerve.

From the standpoint of ultrasonic evaluation, patients with diffuse retinoblastoma are the most difficult to differentiate from those having Coats' disease. In this series, two patients demonstrated the acoustic pattern of an eye filled with diffuse low-to-moderate amplitude echoes. No distinct retinal detachment could be identified; no mass configuration was outlined, even at lowered sensitivity settings, and no acoustic shadowing of posterior structures was seen.

Ultrasonography was the auxiliary diagnostic technique most easily incorporated into the clinical examination. Indeed, it has become a natural extension of the clinical evaluation because of its ease of application, universal patient acceptability, and vast clinical yield.

Although one of the major thrusts of this thesis is to emphasize the increase in diagnostic accuracy that is possible with conjunctive use of all the imaging modalities—ultrasound, CT, and MR—the ability to immediately generate and synthesize ultrasonic information during the course of a clinical examination, without additional anesthesia or sedation, and without radiographic exposure, makes ultrasound the primary diagnostic procedure. The considerations of anesthesia, radiation exposure, cost, and availability compel us to apply CT and MR imaging in a more judicious and sparing manner, but ultrasound can be used more liberally to complement funduscopic examination in documenting growth or regression of intraocular lesions.

In Coats' disease, ultrasound can portray and document progressive retinal detachment and the amount and degree of organization of subreti-

nal deposits. In patients monitored during an extended period who progress to phthisis with or without therapeutic intervention, ultrasound can confirm and document intraocular organization and/or calcifications consistent with the phthisical state.

In patients with retinoblastoma, after the initial description of mass size and characteristics, ultrasound can depict regression of the lesion following therapy, document the appearance of additional subsequent sites of tumor growth and, at times, raise the suspicion of extrascleral extension, to be better characterized with CT or MR.

Plain Radiography

The first formal radiographic studies of patients with leukocoria were reported by Pfeiffer[102] in 1936. He utilized plain radiographic techniques to detect intraorbital calcifications in about 70% of the patients with large retinoblastoma. In our present series, nine patients with advanced Coats' disease seen prior to the era of CT showed no evidence of intraorbital calcifications on plain films. A negative x-ray study was somewhat reassuring, but did not rule out the possibility of retinoblastoma. In the 15 exophytic retinoblastoma patients studied with plain radiographic techniques, calcifications were detectable in 9 patients. These appeared as mottled or flocculent densities within the orbital cavity. Our results support Pfeiffer's findings and suggest that the radiographic detection of calcium in a normal-sized globe strongly supports the diagnosis of retinoblastoma. Calcific nodules and focal ossifications have been noted pathologically in both our patients with Coats' disease and those of other series with grossly disorganized globes.[19] Of additional interest is a case report by Pe'er[103] describing a patient with a normal-sized eye, total retinal detachment, retinal telangiectasias, and subretinal exudation. Despite the clinical impression of Coats' disease, the globe was enucleated because on plain radiography obvious calcifications were seen. Subsequent histopathologic examination was characteristic of advanced Coats' disease with secondary calcification. The author stressed that the presence of calcification in a normal-sized globe can occur in Coats' disease. On the other hand, since retinoblastomas do not always calcify heavily and, in some rare cases do not calcify at all, a negative plain film of the orbit cannot rule out this childhood cancer. Plain radiography has not been routinely used in the past decade because CT is now readily available and is far more sensitive for detected the presence and pattern of intraorbital calcification.

Computed Tomography

Since its introduction in the 1970s, CT has become indispensable in the evaluation of patients with leukocoria. The extreme sensitivity of the technique to subtle differences in electron density of imaged tissue permits the production of high-resolution images. The excellent depiction of intraocular morphology and, in particular, the detection of intraocular calcification has resulted in widespread use of this technique to diagnose retinoblastoma and differentiate it from simulating conditions.[104-108] Sherman and associates[109] reported the inability to distinguish between Coats' disease from retinoblastoma on computed tomographic grounds alone. Later, however, publications by both Haik and associates[110] and Mafee and co-workers[111] reported that CT can differentiate the two diseases with a high degree of accuracy.

Globe Size and Contour—In our patients, globe size and configuration was not a significant factor for distinguishing advanced Coats' disease and exophytic retinoblastoma.

Intraocular Morphology—We found that the computed tomographic appearance of eyes with advanced Coats' disease can be divided into three general morphologic categories: those with total detachment and a residual vitreous cavity, those with detachment and no residual vitreous cavity, and lastly, those with phthisis.

The first pattern was the most common and occurred in 14 patients where total retinal detachments and some residual vitreous were clearly detected. In these patients, a distinct pattern of retinal detachment was seen with attachments at the optic nerve head and ora serrata (Fig 46 A and B). The retinal detachment could be visualized despite the fact that the thickness of the retina is below the limits of CT resolution. In our patients, as in those previously reported by Haik and associates,[110] the configuration of the detachment is demonstrated by virtue of density differences between the subretinal exudate and the vitreous cavity. The detached retina served as an interface between the two compartments of varying radiographic densities, the vitreous cavity measuring 6 to 24 HU, and the subretinal compartment measuring 30 to 60 HU. In all cases, the subretinal fluid was denser than the residual vitreous. The fact that the two compartments were internally homogeneous permits clear visualization of the compartmental interface.

In the second group of patients, a detachment could not be depicted because the highly elevated retina was pushed forward, and the retinal bullae were compressed centrally by massive subretinal exudation (Fig 47 A and B). Therefore, no residual vitreous cavity remained to provide a region of contrasting density. Instead, the globe appeared to be morpho-

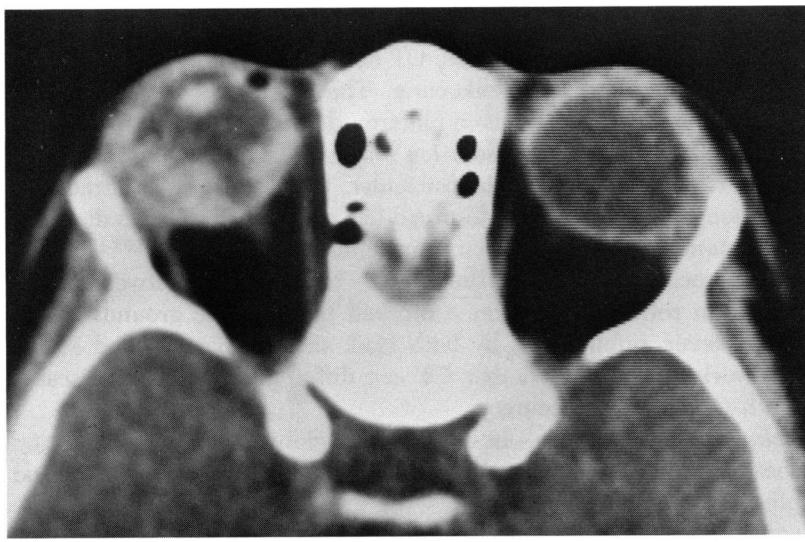
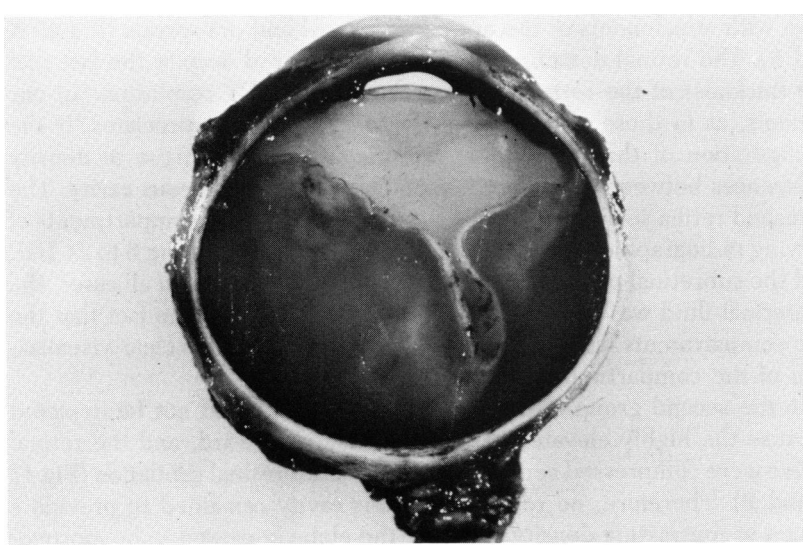


FIGURE 46
A: Axial computed tomogram of a patient with Coats' disease in right eye. Morphologic basis of image is substantiated by accompanying pathologic specimen. B: Gross specimen shows a total retinal detachment separating vitreous from cholesterol-laden subretinal exudate.



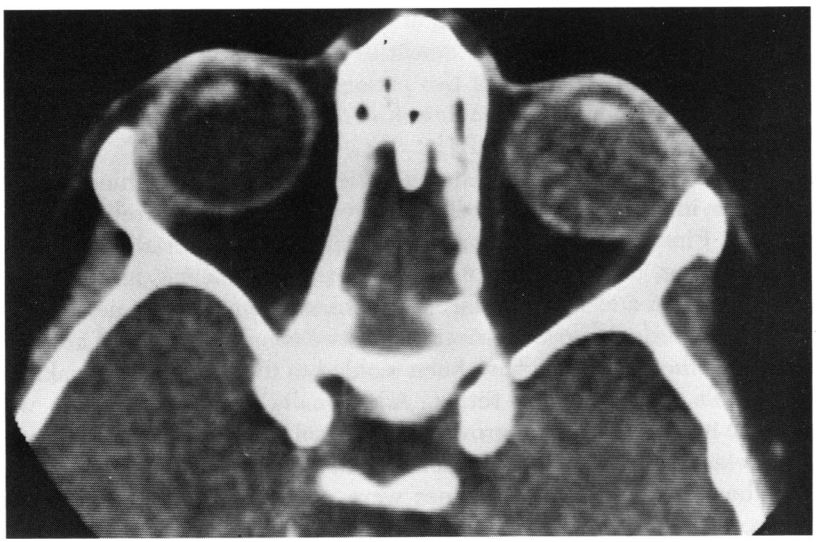
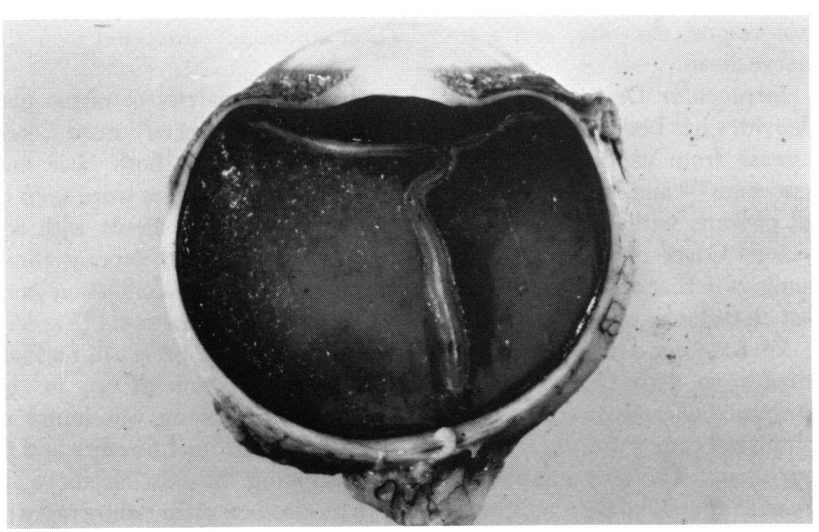


FIGURE 47

A: Axial computed tomogram of a patient with Coats' disease in left eye. Globes are comparable in morphologic appearance, with exception of increased density on left. Contracted and anteriorly displaced leaves of retinal detachment (shown in B) are not seen, and only cholesterol-laden subretinal exudate is appreciated. B: Gross specimen shows contracted and anteriorly displaced leaves of retinal detachment.



logically normal with the exception of an increased density to the intraocular cavity. The intraocular densities ranged from 32 to 72 HU.

The last group consisted of two patients with phthisical eyes. Each of these was microphthalmic (no detachment was seen), and revealed intraocular densities of 35 to 93 HU.

In the exophytic retinoblastoma patients, retinal detachments were only seen in 16.7% of patients. This limited incidence occurred for several reasons. First, and most important, the subretinal material was typically heterogenous, consisting of soft-tissue mass, calcifications, and exudative fluid (Fig 48 A and B). Therefore, the internal homogeneity necessary to outline the retinal barrier separating the two compartments did not exist. Secondly, the retina may have been molded to the tumor mass, making it impossible to distinguish retina. Additionally, in other patients with massive intraretinal tumor growth, the retinal architecture was destroyed and detachment could not be delineated.

Although discrete mass outlines were not seen in Coats' disease patients, a homogeneous subretinal density often filled the entire subretinal space and could easily be misinterpreted as a diffuse tumor mass. An intraocular mass was seen in all of the retinoblastoma patients. In some patients this mass was a distinct nodule confined to a specific quadrant of the globe; in others, the density involved the entire intraocular volume. The subretinal mass was heterogeneous in 51 of the patients and homogeneous in 3 others. Densities ranged from 15 to 538 HU, reflecting the presence of diverse tissues such as active tumor, necrotic tumor, exudate, hemorrhage, and calcification. The mass in retinoblastoma patients did not respect the disc, and a tumefaction commonly extended over the nerve head.

Intraocular Density—Computed tomographic analysis of intraocular densities has been shown to be critical in differentiating advanced Coats' disease from exophytic retinoblastoma. In studies by both Haik and associates[110] and Mafee and co-workers,[111] calcific densities were seen in all patients with exophytic retinoblastoma and in no patients with advanced Coats' disease. The findings in the present study support those findings in that densities of over 125 HU consistent with calcification were not detectable in any of the advanced Coats' disease patients (Fig 49).

We have not detected calcification on CT in any nonphthisical, normal-sized eyes with Coats' disease or found a description of this in the literature. However, pathologic evidence of calcification was found in phthisical eyes resulting from Coats' disease both in the literature and in our series. The only contradiction to this finding, as detailed above, is Pe'er's report[103] detecting intraocular calcification on plain radiography in

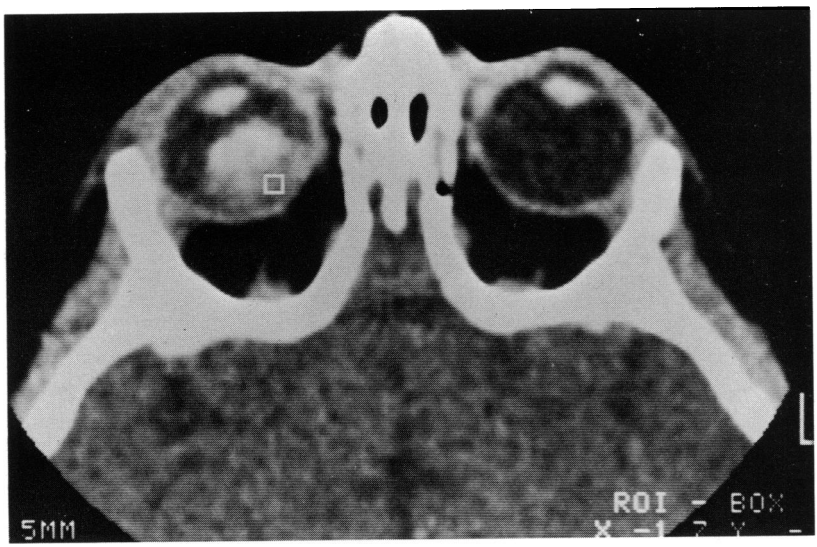
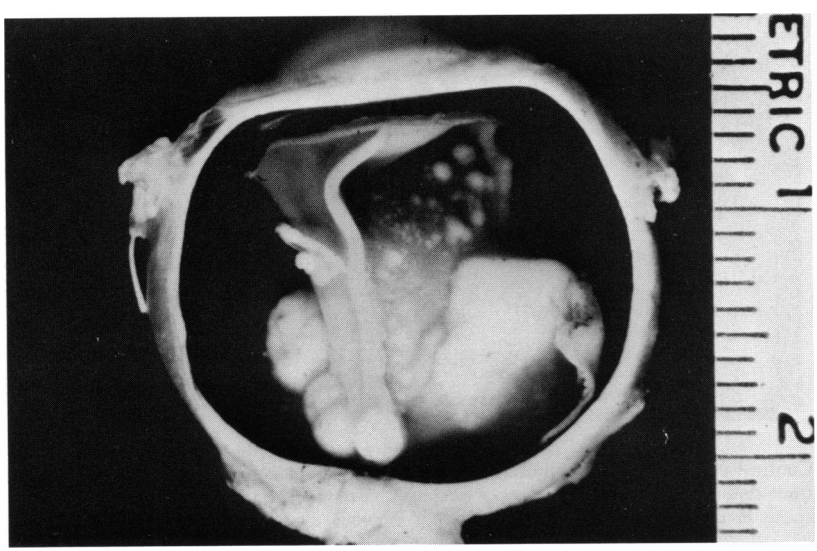


FIGURE 48
A: Axial computed tomogram of a patient with exophytic retinoblastoma, right eye. A large, circumscribed nodule of mixed radiographic density is seen, but no retinal detachment is outlined. B: Gross specimen shows both retinal detachment and complex tissue structures composing the mass.



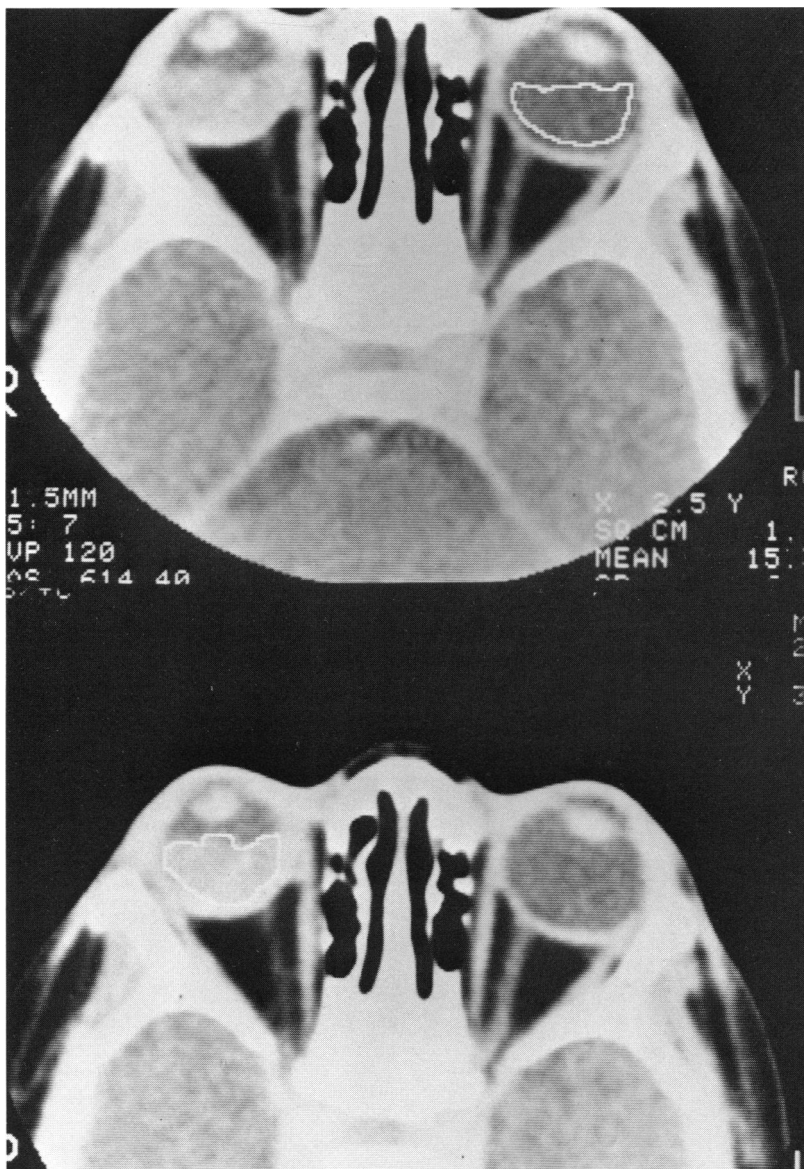


FIGURE 49
Contrast-enhanced axial computed tomogram of a patient with Coats' disease. A free-hand trace delineates comparable areas of posterior vitreous in normal eye (top) and subretinal space in diseased globe (bottom). Normal vitreous averaged 15.32 HU, and subretinal exudate averaged 65 HU.

a normal-sized eye of one patient with Coats' disease.

In retinoblastoma patients, hyperdense areas of tumor that appeared calcified, measuring between 125 and 538 HU (Fig 50) and varying in appearance from fine granules to large masses with the same radiographic density as the surrounding orbital bone, were detected in 52 of 54 eyes. The two outlying cases are significant, clearly demonstrating that even high-resolution CT may not reveal calcium in the subretinal tumor in exophytic retinoblastoma. Thus, a secure diagnosis cannot be made on density determinations alone.

Enhancement—Contrast media are routinely utilized in computed tomographic studies of the eye and orbit. Iodinated contrast materials have an atomic number in the range of 50 to 60 atomic units, whereas the atomic number of most intraorbital tissues varies from 5 to 20 atomic units. Therefore, tissues containing contrast material will have a higher radiographic density than in their unenhanced state. The efficacy of contrast media enhancement depends on the amount and concentration of dye injected intravenously, on the ability of local tissue to carry or concentrate it, and on the interval from administration to time of examination. Even though patients with Coats' disease have abnormally perme-

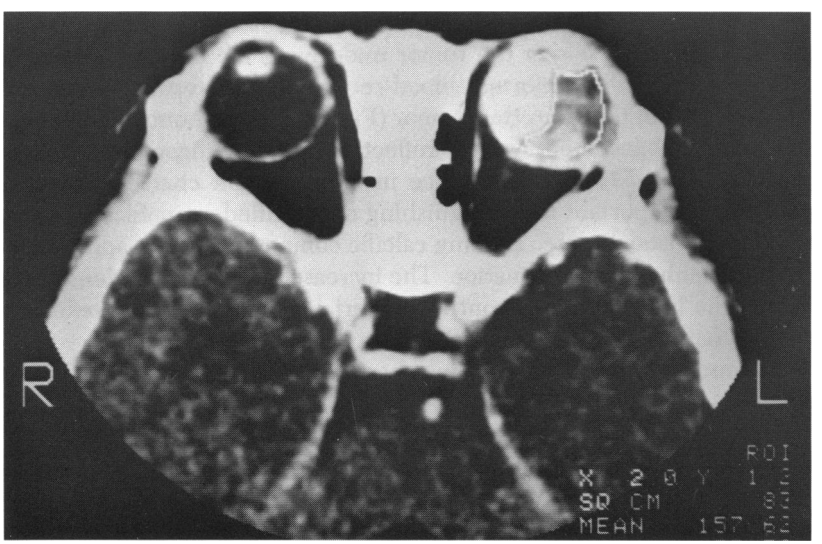


FIGURE 50

Contrast-enhanced axial computed tomogram of a child with exophytic retinoblastoma of left eye. A free-form trace and cursor cross-hairs (*arrow*) identify calcified portion of tumor. The HU value in this region was 157.62, whereas adjacent region averaged 71 HU.

able retinal vessels, measurable enhancement was not seen in the subretinal space (Fig 51, Table XII). Enhancement of the retinal leaves was noted in several patients. Presumably, the lack of subretinal enhancement results from minimal dye leaks that do not diffuse easily into the thick proteinaceous subretinal fluid.

TABLE XIII: CT FINDINGS IN RETINOBLASTOMA AND COATS' DISEASE

Retinoblastoma
Intraocular or subretinal mass or densities
Molds retina; no distinct funnel detachment seen
Heterogeneous appearance
Maximum subretinal density > 125 HU
Contrast enhancement (soft-tissue mass)
Coats' disease
Subretinal densities
Distinct smooth domed funnel detachment
Homogeneous subretinal densities
Maximum subretinal density < 60 HU
Lack of subretinal enhancement

Conversely, in patients with exophytic retinoblastoma, the presence of multiple blood vessels in the tumor underlying the detached retina, as well as a markedly abnormal blood-retina barrier, results in dramatic enhancement of the subretinal tumor (Fig 52). The amount and pattern of subretinal enhancement varies, reflecting the heterogenous subretinal pathology (Fig 53). This difference in enhancement characteristics was particularly important in distinguishing noncalcified retinoblastoma from advanced Coats' disease. Lacking calcific components, both appear similar on nonenhanced examination. The increased radiographic density that follows the introduction of contrast material of retinoblastoma reflects its cellular nature (Fig 54 A and B).

A summary of the distinguishing characteristics is presented in (Figs 55 and 56).

Associated Optic Nerve, Orbital, and Intracranial Abnormalities—No associated optic nerve, orbital, or intracranial abnormalities were noted on computed tomographic studies on either Coats' disease or retinoblastoma patients. Although not seen in this series, the presence of optic nerve enlargement or extrascleral mass would be highly suggestive of retinoblastoma. In addition, pinealoblastomas have been detected in some patients with retinoblastoma; this region, therefore, should be carefully reviewed on radiographic studies. The detection of a pineal mass in a patient with retinal detachment would be highly suggestive of retinoblastoma.

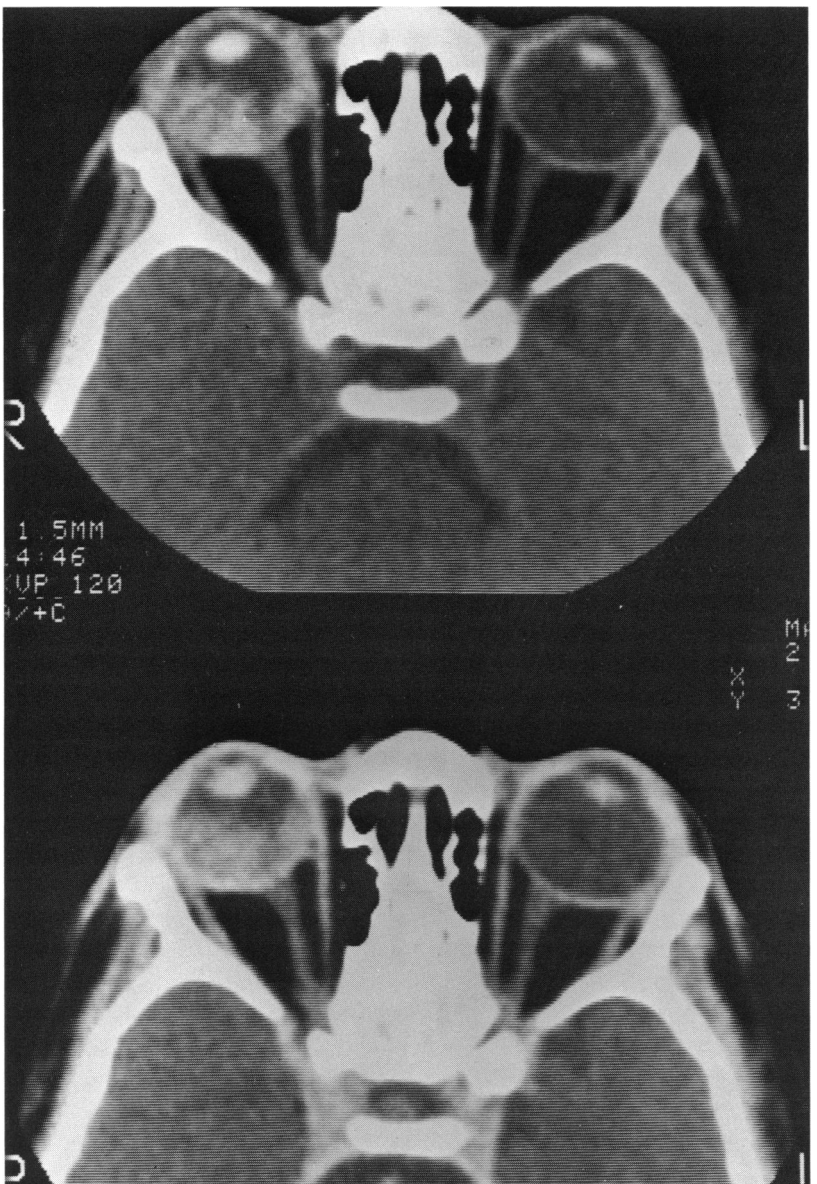


FIGURE 51
Contrast-enhanced computed tomogram of a patient with Coats' disease. Comparison of pre-contrast scan (top) and post-contrast study (bottom) reveals no measurable increase in radiographic density of subretinal fluid.

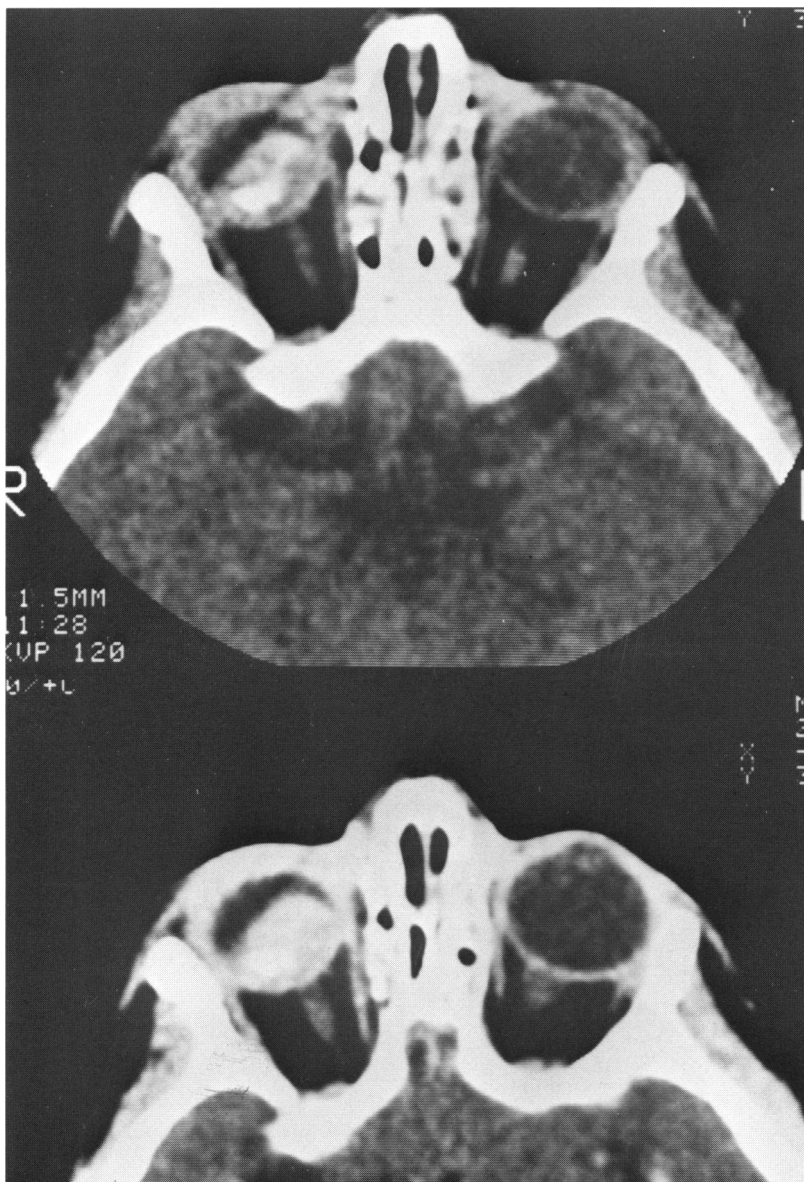


FIGURE 52
Contrast-enhanced axial computed tomogram of a patient with exophytic retinoblastoma in right eye. Prior to contrast enhancement (top), a mass of heterogeneous radiographic density is seen. Noncalcified soft-tissue components enhance dramatically (bottom).

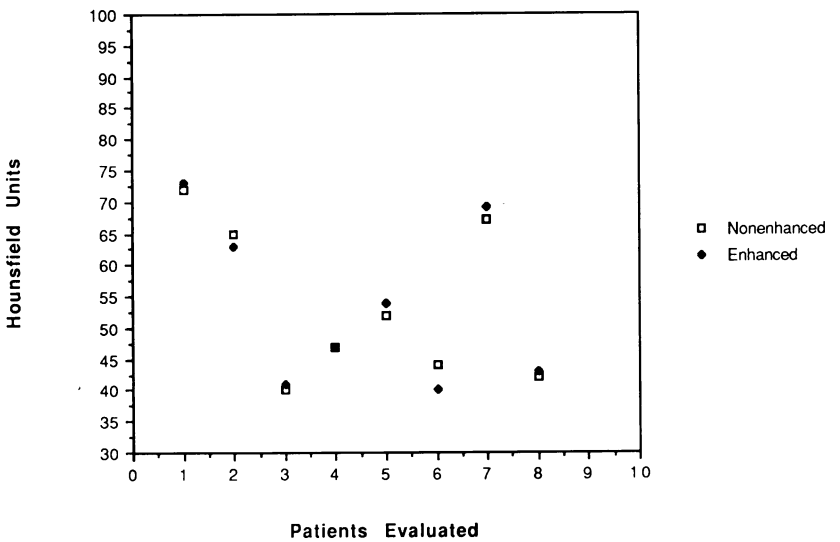


FIGURE 53
Coats' disease. Effect of enhancement on radiographic density.

Magnetic Resonance Imaging

Several reports on the value of MR imaging in the diagnosis of retinoblastoma, Coats' disease, and other pseudoretinoblastomas have been published.[40,111-114] MR has several technical advantages over CT. Among the most important features is the ability to image tissues without use of ionizing radiation. The radiation dose from an orbital-cranial CT scan varies from 2.2 to 6.8 rad, depending on the slice thickness and number of cuts performed.[115] Although a single exposure to such a low dose of radiation carries little hazard, the dose can become more significant if studies are periodically repeated. The MR image acquisition technique allows images to be obtained in any plane without the loss of spatial resolution that can occur with reconstructed CT. The key advantages of MR to the physician are its superior contrast resolution and its ability to provide more specific information on the chemical structure of intraocular abnormalities.

MR has been previously reported to be valuable in differentiating the retinal detachment of Coats' disease from that of exophytic retinoblasto-

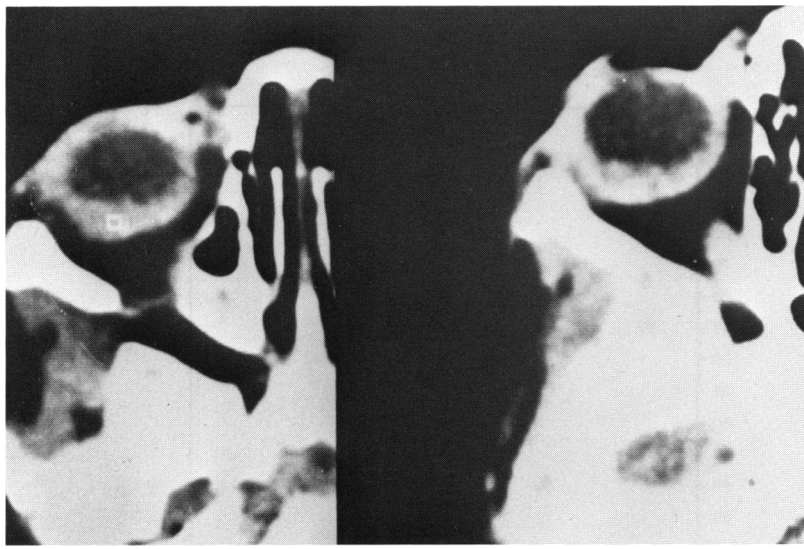
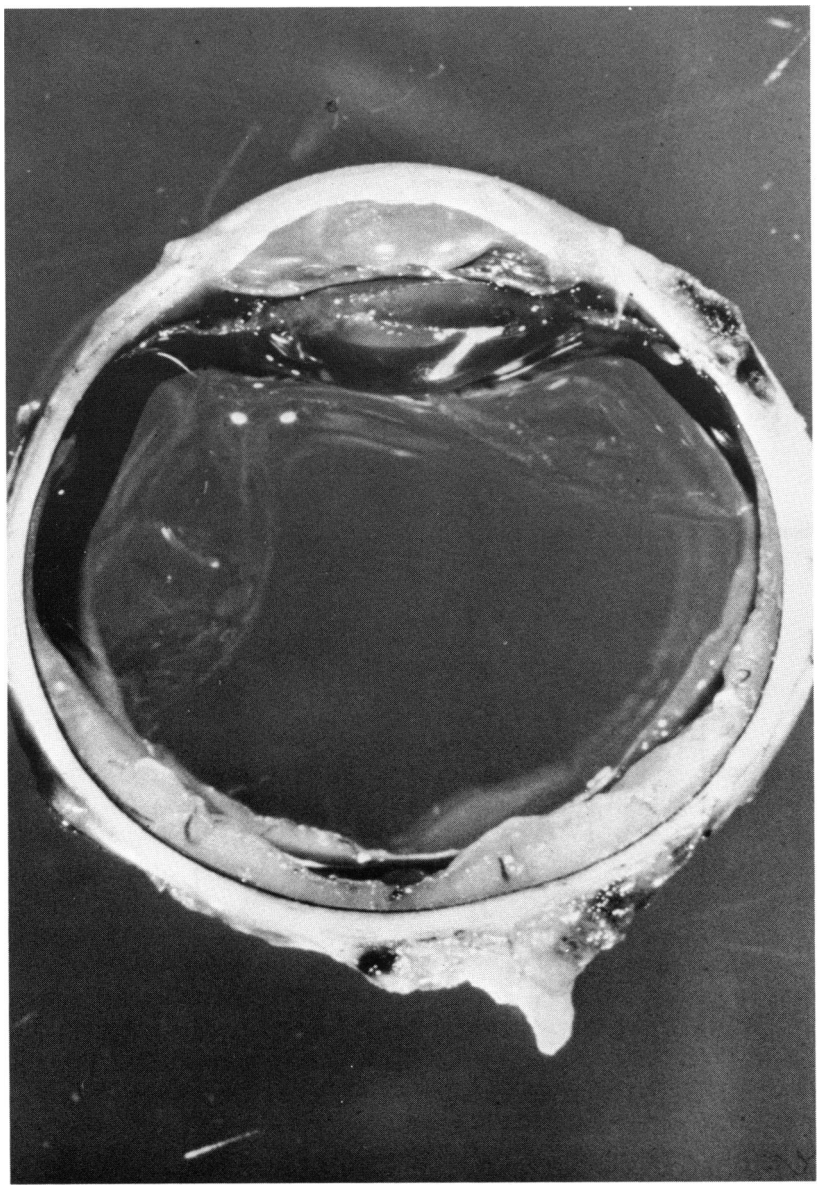


FIGURE 54
A: Contrast-enhanced axial computed tomogram of a patient with noncalcified exophytic retinoblastoma in right eye. Post-contrast scan (right) shows an increase in subretinal density due to abnormal permeability of intra-tumor vascular network. B: Gross specimen of eye enucleated for noncalcified exophytic retinoblastoma.

ma.[40,111] Although these studies involved small numbers of patients and utilized older technology, our findings are in general agreement. On MR evaluation, seven of our nine patients with Coats' disease were found to have homogeneous subretinal fluid of moderate intensity on T_1-weighted studies and high intensity on T_2-weighted studies when compared with the normal vitreous of the fellow eye. As previously discussed, it is somewhat surprising that the subretinal fluid is not remarkably hyperintense on T_1-weighted studies (Fig 57), since the subretinal material is composed of protein, cholesterol, and fine fatty acids. Presumably, this atypical response results from the large size of the cholesterol crystals and the fact that they may be in complexes with surrounding protein molecules.[40] In our eighth patient with advanced Coats' disease, an associated massive subretinal hemorrhage resulted in considerable shortening of the T_1 relaxation time and increased hyperintensity. In our ninth patient, who had secondary phthisis bulbi, internal heterogeneity was observed, and areas of hypointensity suggestive of dystrophic calcification were noted on T_1 and T_2-weighted studies.

In exophytic retinoblastoma, the MR picture was quite different. The



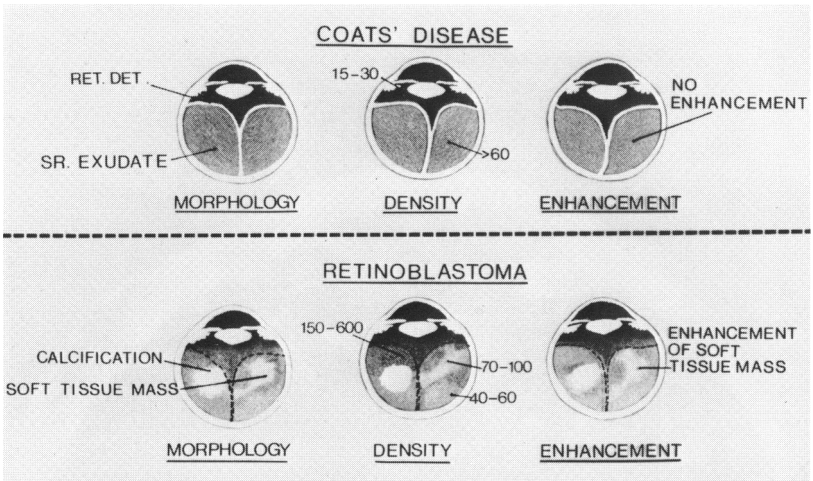


FIGURE 55
Schematic representation of enhancement characteristics of Coats' disease versus retinoblastoma.

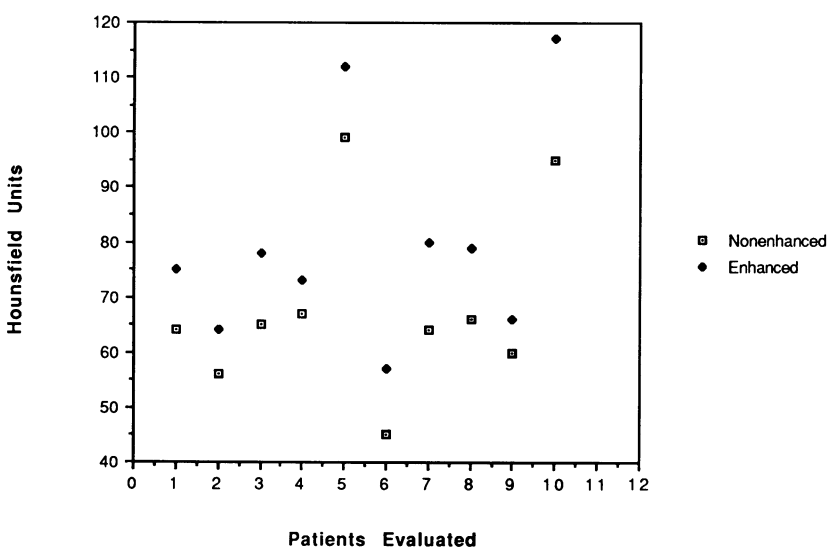


FIGURE 56
Retinoblastoma. Effect of enhancement on radiographic density.

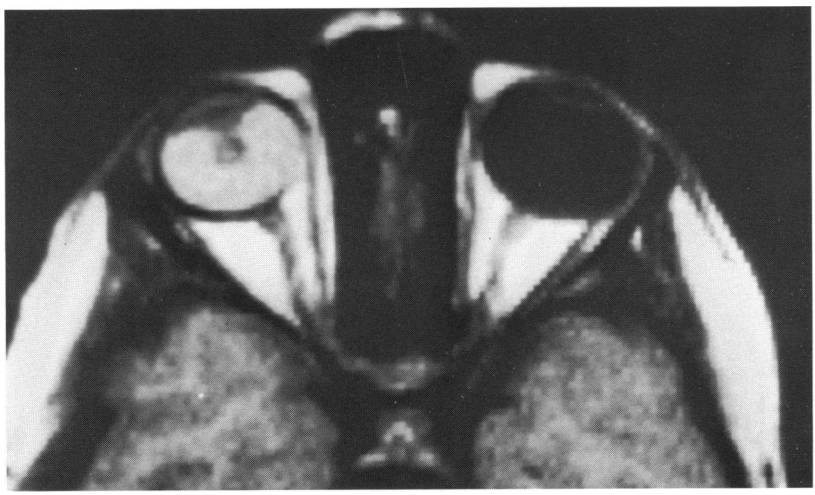


FIGURE 57
T_1-weighted (500/30) MR image of a patient with Coats' disease. Moderate intensity, homogeneous subretinal fluid demarcates retinal detachment.

subretinal material in retinoblastoma patients was heterogeneous with extremely variable subretinal intensities. The main tumefaction was isointense or mildly hyperintense to vitreous on T_1-weighted studies and markedly hypointense on T_2-weighted studies.

The typical calcifications that occur in the eyes of most retinoblastoma patients, easily seen on CT, are detected with difficulty on MR. Calcific portions of the tumor emit only a minimal signal on almost all spin-echo sequences because of their low proton density and the fact that the water present is tightly bound to the crystalline matrix. These calcific portions will therefore appear as hypointense foci within the intraocular mass. Lastly, hemorrhage and proteinaceous exudate was often detectable in these patients, resulting in a highly variable third intensity.

Thus, MR is most valuable in distinguishing between advanced Coats' disease and minimally calcified or noncalcified exophytic retinoblastoma. One should be cautious, however, since both of these conditions may have associated intraocular hemorrhage, which can yield variable image intensities depending on the level of organization or breakdown. In such cases, several MR studies could be considered, since the MR appearance of blood will change with time.

How hemorrhage modifies the image depends on the quantity, distribution, and level of organization.[116] As the hemorrhage within the eye

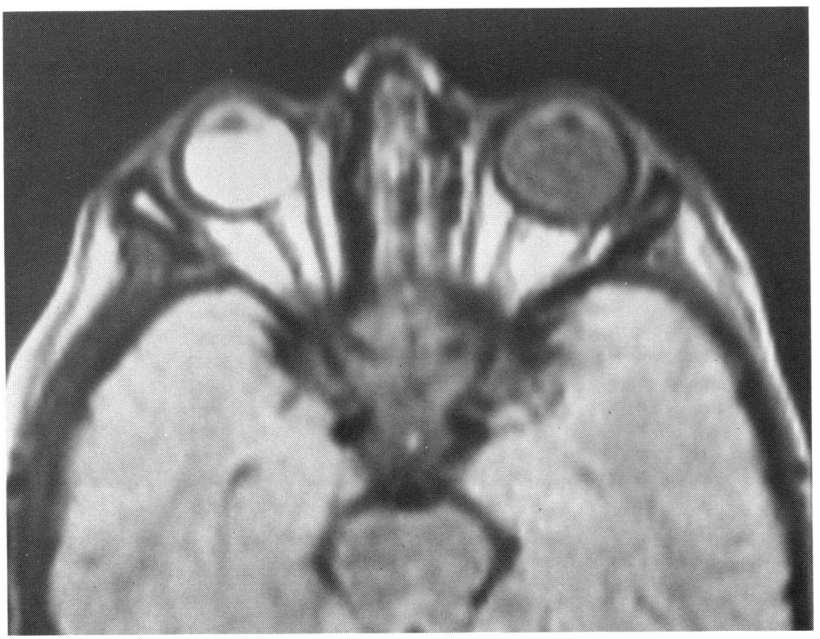


FIGURE 58
T_1-weighted (500/30) axial MR image in a patient with Coats' disease. Subretinal hemorrhage produced marked hyperintensity relative to normal vitreous. On T_2, material remained markedly hyperintense.

evolves, the resultant image will change in a predictable fashion. An acute (usually < 24 to 48 hours) hemorrhage consisting of oxy- and deoxyhemoglobin in intact red blood cells will be of low intensity on T_1- and T_2-weighted sequences. The presence of methemoglobin will dramatically shorten T_1 relaxation time, resulting in a brighter image on T_1-weighted studies performed more than 24 hours after the precipitating event (Fig 58). If the methemoglobin is within intact erythrocytes (> 72 hours), the T_2-weighted images will be of low intensity. However, if the erythrocytes are lysed and the methemoglobin is extracellular, the image will be high on T_2-weighted studies done more than 72 hours after the event. Later, when methemoglobin is oxidized to iron-free nonparamagnetic pigments, the image will be moderately hyperintense on T_1-weighted and markedly hyperintense on T_2-weighted images.

It is therefore obvious that the presence of hemorrhage, proteinaceous exudate, and cellular necrosis will all modify the MR appearance in a patient with retinal detachment, and as with all diagnostic studies, this

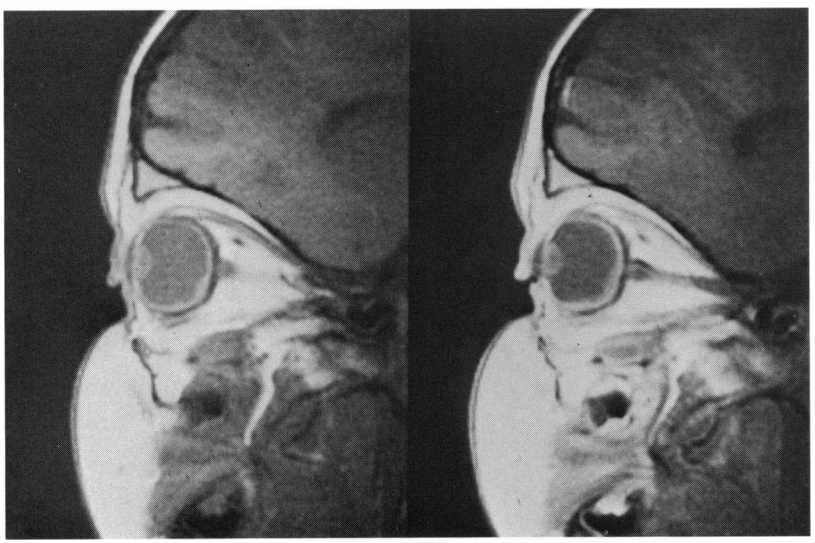


FIGURE 59
T_1-weighted (500/30) oblique sagittal MR image of a patient with Coats' disease, demonstrating a total, shallow retinal detachment. Following Gd-DTPA contrast enhancement (right), subretinal fluid increases in intensity.

test should be interpreted within an appropriate clinical context.

Gadolinium-DTPA (diethyltriamine pentaacetic acid) has recently been approved by the Food and Drug Administration (FDA) as an adjunct for MR imaging. Gadolinium (Gd), a heavy metal with intrinsic paramagnetic properties, is chelated to DTPA to neutralize its toxicity. This material will leak through a defective blood-brain barrier and shorten the T_1 relaxation time of the adjacent protons, thus increasing the SI of the region on T_1-weighted images. Several studies[117-119] have shown that Gd-enhanced MR is superior to noncontrast MR in the detection of ocular malignant melanoma and intracranial extension of optic nerve meningiomas. CNR calculations provided objective evidence of increased tumor contrast in Gd-enhanced MR imaging of retinoblastoma and advanced Coats' disease.

Gd contrast enhancement was not a valuable distinguishing characteristic. The subretinal fluid in one of two patients with Coats' disease did not enhance. In the one Coats' disease patient with a minimally elevated retinal detachment, an increase in subretinal intensity was noted following Gd-DTPA administration (Fig 59). We did not anticipate routine enhancement of the subretinal exudate in Coats' disease because Gd-

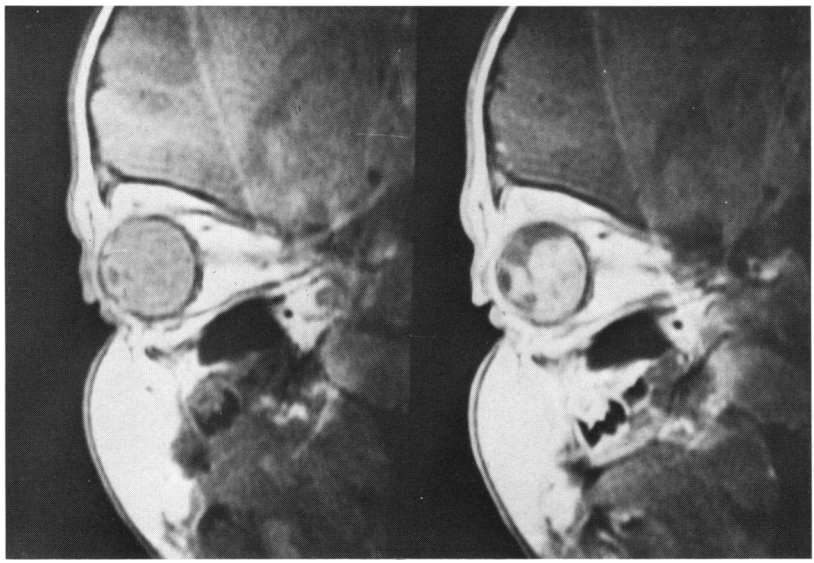


FIGURE 60
T_1-weighted (500/30) oblique sagittal MR image of a patient with exophytic retinoblastoma. Extent of mass is clearly defined by increased intensity following Gd-DPTA enhancement.

DTPA is rapidly cleared from the blood stream, and the small amount of contrast leaked would have difficulty diffusing through the thick protein- and lipid-rich subretinal fluid, as was noted in our previous studies with contrast enhancement in CT. It is difficult to comment on the significance of these conflicting findings. Perhaps, enhancement was noted in this particular Coats' disease patient because over 75% of his retina was involved with extensive telangiectasia, allowing leakage into the relatively small subretinal space under the patient's shallow retinal detachment. In all the retinoblastoma patients studied, the enhancement was markedly higher than in the patient with advanced Coats' disease (Fig 60).

Lastly, contrast-enhanced MR imaging should be the most accurate method of detecting intracranial associations with retinoblastoma, since this technique is extremely sensitive to subtle changes in hydration and fat content.

Aqueous Humor Enzyme Analysis

The aqueous fluid was analyzed biochemically to determine the diagnostic specificity of elevations in aqueous LDH and neuron-specific enolase (NSE). LDH analysis was performed more commonly because the technique was available earlier and LDH is easily evaluated by routine bio-

chemical methods. As evidence accumulated that aqueous LDH levels were not diagnostic in the differentiation of Coats' disease and exophytic retinoblastoma, our attention was directed to evaluating other enzymes. NSE was studied in one patient with advanced Coats' disease after several encouraging reports of its diagnostic value were published.

LDH—LDH is a ubiquitous intracellular enzyme found in all cells using a glycolytic form of metabolism. This enzyume is a member of the Embden-Myerhoff pathway, in which it converts lactate to pyruvate. Dias and associates[120] published a landmark report in 1971 demonstrating a link between elevated aqueous humor LDH levels and the diagnosis of retinoblastoma. Since then, numerous reports supporting the value of elevated aqueous LDH levels in distinguishing retinoblastoma from benign simulating lesions have been published.[121-124] In particular, the aqueous-to-serum LDH ratio has generally been greater than 1 in retinoblastoma and less than 1 in simulating benign disorders. For this reason, we obtained aqueous and serum LDH specimens from 11 patients with Coats' disease and 16 patients with exophytic retinoblastoma. (The diagnosis was later confirmed in each of these patients following enucleation, subretinal cytologic evaluation, or long-term clinical follow-up.)

Simultaneous serum LDH assays were performed to determine the aqueous-to-serum LDH ratio. This is a routine procedure because each laboratory's normal values are slightly different, and this ratio allows for an internal standard permitting comparison with values obtained at other centers. All specimens were evaluated within 2 hours and none was frozen. This rapid evaluation is important since LDH activity decreases with time and in previously frozen specimens. The venous blood samples were immediately spun down and the serum was then evaluated, before red blood cell lysis could occur. This process helps to avoid serum contamination with LDH from lysed red blood cells. Red blood cells contain extremely large amounts of LDH and can elevate serum levels dramatically when they are lysed. In five of our patients, a small amount of blood was seen in the anterior chamber during paracentesis. The aqueous specimen was not tainted pink and, as McDonald and associates[122] have pointed out, the presence of a small amount of unlysed red blood cells does not significantly affect LDH measurements. Normal serum levels for LDH in our laboratory range from 107 to 183.

As Abramson and associates[124] pointed out, there have been no large studies of aqueous humor from normal children's eyes. The mean aqueous LDH level in adults with senile cataracts was found by McDonald and associates[122] to be 37 IU/l (range, 1 to 151 IU/l). In all of these cataract cases, the aqueous humor level was lower than the serum level of the

patient. The mean serum level was 152 IU/l (range, 98 to 251 IU/l).

The aqueous LDH levels in 10 of our patients with advanced Coats' disease averaged 208 IU/l (range, 0 to 1021 IU/l). In one patient, aqueous LDH levels were increased when the test was repeated 6 weeks later (50 IU/l to 175 IU/l). In three patients, elevated aqueous LDH levels and elevated aqueous-to-serum LDH ratios were found.

Elevated aqueous LDH levels have been reported previously in three patients with Coats' disease.[125-127] Jakobiec and associates[126] recommend caution in interpreting LDH aqueous assays in eyes with a glaucoma, phthisis, or those containing large numbers of histiocytes, erythrocytes, and polymorphonuclear leukocytes.

It is not surprising that the LDH levels in exophytic retinoblastoma averaged 410 IU/l (range, 46 to 1024 IU/l). This total LDH elevation is similar to findings by Abramson and co-workers.[124] It is, however, interesting that the total LDH level in aqueous of five exophytic retinoblastoma patients was relatively low. Although low LDH levels in the aqueous of retinoblastoma patients have been previously been reported,[123,128] these findings are important, since they stress the possibility of a false-negative test: five patients with histologically proven retinoblastoma had an aqueous-to-serum ratio of less than 1. The variability of LDH testing in retinoblastoma has previously been reported in clinicopathologic correlation studies.[123,129] Swartz and associates[129] believed that elevated LDH levels correlated best with extensive tumor necrosis, whereas Piro and co-workers[123] found that the only histopathologic factor correlating with highly elevated aqueous LDH levels was the presence of cells in the anterior chamber. None of the patients included in our study had visible cells on anterior chamber examination. All of the exophytic retinoblastoma cases did have tumor necrosis, and it was extensive in most. The finding of a subgroup of relatively low aqueous LDH levels may therefore be based on other factors. It may relate to poor LDH penetration through the retina into the vitreous and anterior chamber since subretinal LDH levels were assayed in three of the patients with low anterior chamber LDH levels and found to be markedly elevated (470, 3080, and 7849 IU/l). Felberg and associates[121] described a similar finding in a series of retinoblastoma patients. They speculated that "the presence of high enzyme ratios in the subretinal fluid, and lower ratios in the aqueous humor may be the result of complex kinetics dealing with diffusion through the vitreous gel and dilution by aqueous humor turnover, among other factors."

Aqueous LDH isoenzyme patterns were tested in three patients with advanced Coats' disease and in five with exophytic retinoblastoma (Tables

VIII and IX). Kabak and Romano[128] reported that the LD_5/LD_1 ratio was greater than 1 in retinoblastoma patients. In fact, four of their five patients had an LD_5/LD_1 ratio greater than 5, and they considered this test to be valuable in differentiating retinoblastoma from benign disease. Our findings of an LD_5/LD_1 ratio of less than 1 in advanced Coats' disease also support this hypothesis. Unfortunately, in two of our five exophytic retinoblastoma patients, LD_5/LD_1 levels were also less than 1. In a large series of retinoblastoma patients studied by Abramson and colleagues,[124] an LD_5/LD_1 ratio of less than 1 was found in 25% of the cases. Therefore, it appears that aqueous LDH isoenzyme patterns are of little value in differentiating advanced Coats' disease from retinoblastoma. LD_1 and LD_2 are elevated in specimens with hemolysis, and contaminated specimens should therefore be reviewed with caution.

In summary, although aqueous LDH levels are generally much higher in exophytic retinoblastoma patients than in patients with advanced Coats' disease, both elevated and normal levels were found in each group. This test is therefore of limited value and should not be used as a means of distinguishing between these two entities.

Neuron-Specific Enolase—NSE is detectable in tumors of neuroectodermal origin, such as neuroblastoma and retinoblastoma.[130,131] Nakajima and associates[132] have recently suggested that elevated NSE levels occur in the anterior chamber of retinoblastoma patients, and not in patients with simulating lesions. A subsequent study by Abramson and associates[133] of 17 children with retinoblastoma revealed NSE in the aqueous of all patients. Shine and associates[134] studied the isoenzyme pattern of enolase in the aqueous humor and serum of multiple patients with retinoblastoma, malignant melanoma, and cataract, and of one patient with Coats' disease. They found elevated levels of NSE in the serum and aqueous of patients with retinoblastoma. Enolase was not detectable in the aqueous of "normal" patients undergoing cataract extraction or the one patient with Coats' disease. Only one of the Coats' disease patients in our study was evaluated for NSE. Our finding was similar to that of Shine and associates.[134] However, further supportive evidence is necessary before this test can be considered clinically useful. Unfortunately, red and white blood cells contain significant quantities of NSE,[135,136] and therefore elevated levels may occur in any patient with intraocular hemorrhage or inflammation and cell lysis, thus limiting the value of this test in differentiating exophytic retinoblastoma from advanced Coats' disease.

In summary, it appears that aqueous LDH levels are nonspecific and not particularly valuable in distinguishing advanced Coats' disease from retinoblastoma. Additional studies on the value of aqueous NSE levels

should be performed to determine if it may be a valuable adjunct in differentiating exophytic retinoblastoma from advanced Coats' disease.

PATHOLOGY

Cytopathology

Subretinal aspiration was performed on 18 eyes enucleated from patients harboring exophytic retinoblastoma. In all cases, small undifferentiated cells were identified. These cells tended to clump; however, no rosettes were seen. Scattered erythrocytes were seen as well as numerous granular deposits and nonpolarizing crystals. Rarely, large pigment-laden cells were observed within a background of tumor cells.

Fine-needle aspiration biopsy has previously been utilized to aid in the diagnosis of certain intraocular disorders. Augsburger and co-workers[137] and Char and Miller[138] have each reported large series of patients showing this test to be reliable in differentiating intraocular tumors from benign simulating disorders. Barishak and Stein[139] performed in intraocular biopsy on a patient suspected of having Coats' disease. They instead identified cells consistent with retinoblastoma and promptly enucleated the eye. The authors did not provide information on the long-term results in this patient. This technique of intraocular biopsy has several disadvantages. The most important is that tumor seeding into the needle tract and surrounding tissues is possible, as has been demonstrated by Karcioglu and colleagues.[140] We have personally encountered two patients referred following misdiagnosis of advanced Coats' disease and inadvertent drainage of subretinal retinoblastoma. We agree that tumor seeding is a serious potential risk and that fine-needle aspiration biopsy should be used only as a final means of diagnostic confirmation when retinoblastoma has already been ruled out by all noninvasive means. In fact, we only recommend its use for confirming the diagnosis of Coats' disease in a controlled manner, before massive subretinal fluid drainage.

The second disadvantage of conventional examination of subretinal aspirates is that cytodiagnostic preparation for Giemsa, Wright, or Papanicolaou stains requires 45 to 60 minutes. This period is too long to permit intraoperative usage of this technique. Haik and associates[141] have described the value of examining fresh unstained fluid in patients with Coats' disease. In our study, we were able to demonstrate the presence of cholesterol crystals and large pigment-laden macrophages in all patients with Coats' disease and in none of the patients with exophytic retinoblastoma. In the patients with exophytic retinoblastoma, amorphous crystals, calcific deposits, and clumps of undifferentiated tumor cells were easily seen.

Our findings in advanced Coats' disease were similar to Haik's in that pigment-laden macrophages and large plates with corner notches and/or envelope-like folds consistent with cholesterol crystals were seen in all patients. In our series, polarizing light was used to confirm that the crystals were cholesterol. Of additional interest was the finding of cholesterol crystals being phagocytized by large macrophages. This is a finding that can only be demonstrated on evaluation of fresh fluid, since cholesterol plates would dissolve in routine stain preparations.

Of greater significance was the discovery of pigment-laden macrophages in fresh preparations of subretinal fluid from enucleated eyes harboring exophytic retinoblastoma. Fortunately, these were always found in a field of retinoblastoma cells. The presence of macrophages in the subretinal fluid of these patients is not surprising, since they can occur in long-standing retinal detachments of any etiology. In all cases, the cytologic evaluation of fresh and stained subretinal fluids proved to be valuable and accurately predicted the diagnosis.

Histopathology

Selected histopathologic sections obtained from our cases reveal extensive structural distortion secondary to diffuse edema and massive exudation with formation of microcystic cavities containing eosinophilic proteinaceous fluid in the inner layers of retina. The bipolar cell and photoreceptor cell layers are also distorted secondary to exudation and degeneration. Vascular abnormalities range from hyalinized thickening of the retinal blood vessels to marked thinning of the vessel walls with irregular, telangiectatic distentions. Many of the retinal blood vessels are distended and contain hyalinized thick walls surrounded by proliferating glial cells, phagocytic cells, and eosinophils. Some of the dilated vessels, on the other hand, have thin walls devoid of endothelial cells and form cyst-like spaces within the outer retina surrounded by diffuse edema and phagocytic cells. The end result of the continuous leakage from abnormal blood vessels is the collection of exudates and hemorrhage within retinal layers and subretinally, which lead to total disorganization of the normal architecture and cause phthisis. The pathology is rather nonspecific, with prephthisic and phthisic changes being evident in later stages of Coats' disease. Therefore, photomicrographs of our cases are intentionally selected from the areas of the retina showing the early abnormalities of the blood vessels and the retina, which correlate very well with the pathogenesis of the disease (Figs 61 and 62).

It is the widely accepted view that the sequence of structural changes in Coats' disease is primarily triggered by a breakdown in the blood-retina barrier at the endothelial cell level, causing leakage of fluid into the

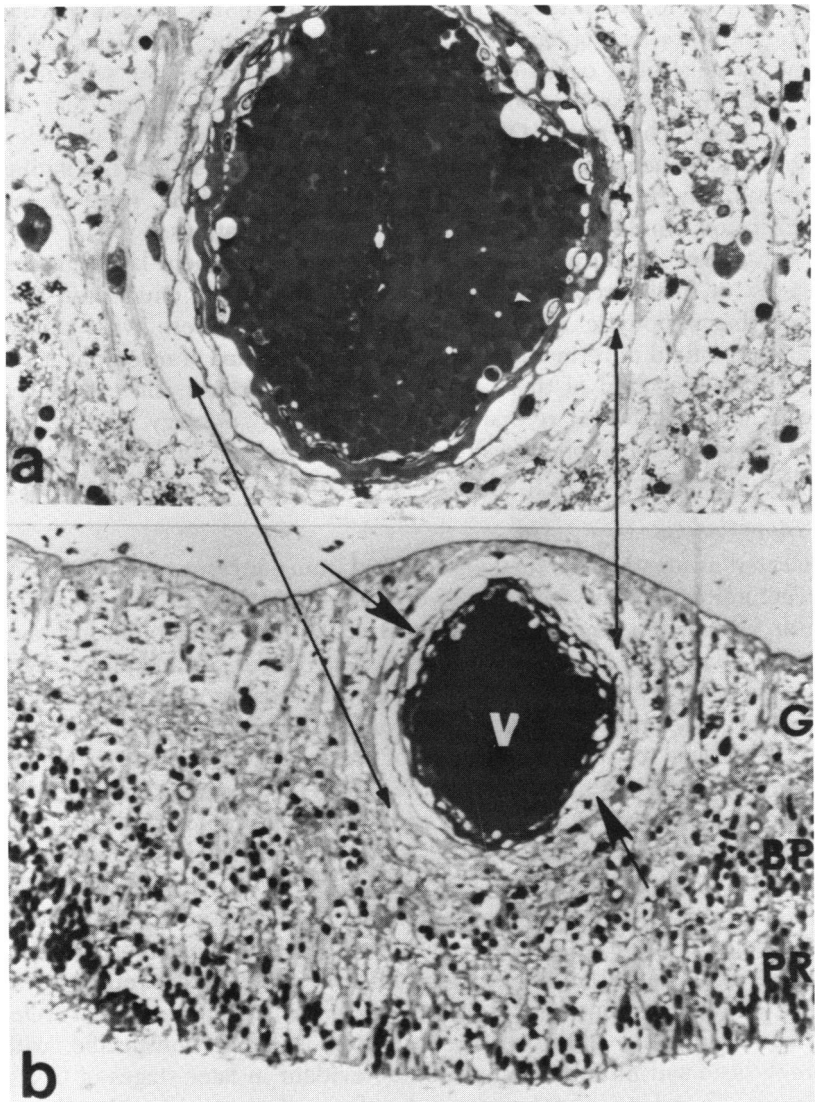


FIGURE 61

Photomicrograph of edematous retina containing a distended blood vessel (V) with laminated appearance (*arrows*) of its wall. Note extensive intraretinal edema and focal exudative deposits, which led to total distortion of retinal architecture and cell loss from all layers of retina, including ganglion cells (G), bipolar cells (BP), and photoreceptor cell nuclei (PR) (methylene blue, original magnification; a, ×400; b, ×250).

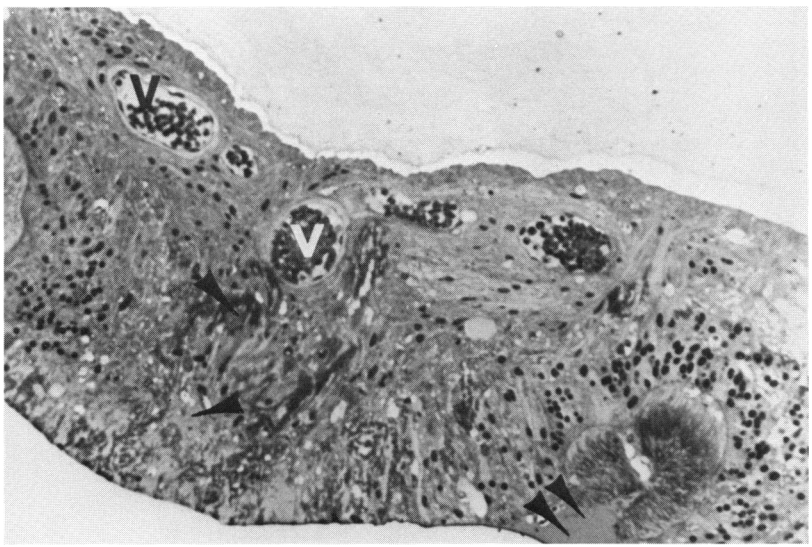


FIGURE 62
Photomicrograph depicting retinal changes in a more advanced stage of disease. Distended and congested blood vessels (V) are apparent, some of which show thick, hyalinized walls and disorganized retinal structure secondary to exudates, gliosis, and fibrosis. Intraretinal (*arrows*) and subretinal (*double arrows*) exudates are clearly depicted (methylene blue, original magnification; ×250).

vessel wall and perivascularly to weaken the vessel structure. This, in turn, leads to further distortion of the vascular structures with aneurysmal dilatations and telangiectasis. The structural abnormalities cause further impairment of the endothelial barrier, and plasma leaks into the surrounding tissues to produce intraretinal and subretinal exudates and hemorrhages.[16] The irregular telangiectatic changes and multiple aneurysm formations in Coats' disease have been well documented with trypsin digestion studies.[33] In later stages of the disease, the retina may be split into several layers because of exudative leakage, and large areas of retinoschisis may be created. The continuous leakage from abnormal blood vessels leads to extensive degeneration and detachment of the retina which may present as a nodular structure later in the disease, when the underlying lipid-rich exudate organizes and mixes with fibrous tissue. The contents of these nodular areas usually include a mixture of lipid-rich exudate, partially organized hemorrhage with cholesterol crystals, and numerous phagocytic cells and proliferations of retinal pigment epithelial cells.

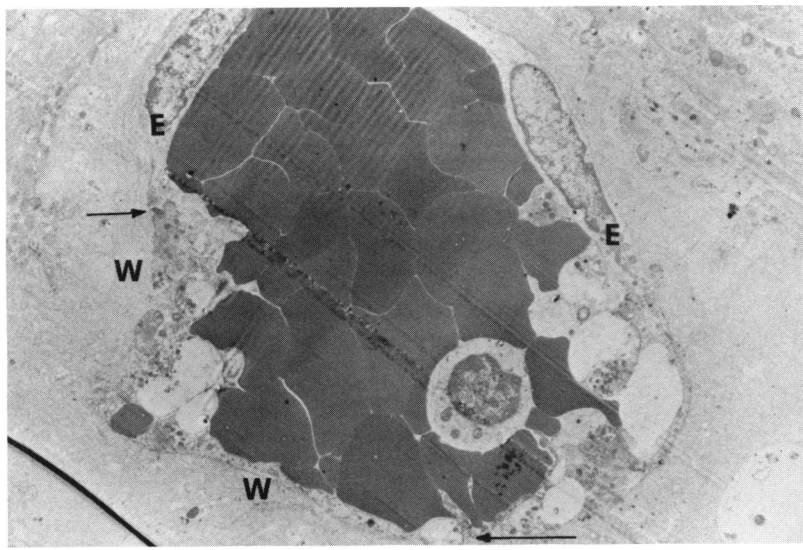


FIGURE 63
Low magnification electron micrograph depicting a retinal blood vessel with damaged endothelial cells (E) and laminated fibrous coat of the blood vessel infiltrated with plasmoid and lipoid material and cellular remnants (W). *Arrows* indicate interruptions of vessel wall secondary to degenerative changes of endothelial cells.

The ultrastructural findings in our specimens were consistent with those in previous studies, including damage and loss of endothelial cells and pericytes, distortion of the blood vessel walls infiltrated with fibrinous material, plasmoid exudates among the retinal cells, and extensive atrophy of the cellular elements, particularly within the inner layers of the retina (Figs 63 and 64). The disorganized layers of the retina were extensively infiltrated by phagocytic cells ("foam" or "ghost" cells) containing lipoid material and clumps of pigment granules (Fig 65).

NATURAL HISTORY AND MANAGEMENT ALTERNATIVES

The natural progression of untreated advanced Coats' disease is toward the development of glaucoma or phthisis (Fig 66 A and B). Of the 25 patients observed, 20 developed painful neovascular glaucoma within 5 years. Three of the remaining patients were comfortable and stable with chronic retinal detachments, but normal intraocular pressures. The last two patients' vascular abnormalities were clearly documented to undergo spontaneous regresion and the retina reattached. Of this entire group of

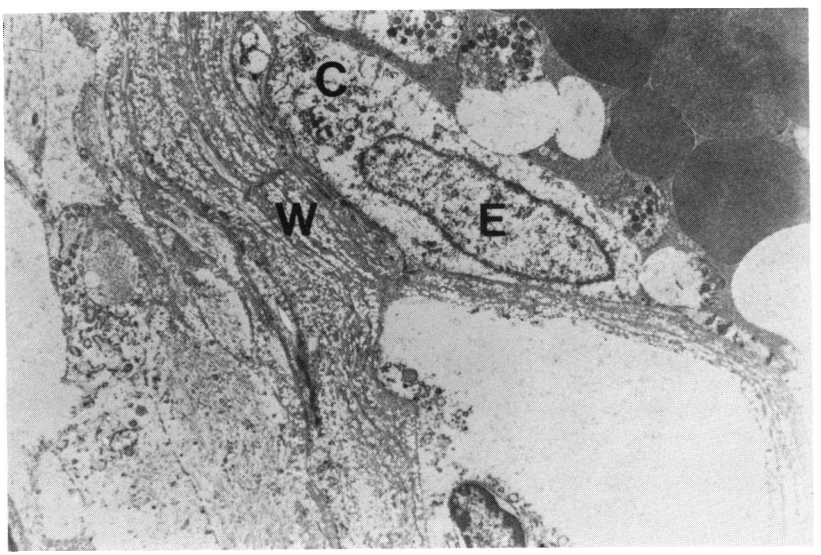


FIGURE 64
Electron micrograph depicting endothelial cell (E) from wall of a retinal capillary with extensive degenerative changes of cytoplasm (C). Laminated appearance of vessel wall (W) adjacent to defective endothelium is also seen (original magnification, × 8000).

untreated patients, only one with spontaneous regression retained light perception vision.

Our findings in five patients also concur with previous reports[10,52] that photocoagulation and/or cryotherapy without subretinal drainage are incapable of controlling advanced Coats' disease. Cryotherapy is at times difficult because the abnormal vessels cannot be reached with the "ice ball" when located on the highly elevated retinal detachment. Xenon arc photocoagulation via direct ophthalmoscopy and argon laser therapy delivered through binocular indirect ophthalmoscopy were generally effective in destroying easily seen vascular abnormalities. Relatively high intensity treatments are required because absorption is limited by the highly reflective yellow or white background. Unfortunately, in some patients, portions of the abnormal vasculature could not be treated because of obscuration by hemorrhage or because vessels were partially hidden from view by the apposition of retinal folds or bullae. Additional obstacles to successful retinal reattachment by destroying vessels alone are encountered in those advanced cases with retinal contraction associated with preretinal, intraretinal, and subretinal gliosis.

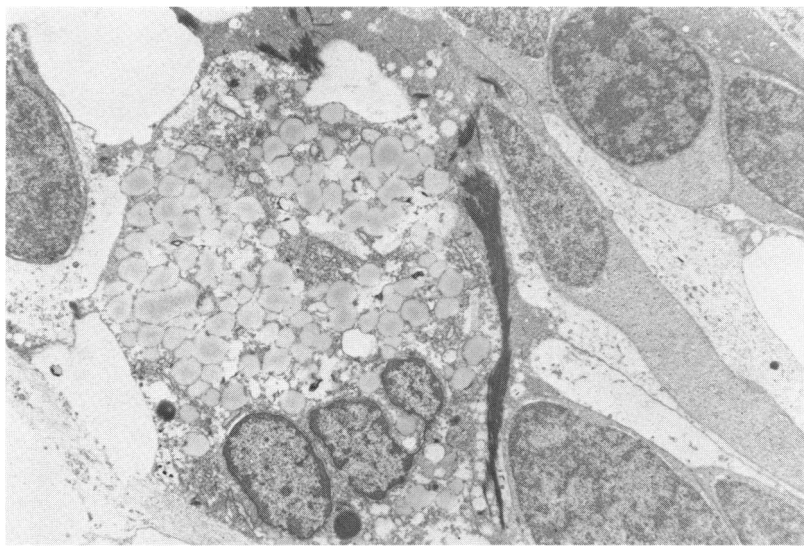


FIGURE 65
Electron micrograph of an intraretinal lipid-laden macrophage ("foam cell") (original magnification, ×8000).

Aggressive vitreoretinal surgery offers the best prognosis for retinal reattachment and ocular survival. In all three of our patients who were treated with subretinal drainage, intravitreal infusion followed by photocoagulation, and cryotherapy, the retina was reattached (Fig 67 A and B). Although not applied in our patient series, infusion of viscous vitreous substitutes, membranectomy, retinotomy, and scleral buckling may be necessary to reattach gliotic, foreshortened retina.

A key step in any retinal reattachment surgery is subretinal drainage, in order to reposit the retina prior to photocoagulation or cryotherapy of the abnormal retinal telangiectasis. This normally innocuous procedure could be fatal if unsuspected retinoblastoma were seeded into the orbital tissues. We therefore advocate intraoperative controlled fine-needle aspiration of subretinal fluid followed immediately by cryotherapy to the self-sealing needle tract. The aspirate may be evaluated in its fresh state intraoperatively; absence of tumor cells and presence of pigment-laden macrophages and cholesterol crystals support the diagnosis of Coats' disease.

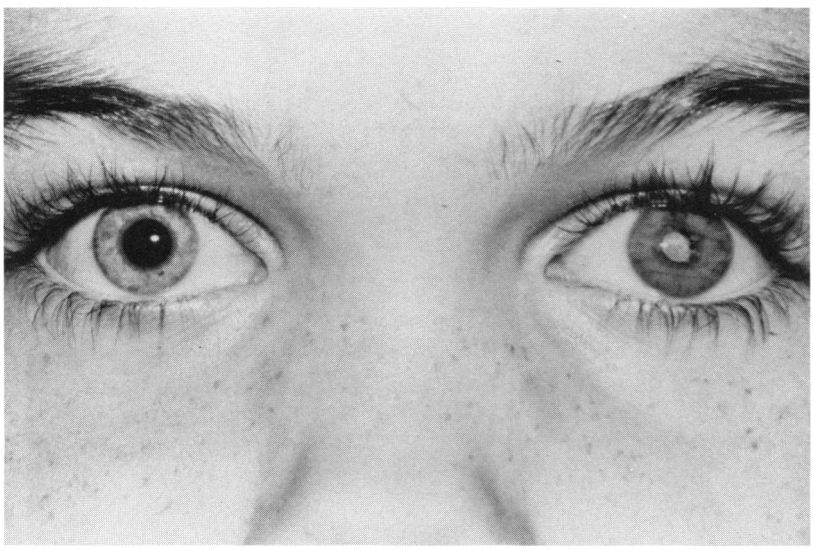
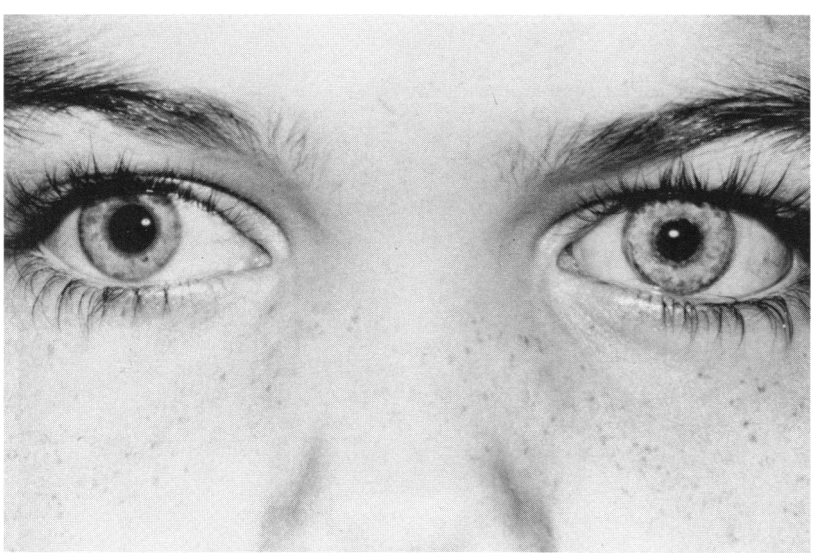


FIGURE 66

A: Child with advanced Coats' disease who experienced intermittent episodes of painful glaucoma, controlled with topical corticosteroids and cycloplegics before progressing to phthisis. B: An excellent cosmetic appearance is obtained following placement of a flush-fitting cosmetic shell.



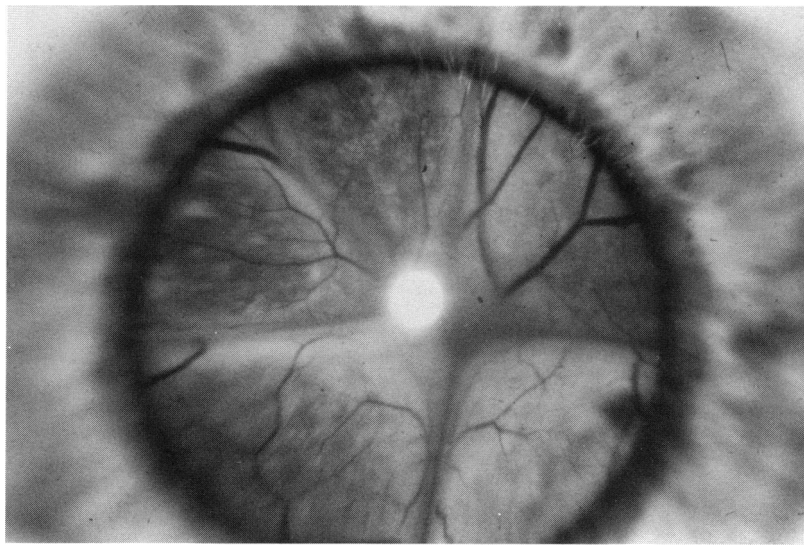
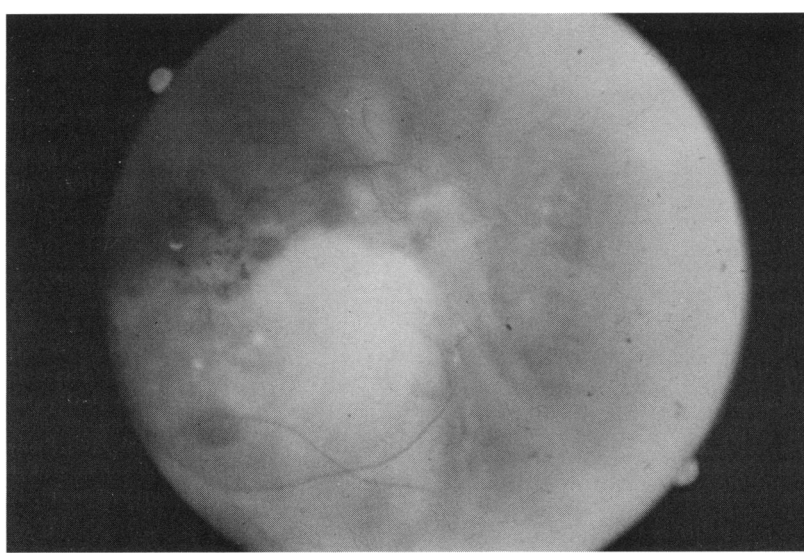


FIGURE 67
A: Bullous retinal detachment in a patient with advanced Coats' disease. B: Postoperative fundus photograph demonstrating retinal reattachment following subretinal drainage, simultaneous infusion, and photocoagulation. Retina remains attached 5 years after surgery despite retinal gliosis.



Although this procedure should only be performed in patients where retinoblastoma has been ruled out by all noninvasive means, if an atypical retinoblastoma were detected on cytologic evaluation, the eye could be promptly enucleated during the same period of anesthesia.

Our findings are similar to those of Silador and associates[51] in that subretinal drainage, combined with vitreous infusion, cryotherapy, and/or photocoagulation, can preserve the globe. Therefore, these patients will experience normal orbital growth and not suffer the cosmetic and psychological side effects associated with enucleation. Our results are also similar to theirs with regard to visual acuity. None of the patients in either series retained useful vision. This disappointing finding may relate to the fact that massive photoreceptor degeneration had already occurred in these patients. More encouraging results might have been obtained if patients had been operated on at a less advanced state.

SUMMARY AND CONCLUSIONS

Advanced Coats' disease and retinoblastoma can both present with the triad of a retinal detachment, the appearance of a subretinal mass, and dilated retinal vessels. Thus, even the most experienced observer may not be able to differentiate these entities on ophthalmoscopic findings alone. Coats' disease is the most common reason for which eyes are enucleated with the misdiagnosis of retinoblastoma.

Ultrasonography is the auxiliary diagnostic test most easily incorporated into the clinical examination, and can be utilized repeatedly without biologic tissue hazard. Ultrasonically identifiable features allowing differentiation between Coats' disease and retinoblastoma include the topography and character of retinal detachment and presence or absence of subretinal calcifications. Ultrasonography is of lesser use in poorly calcified retinoblastoma and in detecting optic nerve or extraocular extension in heavily calcified retinoblastoma.

CT is perhaps the single most valuable test because of its ability to: (a) delineate intraocular morphology, (b) quantify subretinal densities, (c) identify vascularities within the subretinal space through the use of contrast enhancement, and (d) detected associated orbital or intracranial abnormalities. Optimal computed tomographic studies, however, require multiple thin slices both before and after contrast introduction and expose the child to low levels of radiation if studies are repeated periodically.

MR imaging is valuable for its multiplanar imaging capabilities, its superior contrast resolution, and its ability to provide insights into the biochemical structure and composition of tissues. It is limited in its ability

to detect calcium, which is the mainstay of ultrasonic and CT differentiation.

Aqueous LDH and isoenzyme levels were not valuable in distinguishing between Coats' disease and retinoblastoma.

The value of aqueous NSE levels in the differentiation of advanced Coats' disease and exophytic retinoblastoma deserves further study. Specimens from patients with intraocular hemorrhage should be viewed cautiously, since erythrocytes contain high levels of enolase.

Analysis of subretinal aspirates is an extremely accurate method of confirming the diagnosis of Coats' disease. The key diagnostic findings are the presence of cholesterol crystals and pigment-laden macrophages and the absence of tumor cells on fresh preparations. The technique should be reserved for patients where retinoblastoma has been ruled out by all noninvasive means and massive subretinal drainage is anticipated.

The natural progression in advanced Coats' disease is toward the development of a blind, painful eye. Spontaneous regression does rarely occur, and some eyes quietly progress to a phthisical state.

Results with photocoagulation and cryotherapy underscore the fact that these modalities alone or in combination are ineffective in patients with advanced Coats' disease.

Vitreoretinal surgery, including subretinal drainage, and simultaneous intravitreal infusion followed by photocoagulation and cryotherapy offers the best hope for ocular preservation.

The successful treatment of advanced Coats' disease depends on both reattachment of the retina and successful destruction of the abnormally permeable retinal vessels. The earlier the disorder is detected, the more likely is therapy to be successful. Reasonable therapeutic goals include prevention of rubeotic glaucoma, ocular salvage, and the possibility of salvaging peripheral vision. From review of both previous pathologic reports and those of our patients, we clearly find that macular degeneration is a major feature of this disorder at the time of diagnosis and that recovery of central vision is not a reasonable expectation. However, aggressive vitreoretinal therapy can permit ocular salvage and the associated physical benefits of more normal orbital development, as well as the psychological advantage of globe retention.

In summary, the eyes of most patients with advanced Coats' disease were enucleated in the past because retinoblastoma could not be ruled out, or because painful neovascular glaucoma developed in blind eyes. Advanced Coats' disease can now be differentiated from exophytic retinoblastoma in almost all cases by correlating clinical findings with results of noninvasive diagnostic studies. If equivocal or conflicting findings result

in a questionable diagnosis, enucleation should be performed. If, however, all findings are consistent with advanced Coats' disease, vitreoretinal surgery may be confidently undertaken to achieve ocular salvage.

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