RETROLENTAL FIBROPLASIA OR OPHTHALMIC DYSPLASIA OF PREMATURE INFANTS*

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Pediatricians and ophthalmologists have been increasingly beset by the increasing incidence of impaired vision and blindness in children caused by the formation of a white membrane just behind the lens often associated with what was believed to be persistence of the hyaloid arterial structure and other abnormalities of the vitreous and derivatives of the inner layer of the secondary optic vesicle. The ophthalmic literature contains numerous descriptions of these cases. Even the early writers, however, recognized the difference between these abnormalities and glioma or malignant fungus, and these conditions were also known to be different from congenital cataract.

Travers[1] in 1820 described the globe of a child of 8 months which he extirpated and found filled with an "opaque lardaceous substance by which the lens was slightly protruded and the iris rendered convex. The retina for the most part was absorbed and the other tunics perfect." He also observed a child of 3 months who had a similar condition while the pupil of the other eye was constricted and closed by an opaque capsule. Frick[2] in 1826 described what seemed to be the same condition as congenital cataract appearing some days or weeks after birth. Wecker[3] in 1866 observed a persistent hyaloid artery coexisting with luxated cataract and cited Meissner in 1857, Saemisch and Zehender in 1863 as describing persistent hyaloid arteries in man. Nettleship[4] in 1873 studied an eye of a 5-year-old girl who was born at 8 months. She had measles at 6 months when the mother first noted the

* Candidate's thesis for membership accepted by the Committee on Theses.

pupil turn color. The globe was hydrophthalmic. The cornea was normal. The retina was in place and was atrophied. The vitreous was filled with a jellylike material with a thickened and reticulated fibrous hyaloid membrane with 2 vessels in one hyaloid vascular cord running from disc to lens, but none in the other. Gardiner[5] in 1880 described a persistent hyaloid artery with arborization of the branches anteriorly to the posterior lens surface but no opacification or membrane. Holmes[6] in 1881 described a unilateral case. Vassaux[7] in 1883 described the left eye of a 54-day-old infant who had a persistent pupillary membrane with anterior synechiae, a posterior vascular membrane and hyaloid artery behind an amorphous hyaline membrane. There was rupture of the posterior lens capsule, and the anterior capsular epithelium went behind the lens. The zonule and ciliary processes were enmeshed in the membrane. The retina was normal, but the choroid thin. Snell[8, 9] in 1884 classified congenital defects and reported a case of persistent impervious hyaloid artery. Hess[10] in 1889 described the microphthalmic eye of a 3-year-old child with persistent hyaloid artery and complete tunica vasculosa lentis. Another case was in a child who had been prematurely born. Hartridge and Griffith[11] in 1895 described a buphthalmic eye of an infant. The lens fibers were represented by a reticular network of homogeneous material. Adherent to the posterior surface of the lens and extending backward toward the disc was fibrocellular tissue without a hyaloid artery, embedded in a completely detached retina. The ciliary processes were elongated. The subretinal effusion was fibrinous and densely infiltrated with cholesterine crystals. There was a peripheral anterior synechia closing the angle. Rockliffe[12] in 1898 described a case of complete detachment of the retina causing a yellowish white mass behind the pupil with blood vessels on its surface. There were posterior synechiae. Clarke[13] in 1898 described pseudoglioma clinically in 3 siblings, one of which was feeble-minded. There was apparently a detachment of the retina and perhaps persistent

hyaloid artery in these cases. Ridley and Marshall[14] described a left eye with a retinal fold on the nasal side involving the ciliary body and iris which was joined to the lens by connective tissue. There was also a persistent hyaloid artery springing from one of the retinal vessels 4 mm. from the disc and between the disc and the retinal detachment not running in the fold. Flemming and Parsons[15] described the microphthalmic right eye of a 6-month-old child who had a retrolental dense vascularized mass which microscopically showed a persistent hyaloid artery. Collins[16] presented several cases of posterior subcapsular cataract with retrolental membrane and persistence of the hyaloid artery. Brickner[17] reported an eye with persistent anterior and posterior vascular sheath of the lens. Gifford and Latta's[18] third case was a persistent hyaloid artery in one eye of an 11-year-old boy which extended from the disc to an oval opacity below the center of the lens. Lent and Lyon[19] described the case of a 7-year-old girl in which there was arborization of blood vessels over the posterior surface of both lenses, but described no membrane. The vessels appeared to come from the periphery. The vision was 20/100 in each eye. There were no remnants of the hyaloid artery. They also described another case of opaque retrolental membrane in one eye with vessels radiating from the center. Lachman's[20] case was a 3½-month-old white male with enlarged eyes which were removed because of suspected glioma. Both retinae were detached and matted together in a funnel-shaped mass separated from the choroid by a large mass of blood and serum. There was a cyclitic membrane extending across the eye behind the lens which had a posterior subcapsular cataract. The subcapsular epithelium of the lens extended almost to the posterior pole. Pollock[21] described the eye of a 3-month-old baby which had an increasingly dense retrolental membrane and persistent hyaloid artery. The ciliary processes were drawn into the retrolental fibrovascular mass. Lane[22] described a unilateral case of posterior vascular lenticular membrane with persistent hyaloid artery.

He also described another clinical case with a vascular membrane behind one lens and an avascular one behind the other, and 3 other microphthalmic eyes with a vascular retrolental mass into which the ciliary processes were drawn. There was a patent hyaloid artery. Lloyd[25] described a retrolental dense white membrane with a red spot in it in a 5-month-old child. He also described the microscopy of Pazanelli's case which had a disc of connective tissue on the posterior lens surface with a remnant of the hyaloid artery.

However, Terry[26] in 1942 first called attention to the frequency of the condition in prematurely born infants which he called "retrolental fibroplasia." He felt that the condition in full-term infants was present at birth and often unilateral, while that in premature infants developed after birth from 4 to 6 months and was likely to be bilateral. In a series of articles[27-31] he described cases, treatment and experimental work, attempting to reproduce the condition. He stated that his cases showed to a variable degree the following principles:

1. Persistence of all or some part of the hyaloid vascular system.
2. Embryonic connective tissue growth behind the lens referred to as fibroplasia.
3. Persistence of the fibrillar fetal character of the vitreous.

Reese and Payne[32] believed the same lesion may occur in both premature and full-term babies, and felt that it was due to persistence and hyperplasia of angioblastic remnants of the primary vitreous. They felt that the condition was congenital. Reese[33] felt that at least the matrix of the lesion is present at birth and consists of hemangiomatous-like tissues around the base of the vitreous with accompanying hemorrhage, organization and detachment of the retina.

Krause[34] described 18 cases in detail with similar ocular findings but with additional neurologic pathology which he felt made up a syndrome present at birth which he called "congenital encephalo-ophthalmic dysplasia." The principal lesion was an abnormality of the retinal and cerebral neural

ectoderm. Cordes[35] has summed up the papers of these recent authors.

In a posthumous paper, edited by Zacharias, King, Dunphy and Kinsey, Terry[36] described the beginning of the abnormality after birth as he saw it from 3 cases. It began as a small opaque spot posterior to the crystalline lens which might be the periphery and spread in all directions. He therefore believed that it signified a reopening of the hyaloid arterial system.

The Owenses[37] were the first to systematically examine premature babies at intervals to determine the time of onset of the retrolental membrane. From July, 1945, to June, 1947, they followed 214 premature infants and found it present in none at birth. They watched the development of the lesion in 9 cases. All remains of the hyaloid system had disappeared before onset of the disease in all cases. The disease was not the result of persistence of the hyaloid artery. They believed that it developed after birth in normal eyes.

My curiosity regarding the time of incidence and the nature of the pathology of the condition was aroused by the apparent hopelessness of any known treatment of retrolental fibroplasia in my own cases, and the fact that I had seen 2 premature babies while they were still in the nursery and noted no ocular abnormality but who subsequently developed retrolental fibroplasia. I began a program in January, 1948, which is still going on, but for the purposes of this paper, ends with babies born before October 1, 1948. Once each week I have examined all babies who were in the premature nursery of the Hartford Hospital until their discharge. Therefore, some babies were seen within a few hours of birth, while others were not seen until nearly a week old. The small babies were followed much longer in the hospital than the larger ones who were sent home as soon as their general condition permitted. An attempt was made to recall these babies back to an out-patient follow-up clinic at sufficiently frequent intervals to watch the progress of these babies to a

safe period of ocular development, or as long as ocular pathology was present. If no indication of permanent pathology has appeared by 3 months, it seems safe to assume that it will not.

The method of examination is important because of criticism that adequate examination cannot be done without general anesthesia, which is not practical for routine examination, nor necessary at this age to obtain a fairly adequate ophthalmoscopic view of even the anterior fundus. An hour

TABLE 1.—AGE-WEIGHT RELATIONSHIPS (CONVERSION METRIC TO ENGLISH WEIGHTS)

Period	*Gestation*	*Length*	*Weight*
3 weeks	..	3 mm.	..
4 weeks	1 lunar month	7 mm.	..
5 weeks	..	12 mm.	..
6 weeks	..	17 mm.	..
7 weeks	..	26 mm.	..
8 weeks	2 lunar months	40 mm.	−1 gram −1/28 oz.
9 weeks	..	40 mm.	..
10 weeks	..	60 mm.	..
12 weeks	3 lunar months	90 mm.	−12 gram−3/7 oz.
16 weeks	−4 lunar months	160 mm.	−60 gram−2⅛ oz.
18 weeks	..	200 mm.	−120 gram−4¼ oz.
20 weeks	−5 lunar months	250 mm.	−190 gram−6¾ oz.
24 weeks	−6 lunar months	300 mm.	−280 gram−10 oz.
28 weeks	−7 lunar months	350 mm.	−800 gram−1 lb., 12 oz.
30 weeks	..	375 mm.	−1020 gram−2 lb., 4 oz.
31 weeks	..	390 mm.	−1361 gram−3 lb., 0 oz.
32 weeks	−8 lunar months	400 mm.	−1644 gram−3 lb., 10 oz.
34 weeks	..	425 mm.	−1814 gram−4 lb., 0 oz.
36 weeks	−9 lunar months	450 mm.	−2268 gram−5 lb., 0 oz.
40 weeks	−10 lunar months	500 mm.	−3232 gram−7 lb., 2 oz.

before the examination a drop of a paredrine 1% and homatropine 4% mixture is placed in the baby's eyes by a nurse. This gives adequate dilation—5 mm. or more in most cases. For the examination, 2 nurses hold the child on the examining table; one at the head pulls the child's hands above its head and cups the head between its arms to hold it still. The other nurse holds the child's legs with one hand and with the other holds a small retractor, or muscle hook, pulling down the lower lid. The observer retracts the upper lid with the instrument and holds the ophthalmoscope in his other

hand. There is very little movement of the eyes of small babies when held thusly. After 3 months of age examination is not always satisfactory because of ocular movement.

The reader is referred to the following authors for reference for embryology: Reese,[32] Mann,[38, 39] Duke-Elder,[40] Salzman,[41] Haden,[42] Troncoso[43] and Williams.[44]

EYES OF THE PREMATURE INFANT

The difference in the eyes of the premature infant and the term infant is directly proportional to the amount of prematurity. Owens and Walsh[45] have described these eyes very well. During the period of this study I examined 177 newborn premature babies. There were 65 babies 5 pounds or over, approximately 36 weeks or more. There were 78 babies between 4 and 5 pounds, 33 to 36 weeks. There were 28 babies between 3 and 4 pounds, 31 to 33 weeks. There were 4 babies between 2 and 3 pounds, 29 to 31 weeks. There were 2 babies under 2 pounds, 29 weeks or less.

Although birth weight is not a definite criterion of the period of gestation, it seems to be more accurate than the estimated time reckoned from the last menstrual period. Occasionally from the appearance of the eyes and body formation, one would surmise that a baby may be older or younger than his birth weight would indicate. In twins one might be placed in the premature nursery because of small size while the other might not. In most babies the appearance was similar in both eyes, although one eye was often slightly in advance of the other in the progress to the full-term appearance.

At birth all babies under 4 pounds had some remnant of the embryonic pupillary membrane. Under 3 pounds this is a complete circlet of arcades which, however, does not prevent a view of the interior of the eye. Gradually the arcades disappear unevenly, some parts at the center and others at the periphery, and some of the central ones fuse so that as a terminal event perhaps 1 or 2 thin strands are stretched

across the pupil with a few small peripheral loops. The pupillary remnants are more likely to remain longer in babies who develop retrolental fibroplasia in any weight group. In most very small babies at birth one could not see any details of the interior because of a very hazy vitreous. This cleared gradually in the circumpapillary area first and then anterior to the disc where there may be a remnant of Bergmeister's papilla. The peripheral vitreous was hazy in all prematures to a certain extent, especially in the smaller ones. The haze was a nebulous gray and very dense in the anterior periphery so that it obscured the retina and vessels running to it. Because of this, one would not be able to tell what was in the anterior fundus no matter under what ideal conditions the examination was done.

The hyaloid artery, either complete or its remnants, was present often in the smaller babies. It may or may not have had a concomitant pupillary membrane. The central vitreous was usually hazy when the artery was present. In no cases was blood evident in the vessel. The central portion usually disappeared first, then the anterior and lastly the posterior where it stuck up like the end of a church steeple from Bergmeister's papillae. In no case did the artery become patent or persist until the manifestations of retrolental fibroplasia became evident.

The caliber of the retinal vessels in general was in direct proportion to the length of gestation. In the very small babies sometimes the vessels would be scarcely visible at the disc and could be traced only a short way from it. They gradually increased in caliber and visibility to the periphery until in a week or two they became normal in size and extended as far as one could see behind the peripheral vitreous haze. However, the retinal vessels were tremendous at birth in one infant of 2 pounds, 14 ounces, but had shrunk to normal by the third week. This child did not develop retrolental fibroplasia. In premature infants the retinal vessel caliber was quite variable from time to time in the same infant for no

TABLE 2.—EYE FINDINGS IN PREMATURE BABIES

	Birth Weight in Pounds	During 1st Wk.		During 2nd Wk.		During 3rd Wk.		During 4th Wk.		During 5th Wk.		During 6th Wk.		During 8th Wk.		During 10th Wk.		During 12th Wk.		During 14th Wk.		During 16th Wk.		During 5th Mo.		During 6th Mo.		During 7th Mo.	
		Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition	Total No. Examined	No. with Condition
Pupillary Membrane	1–2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	2	0	2	0	2	0	2	0	0	0	0	..
	2–3	4	4	4	4	4	3	4	1	4	1	4	1	3	1	3	1	3	1	2	0	3	0	2	0	2	0	0	..
	3–4	17	17	23	14	23	8	21	6	18	3	17	6	12	4	6	3	8	3	8	1	9	0	9	1	7	0	6	..
	4–5	49	25	63	19	49	10	44	5	15	4	20	2	15	1	11	0	10	0	6	1	4	0	10	0	2	0	3	..
	5	36	12	46	4	41	4	16	3	4	1	9	1	3	0	5	0	3	1	3	0	3	0	0	0	2	0	1	..
Hyaloid Artery	1–2	2	1	2	0	..	0	..	0	..	0	..	0	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	2–3	4	3	..	2	..	2	..	1	..	1	..	1	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	3–4	17	5	..	8	..	2	..	2	..	1	..	0	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	4–5	49	4	..	4	..	4	..	4	..	0	..	0	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	5	36	0	..	0	..	0	..	0	..	0	..	0	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Vitreous Haze	1–2	2	2	..	2	..	2	..	1	..	1	..	1	..	1	..	1	..	1	..	1	..	1	..	0	..	..	..	..
	2–3	4	2	..	2	..	2	..	1	..	3	..	2	..	3	..	3	..	3	..	2	..	2	..	1	..	..	..	..
	3–4	17	15	..	16	..	12	..	7	..	5	..	10	..	6	..	1	..	1	..	1	..	3	..	1	..	..	..	..
	4–5	49	27	..	13	..	12	..	10	..	2	..	6	..	2	..	0	..	1	..	0	..	0	..	0	..	..	..	..
	5	36	18	..	12	..	8	..	1	..	0	..	1	..	0	..	1	..	0	..	0	..	0	..	0	..	..	..	..
Large Retinal Vessels	1–2	2	0	..	0	..	1	..	1	..	1	..	1	..	2	..	2	..	1	..	0	..	0	..	1	..	..	..	..
	2–3	4	1	..	1	..	0	..	2	..	2	..	2	..	0	..	0	..	1	..	0	..	0	..	0	..	..	..	..
	3–4	17	3	..	2	..	6	..	7	..	7	..	7	..	3	..	1	..	2	..	1	..	1	..	1	..	..	..	..
	4–5	49	6	..	12	..	12	..	9	..	6	..	3	..	2	..	1	..	0	..	0	..	0	..	0	..	..	..	..
	5	36	5	..	2	..	3	..	2	..	0	..	0	..	3	..	2	..	0	..	0	..	0	..	0	..	..	..	..
Retinal Hemorrhage	1–2	2	0	..	0	..	0	..	0	..	0	..	0	..	1	..	2	..	2	..	2	..	2	..	2	..	..	..	..
	2–3	4	0	..	0	..	0	..	0	..	1	..	2	..	2	..	1	..	1	..	1	..	1	..	0	..	..	..	..
	3–4	17	1	..	0	..	0	..	1	..	1	..	2	..	2	..	1	..	3	..	1	..	2	..	0	..	..	..	..
	4–5	49	9	..	3	..	2	..	2	..	1	..	1	..	1	..	1	..	0	..	0	..	1	..	0	..	..	..	..
	5	36	5	..	1	..	0	..	0	..	0	..	0	..	0	..	0	..	1	..	0	..	0	..	0	..	..	..	..
Peripheral Pallor	1–2	2	2	..	2	..	2	..	2	..	2	..	2	..	2	..	2	..	0	..	1	..	2	..	0	..	0	..	0
	2–3	4	4	..	4	..	4	..	4	..	3	..	3	..	1	..	3	..	3	..	1	..	0	..	0	..	0	..	0
	3–4	17	16	..	19	..	16	..	7	..	5	..	8	..	5	..	5	..	4	..	4	..	2	..	5	..	3	..	1
	4–5	49	16	..	26	..	17	..	23	..	12	..	10	..	4	..	5	..	3	..	3	..	1	..	5	..	1	..	0
	5	36	15	..	28	..	20	..	6	..	3	..	3	..	5	..	1	..	2	..	2	..	2	..	0	..	1	..	0
Elevated Peripheral Retina	1–2	2	0	..	0	..	0	..	0	..	0	..	1	..	0	..	1	..	1	..	1	..	1	..	0	..	0	..	0
	2–3	4	0	..	1	..	1	..	1	..	1	..	1	..	0	..	2	..	2	..	1	..	2	..	2	..	2	..	1
	3–4	17	6	..	8	..	10	..	9	..	8	..	7	..	3	..	3	..	4	..	3	..	1	..	6	..	3	..	3
	4–5	49	13	..	14	..	16	..	7	..	7	..	3	..	3	..	6	..	1	..	1	..	2	..	0	..	0	..	0
	5	36	9	..	12	..	11	..	4	..	3	..	2	..	0	..	0	..	0	..	0	..	1	..	0	..	0	..	0

apparent reason. The vessels became very large in some infants during the first 4 or 5 weeks, but this was transitory and without tortuosity or aneurisms, but might be accompanied by opacification and elevation of the peripheral retina.

Retinal hemorrhages were rather rare at birth and were more frequent in the larger children but seemed to have no definite relation to the manner of birth. They were thin, uneven, spattered, throughout the fundus but were larger near the disc. They disappeared by the fourth week in all and usually absorbed with great rapidity. The fundus might be literally covered at birth but be free of blood in a few days. These retinal hemorrhages were evidentally traumatic and were unlike those of different pathology which will be described later. McKeown[46] and Edgerton[47] found a higher frequency but the hemorrhages probably had already disappeared in some of my cases which were not examined until several days after birth. Also, in many cases the media was too hazy to see any fundus details at a time when these hemorrhages may have been present.

In premature infants the peripheral retina is gray or white, which seems to be due to a lack of transparency, but may be due to subretinal fluid beneath an incompletely coaptated retina. It is not due to lack of pigment in the fundus. This is not well illustrated in Table 2 because in many newborn prematures the peripheral fundus cannot be seen at all because of the haziness of the central media. In many prematures the peripheral vitreous does not clear for some weeks after the central vitreous has cleared, and the retinal vessels, as they course to the periphery, disappear behind a cloud. The pallor and elevation are likely to be most marked in the lower pole. At times the peripheral retina is actually a pure white and completely opaque. In these cases the peripheral retina may be more than normally elevated, as it is in most premature retinas which appear gray. The more elevated retina with the other features of retrolental fibroplasia may be just an exaggeration of this normal process.

The physiologic cupping of the optic discs may be present at 2 or 3 weeks. The optic disc is quite pale, especially in the smaller prematures. This seems due principally to lack of development of the capillaries on the disc. Often the fundus is quite pale as well, due to lack of pigment development in the pigment layer of the retina and choroid apparently. The larger choroidal vessels can be seen quite distinctly but the choriocapillaris appears absent or poorly developed in the smaller infants. In negro babies, however, there is more pigment in the fundus.

There was a good deal of variation in the refraction of the premature babies which principally depended on the clarity of ocular media. The index of refraction increased with the amount of opacity of the media. Therefore, since most infants had some haziness of the media at birth they were somewhat myopic up to about 10 diopters. In general, the more premature the more the child was myopic at birth. This myopia decreased as the media became clearer and the child older. Some infants became hyperopic in a few weeks up to about 8 diopters. Most of those who developed retrolental fibroplasia even to a mild degree became quite myopic, even though the media became clear. This may be due to lack of lenticular development.

INCIDENCE

Of the 177 babies in the premature nursery between January and October first, who survived to leave the hospital, none had retrolental fibroplasia at birth. There were 10 who developed sufficient ophthalmic dysplasia to come under the terminology of retrolental fibroplasia, although not all developed a retrolental membrane, as will be seen from Table 3. I have included as retrolental fibroplasia all those who had severe vitreous hemorrhages, or other permanent pathologic changes as the result of the process known as retrolental fibroplasia. The incidence in this series is higher than those in any previously reported because our incidence may be

actually higher at the Hartford Hospital and, also, in other series the babies may not have been observed frequently enough or with technique to see relatively minor pathology.

Certainly statistics based on anything but systematic period examinations of the whole series are not satisfactory because children with minor retinal detachments, or folds, might not be sent to an oculist until poor vision in one or both eyes was discovered at school or other examinations and then might be called something else. There is question whether Cases 1 and 10 should be included in this series because they did not develop retrolental membranes, or permanent gross pathologic changes, and they are too young to evaluate properly their retinal receptive elements by testing their central and peripheral visual acuity. Case 2, while not in the series because of subminimal pathology, just missed developing the disease. In addition, some babies did not return for follow-up, in spite of repeated attempts to have them do so, who may have developed quite definite permanent pathology unrecognized or brought elsewhere for ophthalmic consultation. Also, this series comprises too few numbers to represent a perfectly true picture of incidence, but is large enough and accurate enough to demonstrate significant statistics.

TABLE 3.—INCIDENCE OF RETROLENTAL FIBROPLASIA BY BIRTH WEIGHT

Number Babies	*Birth Weight*	*Gestation Period*	*No. With R.F.*	*Percentage With R.F.*
65	5+ lbs.	36 wks.	0	0
77	4 to 5 lbs.	33 to 36 wks.	2	2.6%
22	3 to 4 lbs.	31 to 33 wks.	4	14.3%
5	2 to 3 lbs.	29 to 31 wks.	2	40.0%
2	1 to 2 lbs.	29 wks.	2	100.0%

Of the 177 babies there were 65 babies 5 pounds or over, about 36 weeks gestation or more, of which no babies developed retrolental fibroplasia. There were 77 babies between 4 and 5 pounds approximately 33 to 36 weeks gestation, of which 2 developed the condition. There were 28 babies be-

tween 3 and 4 pounds, 31 to 33 weeks gestation, of whom 4 developed the condition. There were 5 babies between 2 and 3 pounds, 29 to 31 weeks, of which 2 developed retrolental fibroplasia. There were 2 babies between 1 and 2 pounds, under 29 weeks, both of whom developed the condition.

This incidence is in general agreement with the Owenses' series who have seen no cases in babies over 4½ pounds. They did not report cases they did not follow for 6 months, some of whom may or may not have had retrolental fibroplasia. Terry's 7 reported cases were all well under 5 pounds. Krauses' 18 cases were under 5 pounds, with the exception of 5 (Cases 6, 9, 10, 11, 14). Of Reese's and Payne's, 30 were under 5 pounds, or 9 months, and 20 were full-term or over 5 pounds. In the earlier reports, where the significance of birth weight and gestation period were not known to be significant, the data is too meager to evaluate, although Nettleship[4] did state that his case was born at 8 months. Except for the series of the Owenses and this series, one cannot be sure whether or not the pathology was present at birth and whether these cases are an acquired lesion, or whether they are due to arrest or aberrations of development. One may state quite definitely that the incidence increases in proportion to the prematurity and that the acquired form is rare in these infants over 5 pounds at birth.

Of 30 cases of retrolental fibroplasia I have examined, not in this series, only 2 were born at term. One was born at 38 weeks, 1 at 37, 18 between 30 and 35 weeks, and 8 between 27 and 29 weeks. Of these 30, 3 weighed over 6 pounds, 2 were over 5, 6 over 4, 7 over 3, and 11 over 2 pounds, and 1 of which I do not know the birth weight. 15 were males and 15 females. 5 were twins, and of these sets the other twin was normal in 4, and had died at birth in the 5th.

DEVELOPMENT OF RETROLENTAL FIBROPLASIA

It is a little difficult to state what is normal development of a premature eye and where pathology begins. In most of

these infants the retinal vessels were small at birth, and the vitreous somewhat hazy. The vitreous became clearer and the retinal vessels increased to normal size in those who developed subsequent pathology, as did the eyes of those who continued to develop normally. In about a third of the babies under 4 pounds, and fewer in those over, the retinal vessels became dilated to twice normal size for a week or two and the whiteness of the peripheral retina seemed to increase. This vessel dilation might even be present at birth, or as late as the eighth week, but the average greatest dilation was about the fourth week, although earlier in the larger babies. These occurrences usually pertained to those who developed retrolental fibroplasia as well. However, in the latter the dilation of the veins, especially, increased to 3 or 4 times normal size, and at the same time the vessels became tortuous. This tortuosity became very marked and heralded trouble. The dilation and tortuosity continued to the extreme periphery where at the same time the whole retinal periphery or certain quadrants became very white and more elevated, which was most pronounced in those areas where the vessels were the most dilated. Frequently in the midperiphery arteriovenous communications developed in the intervening capillary network, some of which became so large that the main vessels beyond this point decreased markedly in size. At this time the pupil did not dilate well with the usual eyedrops for examination, or with atropine. If any embryonic pupillary membrane remained, the strands became thick and prominent. At this time, also, numerous small striate or oval retinal hemorrhages appeared. The central and peripheral vitreous became definitely hazy.

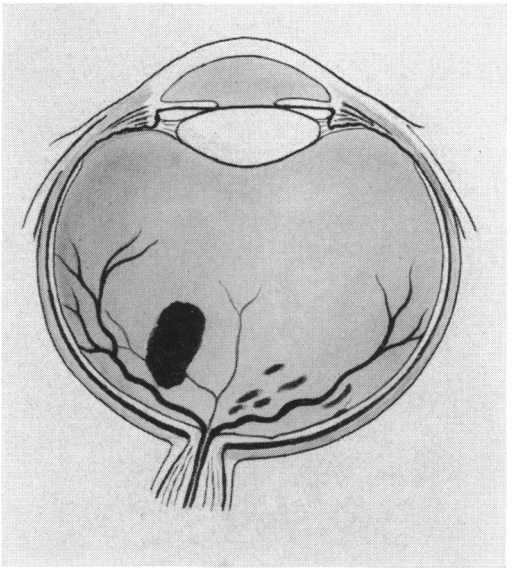
At this point there are 2 distinct ways in which the permanent pathology may develop, which I shall term the *central type* in which the membrane develops through the central vitreous, and the *peripheral type* which apparently is principally enlargement of the peripheral retinal detachment with extension of vascular tissue from the detachment to the

posterior aspect of the lens. Both types may be present in the same eye. All of mine, except Case 7, have been the central type, while the Owenses have seen only the second.

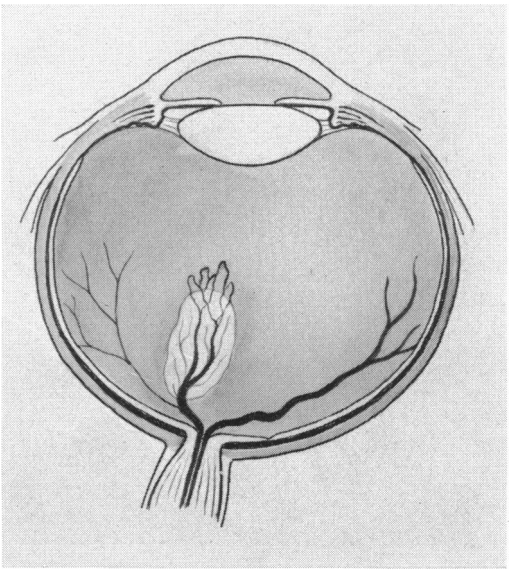
In the central type there is a nebulous hemorrhage into the posterior vitreous usually not far from the disc, which is the result of leakage from the tremendously dilated retinal vessels. This occurs from the ninth to the twelfth week. Organization of the hemorrhage with vascularization from the retinal vessels takes place. Further hemorrhage forward into the vitreous from the newly formed proliferating vessels may occur or the vitreous vessels may grow forward, almost unsupported, by capillary loop formation. However, in Case 2 the vitreous hemorrhage never became vascularized.

The hemorrhage with the newly formed blood vessels migrates centrally to the area of the disc, perhaps because of the natural channel of least resistance provided by Cloquet's canal and the tendency of vessels to extend from their source of origin at the disc. Intervascular tissue appears in these vitreous hemorrhagic masses which is at first pink but gradually whitens as it solidifies. These angioblastic columns gradually reach the posterior lens surface by capillary loop formation usually below and to one side of the center. The lens was reached earliest in the thirteenth week in a 2-pound baby and in the 16th week in a 4-pound baby. The vessels with the intervening angioblastic tissue then spread out on the posterior lens surface covering part, or all, of the pupillary area. The retrolental membrane, at least on the side on which it develops, extends to and fuses with the zonule, ciliary processes, and sometimes peripheral retina. The vitreous in the area of the zonule may change its character and coagulate. Usually, even if complete, the distribution of the retrolental membrane was somewhat patchy so that a fundus reflex could be obtained in certain areas.

The vitreous columns during this time gradually become contracted and white with only a few large blood vessels in them. They cover the whole disc and appear like extensions



A

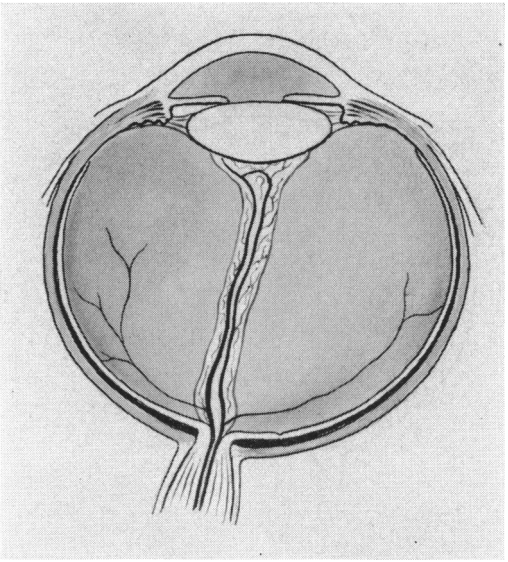


B

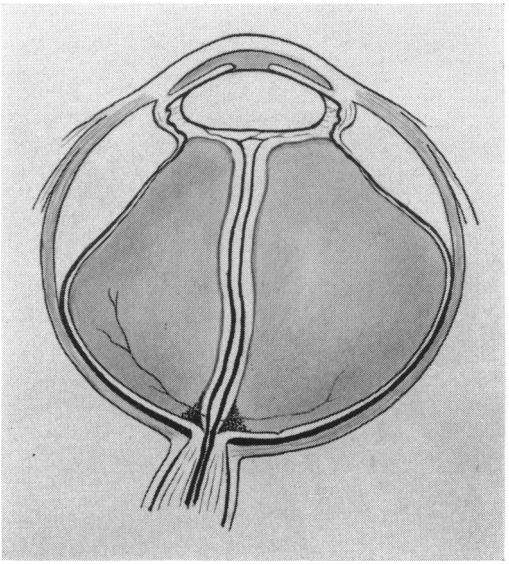
Fig. 1.—Diagramatic illustration, showing mode of formation of central type of retrolental fibroplasia.

A. The retinal vessels are dilated. Retinal hemorrhages and a large vitreous hemorrhage have appeared.

B. The vitreous hemorrhage has migrated centrally, organized, become invaded by vessels from the retina, and now arcades extend farther forward.



C



D

Fig. 1 (cont.).—Diagramatic illustration, showing mode of formation of central type of retrolental fibroplasia.

C. A vascularized angioplastic column extends to the lens. The retinal vessels have shrunk.

D. The column has become white. The retrolental membrane has spread out to enmesh the ciliary processes and retina. It is now contracting and detaching the retina, pushing the lens forward. There is retinal pigment about the base of the column.

of the optic nerve forward. The retinal vessels meanwhile shrink, perhaps because the parisitic vitreous vessels obtain most of the blood from the central retinal artery. The retinal vessels in some cases become very minute, or become invisible, and do not increase in caliber unless there is considerable regression of the vitreous angioplasia. Reese[33] probably has not observed his cases early enough to see the angiomatosis of the retinal vessels. He, therefore, feels that attenuation of the retinal vessels is the only feature of the disease, having seen it only in this late stage. Sometimes there is quite a large lake of blood on the retina about the base of these columns lasting for several weeks. In time a considerable ring of black, probably retinal, pigment may develop eventually about the disc. The choroid in these cases remains quite pale, at least during the active stage, and in some cases the choroidal vessels appear to be dilated at the same time as those of the retina. The vitreous during this whole process is often extremely hazy, probably due to the permeation of blood cells through it, but there may be a physico-chemical alteration in its structure as well, which could be the etiology of the whole pathologic process.

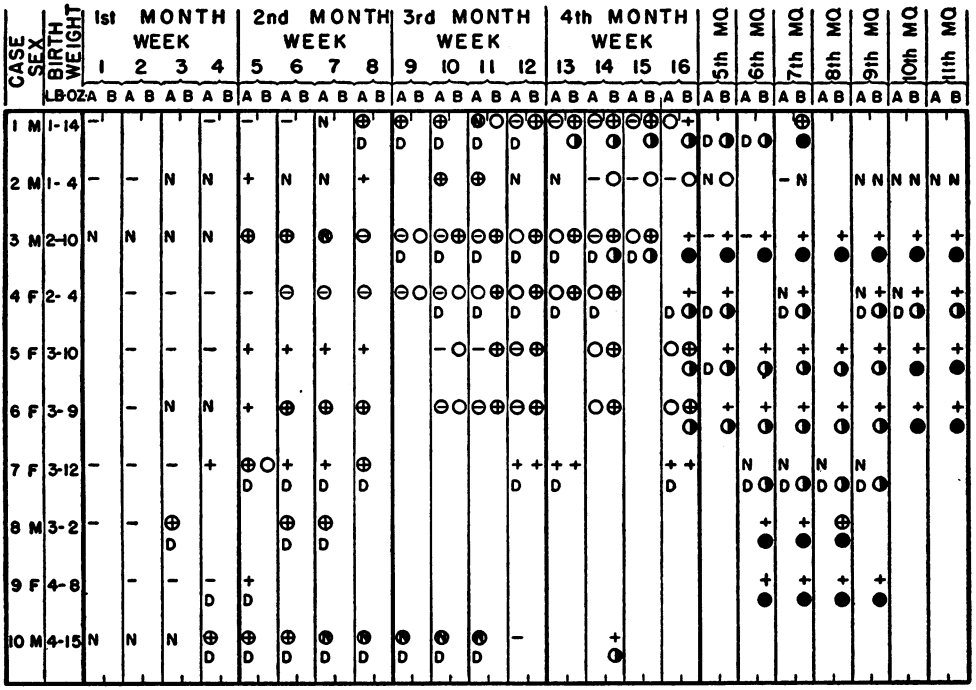
Only one of my cases, Case 7, is the purely peripheral type. This case was seen also by the Owenses in consultation during the 11th week. On 2 occasions an attempt was made to examine some of these babies under rectal pentothal anesthesia as out patients. In all these cases under pentothal the pupils became so contracted that the examination was unsatisfactory, even though mydriatics and cycloplegics were used. This was especially true in Case 7. In most of the cases of the central type, peripheral retinal folds or detachments were visible when the vitreous cleared sufficiently to make out any fundus details.

The active pathology appears to last from approximately the 3rd or 4th week to about the 5th month. However, in Cases 5 and 6, twins, the activity was resumed in the 10th month in the right eye in both, evidenced by extension of the

retrolental membrane which became quite pink due to vascular dilation, which gradually subsided in about a month.

TABLE IV

GRAPH OF TIME OF ONSET OF PATHOLOGY IN CASES OF RETROLENTAL FIBROPLASIA



A COLUMN = RETINAL CHANGES
− = SMALL } RETINAL VESSELS
N = NORMAL
+ = LARGE
O = HEMORRHAGE
D = DETACHMENT

B COLUMN = VITREOUS CHANGES
+ = VESSELS IN VITREOUS OR IN MEMBRANE
◑ = PARTIAL RETROLENTAL MEMBRANE
● = COMPLETE RETROLENTAL MEMBRANE
⊕ = CATARACT
O = HEMORRHAGE

IN EACH INSTANCE THE GRAPH INDICATES THE MORE SERIOUSLY INVOLVED EYE.

After the period of activity has passed there tends to be a regression of the pathology. Retinal detachments subside, or the sides tend to approximate each other to become

folds. Retinal hemorrhages disappear. The vitreous clears and the vitreous columns contract in diameter and the vessels contained shrink, while the retinal vessels may increase in size. If the retinal columns have not extended to the lens, they retract and atrophy a great deal and may practically disappear, to be represented by an almost colorless fibrillar structure in the vitreous, so that in later life few if any recognizable remnants of this pathology remain. Probably, even quite a good deal of actual retrolental membrane is not incompatible with a fair amount of vision, if adequate visual openings remain, or form in it, if the retina has not been hopelessly damaged by loss of its blood supply or become largely detached. The vessels in the retrolental membrane tend to diminish in caliber and disappear as the period of active inflammation passes. If the vessels originate in a vitreous angioblastic column, they often appear to radiate from the center of the membrane. If, however, the retrolental membrane and vessels grow out from the periphery, I would think that they would appear to converge toward the center as some well-formed cases I have seen do. However, I have not seen a severe case of this type in its formative stages, so this is only supposition. When the vessels have atrophied, it is difficult to tell whether the origin is central or peripheral because the caliber is not much greater nearer the point of origin than farther away from it. In most of my cases the more extensive pathology is on the temporal side and the macula is probably damaged or poorly developed. The right eye of most of the babies I have observed has more involvement than the left, but usually, at least in the early stages, there is not much difference between the eyes in the development of the pathology.

If the disease has progressed to the point of a complete, or almost complete, retrolental membrane before the active stage has passed, more pathology may develop due to secondary changes in the existing lesions. The retrolental membrane contracts and increases the retinal detachment by its pull.

The ciliary processes are pulled centrally to give the appearance of the so-called "dentate processes." Posterior synechiae tend to form during the period of activity. Probably the resulting iris bombé and the forward movement of the lens due to the drumhead-like tightening of the retrolental membrane stretched behind it from the ciliary body causes the dome-like appearance of the iris, shallow anterior chamber, and secondary glaucoma. If the iris and lens is pressed against the center of the cornea, a corneal opacity tends to form. In some cases a cataract forms due to rupture of the posterior capsule. The rupture is probably the result of squeezing and wrinkling of the posterior capsule. In these cases the anterior lens epithelium has been found extending to the posterior aspect of the lens which may be the result of the pulling action on the sides of the lens capsule of the contracting and retracting retrolental membrane. In any advanced case the globes remain microphthalmic.

CASE REPORTS

CASE 1.—A 1-pound, 14-ounce white male was born July 28, 1948 at 28 weeks' gestation with poorly aereated lungs. On July 29, 1948 a complete embryonic pupillary membrane existed which remained until August 26, 1948. The vitreous was very hazy at first but gradually cleared. The retinal vessels were extremely small. There were no hyaloid vessels. On September 16, 1948 the retinal veins were dilated and tortuous with intercommunicating aneurisms and retinal hemorrhages. The peripheral retina was very elevated. On September 30, 1948 a vitreous hemorrhage was present in each eye, springing from the lower retinal vessels near the disc into which vessels proliferated from the adjacent retinal vessels. This angioblastic tissue gradually advanced to the lenses by October 28, 1948. The retrolental membranes gradually became avascular. Although the membrane covered only a part of the pupillary area, the fundus details could not be made out well when seen on December 31, 1948 because of the inability to dilate the pupils and the hazy vitreous.

CASE 2.—A 1-pound, 14-ounce white male with hypospadias born February 6, 1948 at 38 weeks' gestation as a twin. The other weighed 5 pounds, 13 ounces and developed normally. A fairly

complete pupillary membrane remained but disappeared by March 11, 1948. The retinal vessels were small, but enlarged to normal by March 25, 1948. On April 22, 1948, in the right eye, a large bright hemorrhage was noted spiraling out from the disc in a ribbonlike form in Cloquet's canal almost to the lens. This gradually disappeared by September 9, 1948 except a few string vitreous opacities as a remnant. The left eye remained normal.

CASE 3.—A 2-pound, 10-ounce male infant was born January 5, 1948 at 31 weeks' gestation. Well-formed embryonic vascular pupillary membranes were present and small posterior hyaloid stumps until February 5, 1948. On February 12, 1948 the vitreous became slightly hazy, the retinal vessels became dilated and tortuous, and there were numerous retinal hemorrhages. A large preretinal hemorrhage was present in the right eye below the disc. The vitreous became very hazy in both eyes apparently due to blood. The peripheral retina in both eyes, especially below and above, was very white and elevated with dilated vessels on its surface. On March 25, 1948 a pink vascular central mass could be seen extending from the disc almost to the lens in either eye. It reached the lens in the right eye on April 8, 1948, but not until May 6, 1948 in the left eye where it reached the lens in the nasal periphery. The retrolental vessels in the right eye gradually arborized over the whole posterior surface of the lens with the formation of a dense white membrane, becoming avascular by November 19, 1948. The fundus in the left eye could be seen better as the vitreous cleared showing an avascular retina with a white vascular column extending from the disc to the nasal side of the lens. There was nystagmoid searching movement on January 7, 1949 but the child seemed to follow light.

CASE 4.—A 2-pound, 4-ounce white female of 27 weeks' gestation was born January 25, 1948. Pupillary vascular strands were present which lasted only a week. There was a complete avascular hyaloid artery in the right eye, present until February 19, 1948. There were hemangiomata of both legs.

The retinal vessels were initially very minute and remained so when numerous small striate hemorrhages were seen on the retina on March 3, 1948 which lasted for 2 weeks when they were replaced by fibrotic-appearing exudate. The vitreous became more hazy but on April 8, 1948 a ribbonlike pink membrane extended forward from the naso-inferior vitreous of each eye, and the peripheral retinae were considerably elevated everywhere. The pupils did not dilate well. On May 20, 1948 the right vitreous membrane had extended

to the nasal side of the lens and covered half of it, and in the left eye was just in contact with the lens nasal to center. In the left eye most of the upper half of the retina was detached. By September 23, 1948 the vascular vitreous membranes could be seen extending as columns from the discs which were surrounded with black pigment, to the posterior surfaces of the lenses. There were small retinal vessels present. On December 31, 1948 the vitreous was quite clear. No retinal detachments could be seen, but there were gray nebulous exudates scattered over the left retina. The membranes had regressed somewhat on the posterior lens surfaces. The mother said the baby could see and pick up things.

CASE 5.—A white female identical twin of 3 pounds, 10 ounces was born January 28, 1948. There were marked pupillary membranes, the vitreous was hazy and the retinal vessels were very small. On February 19, 1948 the retinal vessels became large and tortuous. Intercommunicating retinal aneurisms were seen the following week, and the pupillary vascular loops were very dilated. The baby was discharged from the hospital and not seen again until April 3, 1949 when there were dense vascular membranes with fimbrialike foreward extensions in the vitreous projecting from the region of the discs and just touching the lenses nasally. The baby was given oxygen but contracted virus pneumonia and was very sick for 6 weeks. On June 10, 1948 the vitreous tissue had contracted. A retinal fold developed in the left eye temporally. On November 19, 1948 the posterior surface of the right lens was completely covered with a well-vascularized membrane, indicating reactivity, while the left eye remained unchanged. On January 21, 1949, under ether examination, there was a dense retrolental membrane in the right eye in which the activity had subsided. In the left there was a small Mittendorff's dotlike opacity below and nasal to the center of the lens which was not attached posteriorly. There were several veil-like membranes extending from the disc onto the retina a short distance containing blood vessels which extended from them onto the retina but there were no other retinal vessels. The mother believed that the child saw very well.

CASE 6.—A white female, the twin of Case 5, weighed 3 pounds, 10 ounces. The appearance of her eyes and their subsequent development were like those of her sister. The vitreous membranes were more spread out or looser however. There was some reactivity in the right eye at the same time as her sister but not as severe. On January 21, 1949, under ether examination, there was a fairly dense

retrolental membrane in the right eye which was thinnest in the upper nasal area. There was one thick pupillary embryonic strand. In the left eye the nasal third of the lens was covered with membrane which extended back to the nasal side of the disc which was surrounded with a heavy pigment ring. There were numerous apparently free, clear, cystlike vitreous bodies. There was a flat, dense, gray avascular membrane about 3 disc diameters size on the temporal retina. There were no retinal vessels. The retina was in place and the choroid appeared normal. The mother believed that this baby had very poor vision.

CASE 7.—A 3-pound, 12-ounce female was born at 33 weeks' gestation on April 1, 1948 with prominent pupillary membranes which remained only a week. The retinal vessels became dilated and tortuous in the fourth week with numerous retinal hemorrhages which did not extend into the vitreous. The retina, except for the central portion, became very elevated and white on the fifth week, and in the right eye quite bullous above and temporally. The retinal vessels became smaller by the thirteenth week. At the end of the fifth month a patch of avascular membrane was present on the back of the right lens in the upper temporal periphery, but did not spread. The pupils remained very small in spite of cycloplegia. A retinal fold could be seen in the left eye in the sixth month extending from the disc to the 2 o'clock periphery along the summit of which a large retinal vessel ran. On December 29, 1948 the upper half of the right retina was seen detached and the fold in the left remained unchanged. Vision seemed poor. The refraction was −10 in each eye.

CASE 8.—A white male of 3 pounds, 2 ounces was born June 6, 1948 at 28 weeks' gestation. There were complete pupillary membranes and the retinal vessels were very minute. The vessels remained fairly small, but very tortuous with numerous small retinal hemorrhages and a peripherally elevated retina below in both eyes on June 24, 1948. The pupillary strands were dilated and were unchanged when seen just before discharge from the hospital on July 29, 1948. The patient did not report to the clinic until November 12, 1948, when there was a rather thin, patchy retrolental membrane in both eyes with vessels arborizing from the center. There were dense posterior synechiae. There has been no change since.

CASE 9.—A white female was born on April 29, 1948 at 33 weeks' gestation weighing 4 pounds, 8 ounces. There were fine pupillary

vessels and a posterior remnant of the hyaloid artery in the right eye with a good deal of peripheral retinal elevation. On May 27, 1948 the retinal vessels became dilated and tortuous without hemorrhages, but on June 4, 1948 the stools were bloody without evident cause. She was discharged on June 6, 1948 and not seen in the clinic until October 21, 1948. There were transparent gray folds of retinal and ribbonlike masses of tissue in the vitreous running anteroposteriorly in which were blood vessels which rather loosely touched the lenses. The discs could not be seen. The globes were small. The eyes did not change. Mother was sure baby could see large objects.

CASE 10.—A white male was born on September 10, 1948 at 36 weeks' gestation weighing 4 pounds, 15 ounces. On October 21, 1948 the retinal vessels were dilated and tortuous with several arteriovenous aneurisms. There was a large hemorrhage in the 1:30 periphery of the right eye where the retina was very elevated. The left retina was spattered with hemorrhage. The dilation and tortuosity of the retinal vessels gradually subsided except for the upper periphery of the right eye. He was discharged from the hospital on December 3, 1948. On January 4, 1949, in the out-patient clinic, the vessels were of normal size and the retina was normal, but there was an artery which started at left disc coursing upward and temporally, ending in a colorless vitreous membrane attached to the lens.

CASE 11.—A white male was born on May 11, 1948 at 35 weeks' gestation, weighing 2 pounds, 15 ounces. His eyes were examined May 20, 1948. There was no pupillary membrane but there was an almost complete avascular hyaloid artery in the right and the retinal vessels were small. On June 10, 1948 the retinal vessels were becoming a little dilated and tortuous and this continued to increase, reaching its height on June 24, 1948, where the lower retina in each eye was markedly elevated with scattered retinal hemorrhages. However, the pathology subsided and the eyes were normal on November 23, 1948.

CASE 12.—A male infant of 18 months was seen November 8, 1940 because the right eye had movement and turned in at times. His birth weight was 2 pounds, 3 ounces at 30 weeks' gestation. There was horizontal nystagmus and an esotropia of 15 degrees of arc. In the right eye there was a complete avascular vessel running from the disc to the nasal periphery of the lens where there was an area of retrolental membrane. The fundi were best seen with −6. On November 4, 1946 his refraction was O.D. −7.00 S. 20/200,

O.S. −6.00 −1.50 × 160 20/20. There was no vitreous vessel in the right eye, but there was an apparently unattached anterior vitreous, colorless, weblike tissue and some connective tissue on the disc.

CASE 13.—A white female 9 months of age, weighing 2 pounds, 5 ounces at birth was seen on March 11, 1947 because of an alternating esotropia. Refraction was −8 in each eye. Vision appeared good. The fundus was normal.

CASE 14.—A white female was seen at 3 years of age on April 28, 1948 because the left eye had always turned in. Her birth weight was 3 pounds, 2 ounces at 6½ months' gestation. There was a left esotropia of 20 degrees arc with a slow horizontal pendular nystagmus. Fixation in left eye was questionable. Refraction was O.D. −10.00 O.S. −6.00 S. The fundi were normal. Glasses were ordered.

CASE 15.—A white female seen on December 1, 1945 at 12 years of age. She was in the 7th grade. Birth weight was 5 pounds, gestation period 8 months. The left eye turned in since birth. Refraction was O.D. −10.50 −1.00 × 25 20/30, O.S. −6.00 S 20/200. There was a left exotropia of 15 degrees arc. There was a sinuous white cord extending from the center of the right disc to the lens which branched into several translucent filaments before reaching it. There were 4 large extra papillary Colobomas with a ring of black pigment and white centers. The retinal vessels ran over them without alteration. There was a sinuous white cord in the left eye extending from the disc, but it ended in the midvitreous. There were 4 colobomas in the left, the largest of which covered the macula. There was no abnormal calcification of the skull by x-ray.

CASE 16.—A white male was seen on March 17, 1942 at 5 months of age because his mother noticed 2 months previously that his pupils were gray. Gestation period was 34 weeks. Under ether, there was a white vascularized column extending from each lens to the disc. The retinal vessels were small. Dr. Terry made a diagnosis of retrolental fibroplasia in 1946. Best vision was O.D. 3.00 S 3/200, O.S. 1.00 S 25/100 in 1947. In 1948 he was in the first grade of school and getting along well. There had been no change in the appearance of his eyes.

CASE 17.—A white male was seen at 4 months of age on July 25, 1938. He was of 32 weeks' gestation. He seemed to follow the light. On the back of the lenses was a dense white membrane which was vascular. There were posterior synechiae. There was no calcification of the skull but the sutures were slightly spread. Tension was

76 mm. Schiötz in the right and 48 mm. in the left. A bilateral trephining was done. The tension remained normal. In March, 1939 a series of needlings were begun on both lenses without a permanent opening in the membranes ever resulting. In April, 1940 a good deal of tissue was removed from the vitreous with a punch in the left eye. On probing, the vitreous cavity seemed filled with this tissue. The tissue was sent to the laboratory, but was lost. The child became completely blind and mentally retarded.

CASE 18.—A white male was seen December 11, 1945 at 10 months of age because his mother noted that his eyes crossed at birth and he never reached for anything. He was born at 32 weeks' gestation, weighing 2 pounds, 8 ounces. There were bilateral, dense cataracts without posterior synechiae. Repeated needlings were done in both eyes without obtaining a permanent opening because of a retrolental membrane which continued to close over. There was questionable light perception.

DISCUSSION

Undoubtedly retrolental fibroplasia is the basic pathology of many so-called congenital abnormalities described in the literature. Ida Mann[38, 39, 48, 49, 50, 51] has so ably presented the story of the embryology and developmental abnormalities of the eye in many publications. In the light of new knowledge of retrolental fibroplasia, many cases of retinal fold, septum frontale, vitreous cysts, retinal fibrosis, extrapapillary coloboma, and other pathology described by Weve,[52, 53] Theodore and Ziporkes,[54] Gartner,[55] Guerry,[56] Iles,[57] Coates,[58] Heine,[59, 60] Tillema,[61] Collins and Mayou,[62] DeVeer,[63] Beauvieux and Bessieres,[64] Canales,[65] Rosen,[66] Reese,[67] Van Manen,[68] Klien,[69] Levitt and Lloyd[70] and others may be clarified.

Although the Owenses and I have seen the beginnings of the development of retrolental fibroplasia only in infants under 5 pounds, it does occur in full-term babies, as evidenced by cases I have seen and those described in the literature. It may develop in much the same way in the mature infant and probably due to some of the same factors, although the apparent important factor of prematurity is not present. It is even possible that in these mature babies the same or similar

set of circumstances may be present *in utero*, as occurs in premature infants after birth, with the result that the condition is present at birth. Undoubtedly persistence of the hyaloid artery, congenital retinal folds, and falciform ligaments do occur as arrests, or aberrations of development, entirely unrelated to the retrolental fibroplasia seen in premature infants. Some of the delay in the knowledge of the progress of the disease has been the mistaken interpretation of the pathologic specimens. My thesis is somewhat weakened because none of my observed cases have died; thus pathologic specimens have been unavailable.

Since the disease has been present in both eyes of all those observed during its developmental stage, one might believe that this is a general disease which would cause other manifestations than the ocular ones. Krause's experience is different from that of most others who have observed large numbers of these cases, as Merrill King,[71] Frank Carroll,[71] Reese[71] and the Owenses.[71] I have seen cases who had clinically fully developed retrolental fibroplasia and serious abnormality of the central nervous system, and I am not sure but that they, like Krause's cases, are a different pathologic entity. Reese has stressed the frequency of hemangiomas in premature children. It is difficult to evaluate the intelligence and personality of blind children, but I have an impression, and it is only that many of these children are somewhat abnormal. Many of them seem to have a restless activity, an emotional instability, and an impish perverseness, which is more than the lack of vision would account for. Two of my cases had bloody stools during the period of dilated tortuous retinal vessels with retinal hemorrhages, which may indicate blood dyscrasia.

High myopia discovered at birth or shortly after, especially without familial background, can be suspected of being retrolental fibroplasia (Cases 12, 13, 14, 15, 16). Eames[72] has stressed the high incidence of defective vision in prematurely born children. It is possible that some cases previously classi-

fied as toxoplasmosis or congenital pigmentation of the retina, may be the result of retrolental fibroplasia after disappearance of most of the pathologic features except the retinal lesions (Case 15).

CLINICAL SYMPTOMS

The mother is often the discoverer of the pathology. The infant may pay no attention to people or movements which normal children do. A little later it is noticed that he does not reach for objects, or may sit hanging his head. Most of these children rub their eyes a great deal, which is a prominent symptom to the parents. A gray or white pupil may be noticed but this is usually a late sign, more likely to be noted by the pediatrician. Nystagmoid searching movements, which are usually irregular and horizontal of the pendular searching type, occur if vision is more than perception of light and yet without macular function. Strabismus is often the first noticed abnormality. Ciliary injection is noted if glaucoma occurs, which is a transitory feature in many of these cases. Later the eyes appear sunken and the corneae small from microphthalmia.

TREATMENT

Atropine begun as soon as the diagnosis is made, preferably at the stage of dilated tortuous retinal vessels, seems to be of some value in ameliorating the severity of the process. In the more advanced stage when the retrolental membrane forms it seems of more definite value in the prevention of posterior synechiae, with subsequent complications. I use ½% instilled once a day. The process seems to be inflammatory, involving the iris, ciliary body, vitreous, and retina, and cycloplegia seems the logical treatment and appears to be at least somewhat effective in preventing the latter complications of the anterior uveitis. Cases 8 and 9, who had no atropine until fully developed, have progressed to a much more serious condition than the other cases of the series who were given atropine during the acute phase. None of the cases of this

series have exhibited evidences of glaucoma. The glaucoma in these cases is probably due to forward movement of the lens against the iris and angle of the anterior chamber, caused by drumlike contraction of the retrolental membrane. Glaucoma is a late feature, is transitory, and probably by this time the secretory function of the ciliary body is damaged and indicates that the process has gone to a pretty hopeless state as far as vision is concerned anyway. In earlier cases than this present series, I have not felt that the glaucoma was benefited by pilocarpine.

Surgical therapy by trephining has not been satisfactory to Terry, nor in my hands either. Sealing of the vitreous vessels by Terry[26, 27, 31] was unsatisfactory. Attempted removal of the fibroplasia behind the lens was unsuccessfully attempted by Terry.[26, 27] I did repeated needlings in 2 cases (16 and 17) without visual benefit; the first before I knew the nature of the lesion and the second because of cataracts which I believe to be congenital. Certainly one cannot expect to gain much visual effect even if a pupillary opening is obtained if the retina is completely detached, or functionless because of incomplete development and inadequate blood supply.

X-ray therapy has been used without satisfaction by Terry, Reese[71] and M. F. Little,[71] in an attempt to shrink down the retrolental vessels.

In the thought that the anemia of prematurity might be an etiologic factor, repeated transfusions were done in many of these cases, which certainly seemed of no benefit to Case 1, who received the most, and I doubt it has been of any appreciable benefit in any. Oxygen inhalation therapy, either with a mask or incubator, was used in several cases; it seemed of doubtful benefit in Cases 1, 5, 6, and in a baby not in this series a definite exacerbation of the process began with the initiation of oxygen therapy.

To be of value, treatment must be preventative, or at least in an early enough stage to prevent loss of the retinal blood supply and to assure full retinal development.

I believe that the poor vision found in milder cases of the disease is due to the shrinkage of the retinal vessels by the parasiticlike action of the large vessels in the angiofibrous columns, with consequent inadequacy of the retinal blood supply at a crucial period of development, particularly of the macula.

ETIOLOGY

Questionnaire forms were printed and complete histories of the mothers' pregnancy were taken in the completely followed series and in the 30 cases of retrolental fibroplasia first seen after development. There seems to be no significant factor in prenatal history. This includes: season of the year, place of conception, residence of the mother during pregnancy, race, number of previous pregnancies, age of the mother and father, RH factor, vaginal bleeding, nausea of pregnancy, gain in weight, toxemia of pregnancy, attempted abortions, infectious diseases, including upper respiratory, diet, medication including vitamins, laxative, immunilogic, x-radiation, evident cause of prematurity, type of delivery, duration of the first and second stages of delivery, presentation of the child, location and type of placenta, labor premedication, anesthesia used. Geographic location of delivery may be significant. Boston and Hartford, according to V. E. Kinsey[71] of Boston, seem to have a particularly high incidence, while in other sections retrolental fibroplasia seems to be a rarity. The amount of prematurity and the birth weight seems to be proved by the Owenses' series and mine to be a very definite factor, but it is not the only one because not all babies in the smaller groups get the disease, and what selects the few who get it in the more mature? I feel that it is extremely doubtful that there is any factor derived from the mother or intrauterine development, unless it could be a maternal hormone or nutritional entity which did not pass from the mother to some of these children in sufficient quantity by the time of birth to carry the child successfully

through the postnatal period of ocular development in these prematures, which under normal circumstances would be received by the child *in utero* until full term.

A questionnaire was also prepared for the history of the infant in the earlier series of cases before the early time and nature of onset of the disease was known. This included sex, race, date of birth, birth weight, gestation period, RH factor, gain in weight by months, history of previous siblings, resuscitation necessary at birth, ateliectasis, cyanosis, sternal retraction, abnormal crying, evidence of birth injury, jaundice, infection, diarrhea, bodily temperature, telangectases or other abnormalities, medication at birth and subsequently, including vitamins, blood transfusions, saline infusions, length of time in incubator, feeding—type of food, brand, and amount—x-radiation, and location of early life. None of these seemed any factor, except that Hartford seemed to be a precarious place for a premature infant to be born in, not because he did not receive adequate pediatric care but perhaps because his chances of survival in Hartford, if premature, were too great.

My experience agrees with that of Terry[36]; it has not occurred in more than 1 individual of a single family except in multiple births, and then might affect only 1 of the number; twinning is a factor only as a cause of prematurity. No yet discovered factor during pregnancy, or manner of delivery, seems to offer a clue. The cause of the prematurity seems no factor, for some early deliveries were spontaneous and others induced by accident, surgery, or medication. Charts and graphs have been made of the early postnatal life of the series of infants studied from birth. The following factors seem to be no cause: the condition of the child immediately after delivery, subsequent rapidity of weight gain, infections, sulfonomides, biochemicals, other medications, bodily temperature, ocular exposure to light, fluid intake, or oxygenation by mask or incubator. In an earlier paper[73] I felt that the anemia of prematurity itself may be a factor in etiology. This I rather

doubt at present because in some of these cases frequent transfusions to maintain a relatively high hemoglobin and red blood cell count have neither prevented nor seemed to arrest the process. However, as a minor factor, anemia cannot be ruled out altogether. Many of the smaller prematures had hemoglobins under 8 gm. and red blood cell counts under 3 million without evident eye pathology except choroidal pallor.

In my earlier paper I pointed out the similarity of the condition to the formation of granulation tissue elsewhere in the body, or to retinitis proliferans, or to an angiomatosis retinae. I have seen simulation of the early picture of retrolental fibroplasia in diabetic retinopathy and Coats's disease. The pathology seems to be an enophthalmitis, perhaps physicochemical in nature, involving at least the anterior uvea, vitreous, and retina, causing angiomatosis, retinal hemorrhages and angioplasia in the vitreous.

Kinsey[71] currently feels that intake of ViPenta drops perhaps because of their glycol content, plus ferric iron is the crucial factor in retrolental fibroplasia. In my cases these appear not to be a factor because only 6 of the 10 cases developing retrolental fibroplasia received ViPenta drops and none received ferric iron.

In spite of charts of everything ingested by the child during his stay in the premature nursery, there does not yet seem to be any definite clue of the cause of this bewildering disease so common in premature children. I believe that the clue is in the diet, but what factors in it I am not able to say.

SUMMARY

1. 177 premature babies were ophthalmoscopically examined at weekly intervals from birth. Neither retrolental fibroplasia, nor any indication of its inception, was present at birth.

2. 10 cases of retrolental fibroplasia, or ophthalmic dysplasia, were observed from birth, through the onset and

development of the disease. It is not due to the persistence of nor the redevelopment of the embryonic hyaloid vascular system.

3. The incidence of retrolental fibroplasia in prematures bears a direct relationship to the amount of prematurity.

4. The process appears to be inflammatory, involving the anterior uvea, vitreous, and retina, causing angiomatosis, retinal hemorrhage, and angioplasia in the vitreous.

5. There are 2 main clinical types of the disease. The central type has the main feature of formation of angioplastic columns through the central vitreous to the back of the lens. The peripheral type has the main feature of peripheral retinal detachments and angioplastic adhesions between the peripheral fundus and the lens.

6. Prematurity is a predisposing factor in the causation of the process. The other factors are obscure. Diet may be the main factor.

7. Many so-called congenital ocular anomalies described in the literature may be merely clinical features of retrolental fibroplasia, or ophthalmic dysplasia. They include: persistence of the hyaloid artery, retinal folds, septum frontale, retinal fibrosis, congenital retinal pigmentation, vitreous veils, vitreous cysts, pseudoglioma, microphthalmia, diktyoma retinae, congenital high myopia, some cases of toxoplasmosis of the eye and extrapapillary coloboma.

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