PROGRESSIVE VISUAL LOSS IN ADULTS WITH RETINOPATHY OF PREMATURITY (ROP)*

BY *William Tasman*, MD, AND

(BY INVITATION) *Gary C. Brown*, MD

INTRODUCTION

RETINOPATHY OF PREMATURITY (ROP) IS A PROGRESSIVE CONDITION THAT requires periodic monitoring for a lifetime. The International Classification of ROP has improved our understanding of the stages of the disease and has led to a collaborative study to evaluate the effectiveness of cryotherapy in active ROP.[1,2] It also includes a list of ocular sequelae that includes late-onset retinal detachment, retinal pigmentary changes, myopia, and dragged retina.

In this study, two visually monocular patients with ROP, myopia, and dragged retina were followed for 14 and 5 years, respectively, during which period progressive loss of vision was noted. One of the two patients was operated on for a retinal detachment, but postoperative visual acuity was good. No new fundus changes developed that would explain the subsequent visual loss. Possible explanations for the decreased visual acuity will be discussed.

CASE REPORTS

CASE 1

KM, a 20-year-old male, was first examined in 1973. There was a known history of prematurity and ROP confirmed by a birth weight of 900 g. The right eye had been blind since infancy, but the left eye was 20/30 with a high myopic correction. Intraocular pressures have always been normal. On the initial fundus examination there was retinal pigment epithelial attrophy in the posterior pole and macular

*From the Wills Eye Hospital Retina Service, Jefferson Medical College, Philadelphia, Pennsylvania. Supported inpart by an unrestricted grant from Research to Prevent Blindness, Inc.

heterotopia, but no significant dragging of the retinal vessels. Peripheral lattice-like changes and retinal breaks were noted in 5:30.

The patient has been followed for 14 years, during which time increasing vitreous traction has led to avulsion of a retinal vessel. During the last 4 years graying of vision has been noted by the patient, and visual acuity has diminished to 20/400. The visual field is constricted. Fluorescein angiography demonstrated atrophy and clumping of the retinal pigment epithelium (Fig 1). This was even more marked in the most recent angiogram performed in April, 1988 (Fig 2).

Visual evoked response (VEP) indicated an intact visual pathway from the optic nerve posteriorly, and electroretinopathy (ERG) showed a normal a and b wave with good flicker response.

CASE 2

PE, a 30-year-old woman, was first examined in 1983. She had a birth weight of 1000 g and a history of ROP that had led to enucleation of the left eye in infancy. There was a history of cryotherapy to abnormal lattice-like changes superiorly in the remaining eye, and referral was made because of an inferior temporal rhegmatogenous retinal detachment. This was repaired with a localized episcleral silicone

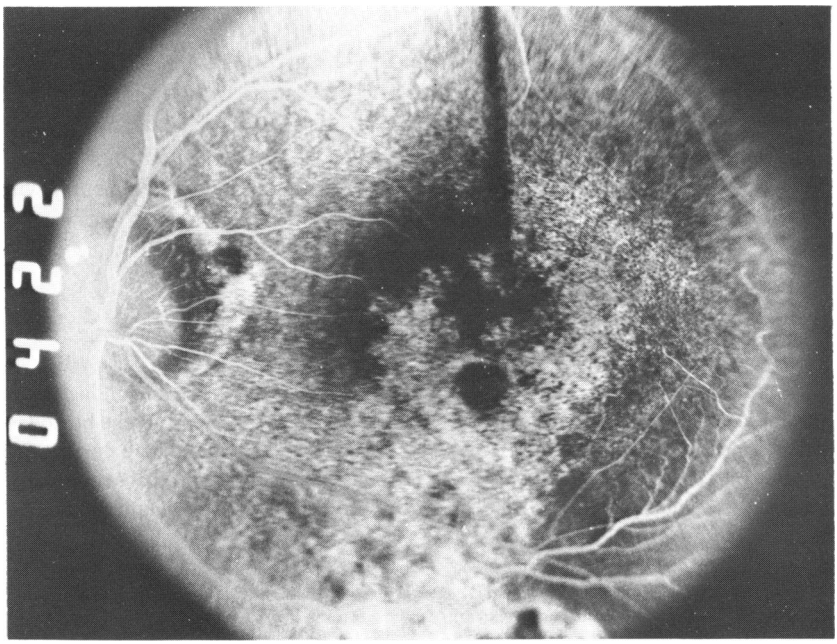

FIGURE 1
Fluorescein angiography confirming retinal pigment epithelial atrophy and clumping just above the fovea in patient 1.

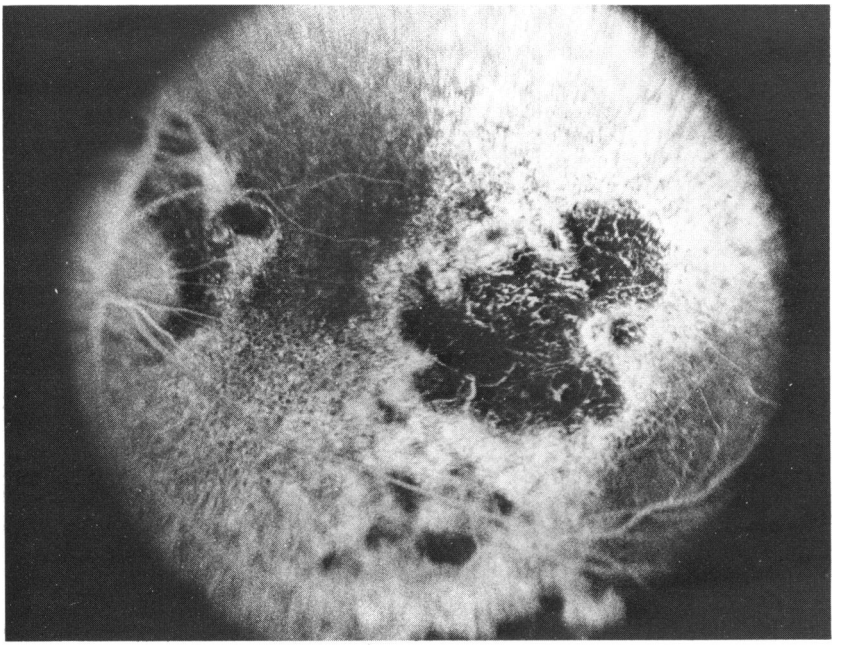

FIGURE 2
Recent fluorescein angiogram taken 8 years after Fig 1 demonstrating marked retinal pigment epithelial atrophy and increased migration of pigment in the posterior pole.

rubber sponge and cryotherapy to the break, without drainage of subretinal fluid. The macula was not detached, although there was temporal dragging of the retina. RPE change was present in the posterior pole and best vision with myopic correction was 20/60 (Figs 3 and 4). This vision was maintained for 2 years after surgery before decreasing. Vision loss was associated with graying of vision and gradual constriction of the visual field (Fig 5). Vision is now at a level of count fingers, even though there have been only minimal new retinal findings and intraocular pressure is normal (Figs 6 and 7).

A VEP was within the normal range, but ERG amplitude for the a and b waves was reduced by approximately one-third. The electro-oculogram was consistent with latent nystagmus and indicated a best attainable acuity of 3.94 cycles per degree, which is equivalent to about 20/200—slightly better than the count fingers recorded clinically.

DISCUSSION

The cause of the decreased vision in these patients is a matter for specula-

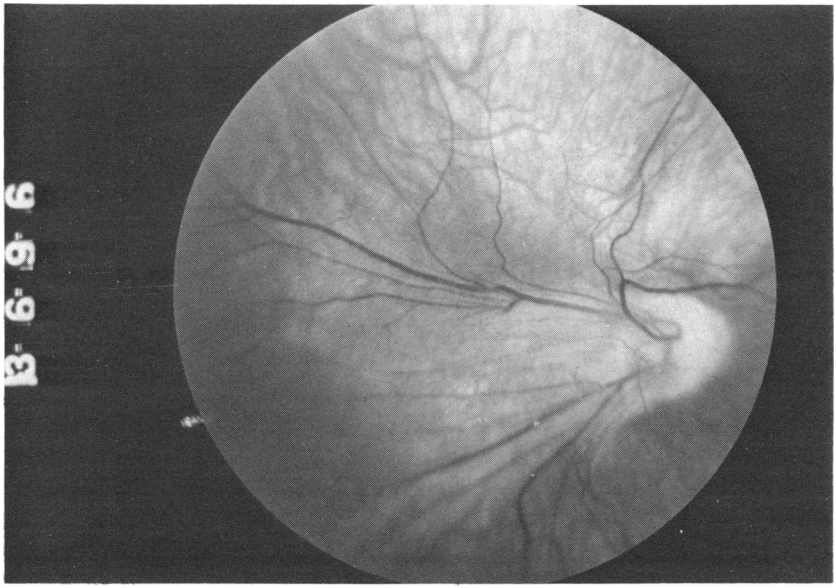

FIGURE 3
Red free photograph showing temporal dragging of the retina in patient 2.

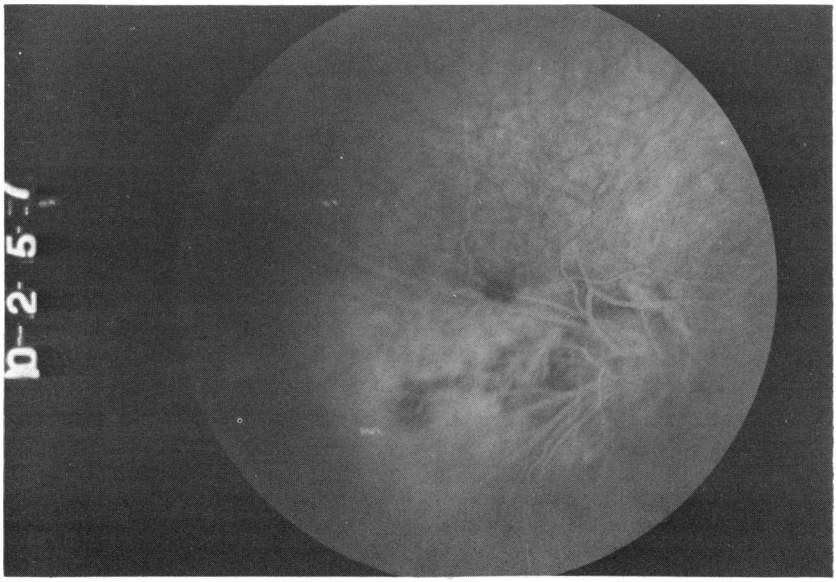

FIGURE 4
Fluorescein angiography demonstrating retinal pigment epithelial changes in patient 2.

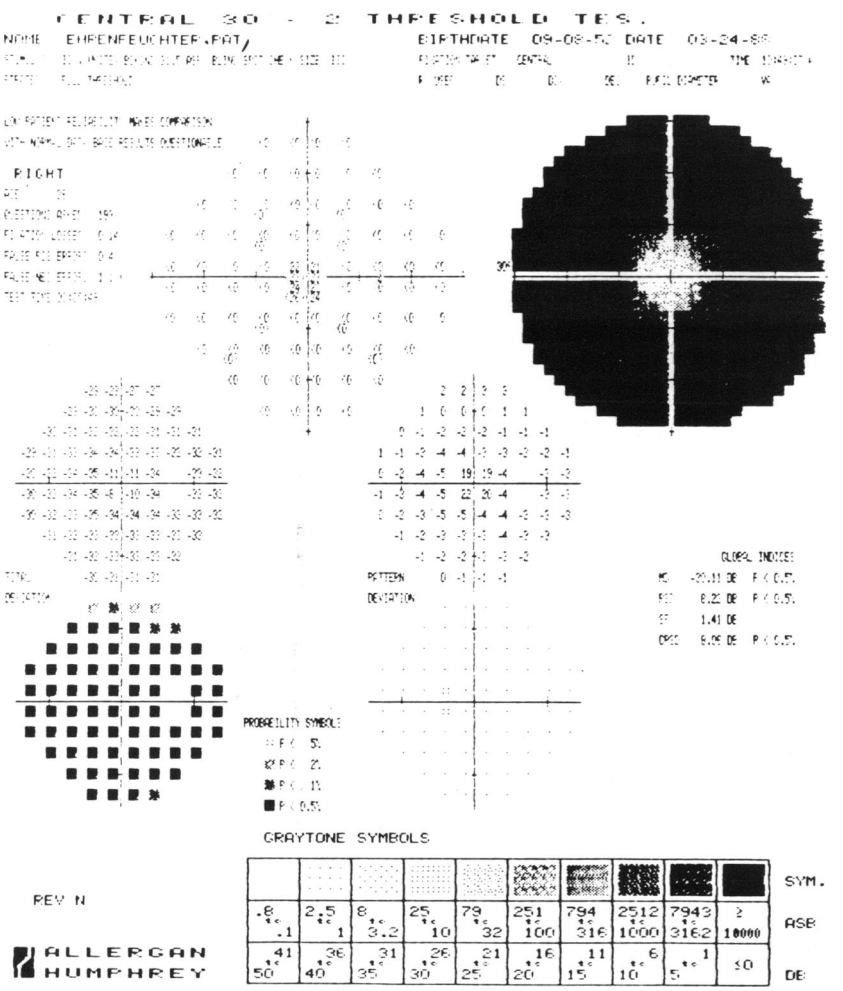

FIGURE 5
The visual field in patient 2 is constricted to within 10 degrees.

tion. Both were premature, both suffered from myopia, and both were monocular. The retina was markedly dragged to the temporal side in one patient, while the other showed only slight macular heterotopia. The fact that one of the patients had a surgical procedure performed to reattach the retina must be taken into consideration. However, cryotherapy was not excessively applied, subretinal fluid was not drained, and the globe was not encircled. The latent period between the time of surgery and the visual

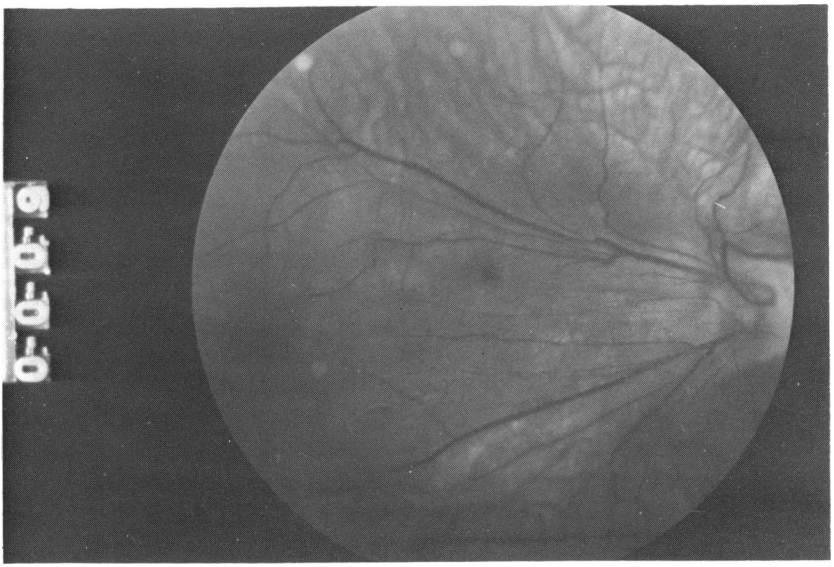

FIGURE 6
Red free picture of patient no. 2's retina taken 2 years after Fig 5. There is no apparent significant progression of fundus findings.

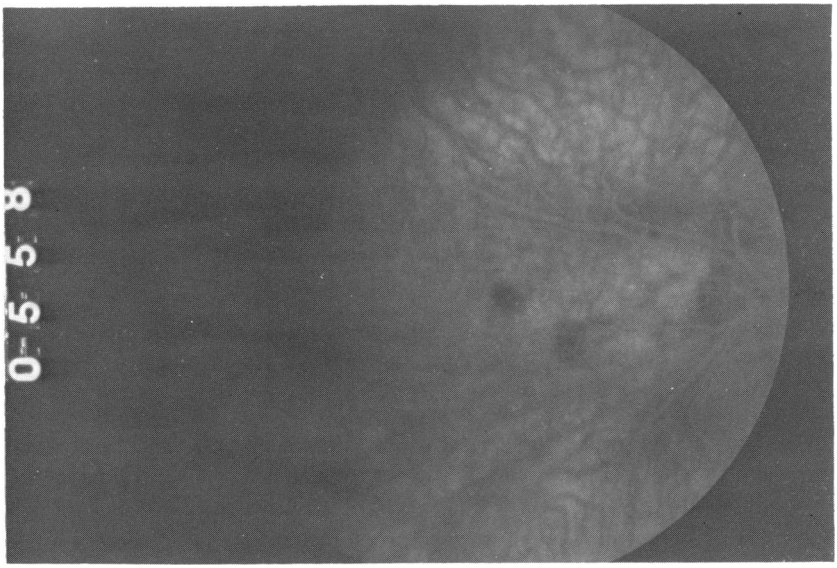

FIGURE 7
Fluorescein angiography of patient no. 2's retina shows changes similar to those noted 2 years earlier (Fig 5).

loss, and the fact that the other patient had comparable loss of vision in the absence of any surgical treatment argue against surgery as an etiology.

In a series of 90 eyes operated for retinal detachment with a preoperative vision of 20/30 or better, Wilkinson[3] found that 8% experienced some loss of vision after surgery despite successful retinal reattachment. Macular pucker was the most common cause of this postoperative reduction in vision. Epiretinal membranes causing macular pucker have been described as a postoperative complication causing visual loss in 7.5% to 17% of eyes following otherwise successful surgery for retinal detachment.[4] However, patient 2 in our study had no macular pucker.

Cystoid macular edema (CME) may also follow retinal detachment surgery,[5,6] but fluorescein angiography failed to confirm the presence of CME in patient 2.

Jarrett and Brockhurst[7] studied 11 patients with unexplained visual loss and optic atrophy following retinal detachment surgery in non-ROP cases. The pathogenesis in their patients was obscure. Both patients in this study, however, had a normal VEP.

Both patients had retinal pigment epithelial changes. This is often noted with dragging of the retina in ROP (Fig 8). Thus, a possibility exists that

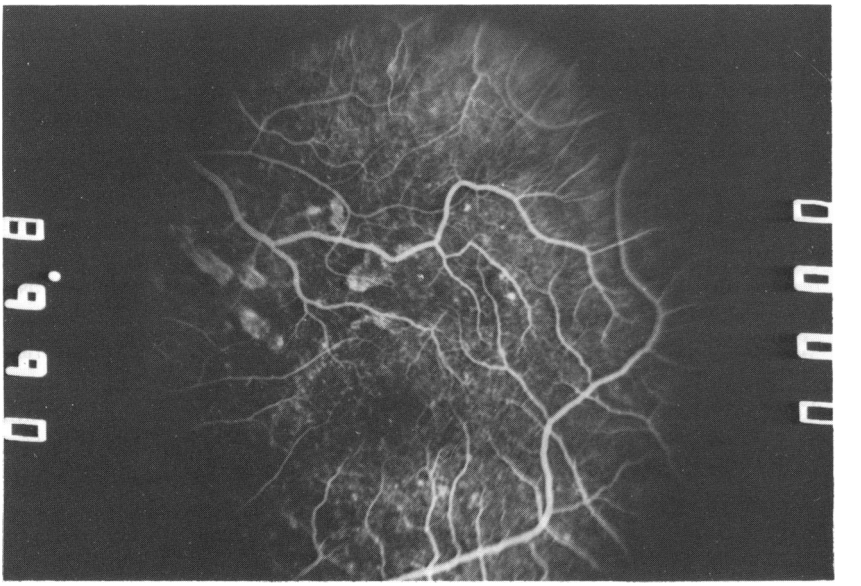

FIGURE 8
Retinal pigment epithelial changes in the posterior pole of a patient with ROP and dragging of the retina.

dragging may in some way compromise the photoreceptors.

In 1976, Sawyer and associates[8] described three cancer patients who were blind as a result of retinal degeneration of obscure pathogenesis. A similar report by Keltner and associates[9] described a patient with photoreceptor degeneration associated with an undifferentiated cervical neoplasm. Their patient differed from the cases of Sawyer and co-workers in that the patient initially responded to systemic steroids with visual improvement. Antibodies were found in the patient's serum that reacted against normal photoreceptors from fresh retinal tissue obtained at autopsy. These findings suggest a possible autoimmune disorder, as do those of Kligele et al,[10] and raise the possibility of this mechanism in photoreceptor degenerations such as retinitis pigmentosa, but such an etiology seems unlikely in ROP.

Johnson and Ahdab-Barmada[11] described a cytologically distinctive type of acute hyperoxemic injury of retinal neurons in premature neonates. According to the authors, exposure of ganglion cell nuclei in the central well-vascularized neonatal retina to excessive oxygen led to karyorrhexis. The highest incidence occurred in the 24 to 27 week group, where 13 of 21 patients (62%) were involved. On the other hand, Brown and associates,[12] while concurring that karyorrhexis is an observable phenomenon within the ganglion cell layer in neonates, indicated that supplemental oxygen therapy does not completely account for retinal neuronal necrosis and that neurons may not be the only cell type involved.

Kushner[13] found a higher incidence of amblyopia and strabismus in babies with regressed ROP and a possible increase in incidence in babies who received oxygen but did not develop ROP. The mechanism of the amblyopia was obscure in some instances, and Brown and colleagues suggest that some of these cases may reflect early hyperoxemic retinal ganglion cell necrosis.

One can only speculate as to the role that hyperoxemic retinal necrosis plays in the final visual acuity of survivors. Conceivably, the individuals in this study may have had a degree of neuronal impairment for which they were able to compensate over a period of years. With the passage of time, however, these compensatory mechanisms may give out in association with retinal pigment change, so that the remaining functional photoreceptors gradually fail. Whether there is a cause and effect between the retinal pigment epithelial alterations and photoreceptor impairment remains an unanswered question, however.

ACKNOWLEDGMENT

I would like to thank A. Rodman Irvine, MD, for kindly providing me with Figs 1 and 2.

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DISCUSSION

DR A. RODMAN IRVINE. Doctors Tasman and Brown report two patients with retinopathy of prematurity (ROP) and adequate vision through childhood and adolescence who then developed progressive visual loss in the third and fourth decades of life. Is this report significant? I would submit that the significance of a new clinical observation depends not so much on numbers and *P* values as on whether the observation stimulates other clinicians to start looking and come up with similar cases. I applied this test to Doctors Tasman and Brown's observation, and came up with the following cases from the University of California.

Case 1 (CM). This 20-year-old woman was born 3 months prematurely, weighing under 2 pounds, and developed ROP with a falciform fold through the left macula limiting vision to count fingers in that eye. The right eye had marked dragging of the macula but had 20/100 vision until age 20, when vision fell to 20/400. Although her

fovea seemed to show cystoid changes on slit lamp biomicroscopy and her vision seemed to fluctuate with periods of improvement, fluorescein angiography showed just speckled hyperfluorescence in the fovea consistent with retinal pigment epithelial transmission and no capillary leakage or late cystoid pattern.

This patient seems very similar to those of Doctors Tasman and Brown. The next two patients are also very similar but show the presence of definite cystoid macular edema.

Case 2 (TR). This 24-year-old man was born prematurely and developed ROP with a large falciform fold through the left macula. His right eye had a dragged macula but retained 20/40 vision until age 23, when vision gradually fell to 20/80. He showed obvious cystoid spaces in the fovea on slit lamp biomicroscopy, and fluorescein angiography reveaaled cystoid macular edema.

Case 3 (KR). This 31-year-old woman was born 2½ months prematurely with birth weight under 3 pounds. She developed severe ROP in the right eye, leading to retinal detachment and phthisis. The left eye did well initially. At age 14 and again at age 18 she underwent prophylactic cryopexy to areas of tractional retinal changes in the temporal periphery of the left eye. At age 29, vision in the left eye fell to 20/30, and fluorescein angiography revealed the presence of cystoid macular edema, There seemed to be leakage not only at the fovea but also temporally. This has presisted for 3 years.

In short, the observation by Doctor Tasman and Brown of delayed visual loss in patients with ROP does indeed pass the test of proving reproducible in other practices, once clinicians have been alerted to look for it. Doctors Tasman and Brown pointed out a problem which I believe is both serious—often affecting vision in the only eye of young adults—and relatively common. Having been forced by their observation to look for such cases, I noted that at least some of them showed evidence of cystoid macular edema. I would ask Doctors Tasman and Brown whether they think this may be the result of retinal degeneration, analogous to its occurrence in retinitis pigmentosa, whether it may indicate that tangential traction along the surface of the retina is affecting retinal capillary permeability, as occurs occasionally in spontaneous macular pucker, or whether it may somehow be the result of early vitreous liquefaction predisposing to mild vitreal inflammation.

Dr Robert E. Kennedy. I feel Doctor Tasman's paper is most interesting. I am so old as to date back to the time when the Owens first saw this and it was called retrolental fibroplasia. Having an interest in this from residency days, I returned to my hometown of Rochester, New York, and began watching some of the young premature babies. I would like mention a lady now 37½ years old, born in December 1950 at 3 lbs 4 oz who's weight went down to 2 lbs 12 oz. At the present time you can see her fundus photographs which with approximately a −10.00 sphere allows her a vision of 20/30, J-1. She has the characteristic dragging of the blood vessels temporally from the disc, and I can remember the marked temporal peripheral edema. She is functional as an assistant to a dental surgeon and sees very well wearing contact lenses. She is presented to show that there can be some encouragement for many of these people and not all of them are headed for trouble.

My father practiced ophthalmology for 60 years and I have only 17 more years to go before I can also retire. That would make her 54 when she will be seeing someone else. Accordingly, she has these fundus photographs for future reference.

The two questions I would like to ask are: (1) Would it be worth doing a survey among the various schools who would have records of people dating back to the 40s or early 50s and see what a larger series would produce later in life for people who had this problem in infancy. (2) Aside from fundus photographs, what might a doctor do for a single patient as far as studies so that she would have protection or something to fall back on in cases of being seen by a different ophthalmologist.

DR RONALD M. BURDE. Doctor Norton, Doctor Kearns, members. I think that this was an extremely important paper and I would just like to raise a few points. In terms of talking about the so-called CAR syndrome, this is now a diagnosis that can be confirmed by laboratory testing. Appropriate serum samples should be drawn, frozen and sent to Doctor Keltner's laboratory at the Department of Ophthalmology, University of California, Davis. They are not only capable of looking for general antiretinal antigens but also against specific photoreceptor components.

We have reported a case of the so-called CAR syndrome entitled Paraneoplastic Retinopathy which I think is of interest because we have demonstrated that early on in its course the visual loss associated with this syndrome is responsive to treatment with corticosteroids. Since many of these patients are going to die within a relatively short period of time if they can be kept seeing by the judicious use of corticosteroids it makes the quality of life that much better.

For those of you who have not had the opportunity to examine a patient with the CAR syndrome, it is important to know that these patients have a peculiar beaten-metal appearance to their maculae as well as attenuation of the vascular tree with their visual loss. In some cases, the visual loss may precede the diagnosis of an occult malignancy by months. A carry home message is that in an adult, the diagnosis of CAR should be considered in any patient with a peculiar metal-beaten appearance of the maculae and vascular attention with or without visual loss especially in the face of a known malignancy. A corollary is that this diagnosis should also be suspected in patients with unexplained visual loss of the appropriate age group. The diagnosis of CAR syndrome can be definitively made by sending serum samples to Doctor Keltner's laboratory (also to that of Doctor Tso's in Chicago). Treatment of these patients with corticosteroids may ameliorate the downward slide of visual function.

With specific reference to these cases, I was especially impressed while studying Doctor Kennedy's slides by the pallor of the optic nerveheads in a case of what appeared to be relatively normal retinal arterioles and veins. The relatively normal size of the retinal vessels in my experience generally precludes the diagnosis of a retinal pigmentary degeneration of any type including that associated with the so-called CAR syndrome.

It is of interest that we have followed a number of patients with the diagnosis of classic ischemic optic neuropathy presenting with bilateral central visual loss and altitudinal defects who seem to stabilize for a period of time and then begin to have a

slowly progressive visual loss unresponsive to therapy. They eventually go blinid. We have not yet fully correlated all the information about these cases so I cannot give you further information.

It is my contention that many of the patients presented here today might have optic nerve disease rather than retinal disease. In the future simultaneous VER, PERG, and ERG recordings might be helpful in determining whether the visual loss is due to an optic neuropathy or a retinopathy.

DR JOHN T. FLYNN. I would like to thank you also for bringing this to our attention and to continue the confessional mode started by Doctor Irvine to say that I too have two patients like Doctor Tasman's in my practice. I did not bring any pictures but I think the incidence may be even higher than we think it is because the first patient said to me, "I never go to you doctors because all you do is shake your head and tell me there is nothing that you can do for me." I think there are a number of older, ROP patients that are out there that just figure this is part of their disease, the doctors are not going to be able to do anything about it so they don't go near them. I share the concerns of Doctor Burde with regards to the possibility of optic nerve disease and I would like to ask Doctor Tasman if he looked at their pupils for Marcus-Gunn defects. I don't think visual fields are going to be helpful, but pupillary signs might indicate, without going into a very high tech work-up, the possibility that you do have some optic nerve disease. Finally, with regard to the etiology, the problem for me is that in my two patients, pictures of their retinal pigment epithelium have not changed a bit yet their visual loss is slowly progressive. We have not seen anything like cystoid macular edema which would be a simple straightforward explanation. So, I wonder if there isn't some kind of true photoreceptor dropout without any changes in the RPE and without any cysts—things that perhaps a ganglion cell ERG or a scanning laser ophthalmoscopy might delineate for us. It is a very interesting syndrome and it brings to mind the fact that when we say these "preemies" have regressed ROP that does not, by any means, mean that they are cured. They need a lifetime of our follow-up and careful care.

DR J. WALLACE MCMEEL. Doctor Norton, Doctor Kearns, members and guests. It was very interesting to hear Doctor Tasman discuss the slow visual loss as a late sequela of ROP. In the early stages of the disease ROP in some ways replicates proliferative diabetic retinopathy in its active angiopathic stage. We have a series of approximately 100 cases that were reported 2 years ago at the International Congress in Rome. We had had a good visual result following vitrectomy and our criteria for success was that they had maintained improvement in vision for at least 6 months after the surgery. Subsequently, approximately 40% of these had a progressive slow deterioration of vision. In looking at the angiograms and photographs on these we felt it was probably associated in part with an inexorable shutdown of the vascular system. That seemed to be the case in your ROP cases and it was of particular interest to me that there is a parallel in the late stages of the disease as well as in the early.

DR WILLIAM TASMAN. I would like to thank all of the discussants. I think they raise some very important points. I am particularly grateful to Doctor Irvine for his very thoughtful discussion and for the fact that he was able to present additional cases and to demonstrate conclusively that in some instances visual loss can be due to cystoid macular edema. In answer to his question as to whether or not visual loss may be related to retinal degeneration, as we sometimes see in RP, or to liquefaction of the vitreous leading to inflammation, or to tangential traction on the retina, I think that I would favor the hypothesis of tangential traction on the retina. There are several reasons for that. In some non-ROP patients, we see cystoid macular edema, epiretinal membrane formation, and macular pucker, all of which are due to vitreoretinal traction. In addition, some adult ROP patients demonstrate vitreous traction as evidenced by elevation of occasional retinal vessels. In fact, patient 1 does have such a vessel. So I think that primarily it is the tangential traction on the retina that leads to the cystoid macular edema. Perhaps the traction in some way secondarily plays a role in the RPE changes as well.

With regard to Doctor Kennedy's question about the 37½-year-old lady, I would encourage him to reassure her, since the majority of adult ROP patients will continue to see well. As far as going back to do a survey in schools for the blind is concerned, I believe that doing so might be logistically difficult. In answer to Doctor Kennedy's question about what should he do for the protection of his patient's sight, I think he has done the most important thing, and that is to photograph the fundus and then to give that patient reassurance that visual decrease is, fortunately, the exception rather than the rule.

Doctor Burde, I believe, made some very important observations about the CAR syndrome. We are aware of Doctor Keltner's lab, and blood samples from the patient I described have been sent to Doctor Keltner. The beaten-metal appearance Doctor Burde referred to was not yet apparent in the patient that I presented. Sawyer and his group did demonstrate a response to steroid therapy, but the effect produced was only temporary.

Doctor Burde raised a question about this being optic nerve disease, and that certainly was a concern we shared as well. As I said, the VEPs that we obtained were normal, and neuro-ophthalmologic consultation indicated that the optic nerve and central nervous systems were not affected.

Doctor Flynn, too, raised the question of optic nerve disease, but neither of our patients had an afferent pupillary defect. I still feel that the most likely explanations for the visual loss are RPE changes or photoreceptor drop out.

Finally, I want to thank Doctor McMeel for bring to our attention the parallelism between ROP and diabetic retinopathy. Although in his cases vascular shutdown may well have been the cause of visual loss, I do not think this is the explanation in the ROP patients.