tions about the effect of temperature are covered in the published text. In the oral report these were omitted for lack of time.

Dr. Verhoeff's question as to the possible presence of amitotic division is one which we are unable to answer. We have seen no cells in our preparations with double nuclei, but our failure to find such cells does not rule out the possibility of amitotic division. Current trends of thought among biologists have raised some doubts as to the existence of amitotic division as a general phenomenon. Many of the instances in which this type of division was formerly thought to have taken place have been shown to exhibit only mitotic division. In regard to the cornea, the question is still open.

RETROLENTAL FIBROPLASIA IN THE PREMATURE INFANT: V. FURTHER STUDIES ON FIBROPLASTIC OVERGROWTH OF THE PERSISTENT TUNICA VASCULOSA LENTIS

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Since the last reports[1] on retrolental fibroplasia, sufficient further data have been collected to warrant another communication.

At the present time the number of cases registered in this study is 105. In Chicago 20 more have been observed by Dr. E. V. L. Brown[2] and Dr. Justin Donegan[2] and an additional 20 by Dr. Sanford Gifford.[2] Dr. Milton Little,[3] of Hartford, Conn., has at least 15 such infants under his care. Dr. Stewart Clifford,[3] of the Pediatrics Staff of the Boston Lying-In Hospital, finds that the disease is occurring in 12 per cent of infants weighing 3 lbs. or less at birth, but since this percentage is based on less than 50 cases it is not necessarily representative.

In the cases in this study it is observed that, when no complications arise, the opaque tissue making up the retrolental fibroplasia usually becomes less dense, so that in places a red reflex can be obtained and in some instances the fundus can

be observed in detail. Although this improvement may represent resolution and liquefaction of this opaque tissue, it is more reasonable to presume that the embryonic connective tissue contracts as it matures. As it contracts, its antero-posterior thickness is reduced and may tend to shred, giving rise to spaces, or meshes, through which one can see the fundus detail. It is obvious that, when this occurs, the opaque tissue is not forming a thin membrane behind the crystalline lens only, but tends to invade the entire vitreous humor. The edges of the opaque tissue may appear sharp, but usually, when viewed with a slit lamp, the fibrillae are gradually reduced in number and density, finally disappearing like the edge of a fleecy cloud. Of course, the apparent reduction in the amount of opaque tissue which is usual could result from a growth of the eye without a growth of the fibroplastic tissue, but this seems unlikely, since eyes affected with retrolental fibroplasia usually grow slowly, if at all. The apparent resolution rarely develops sufficiently to permit good vision. A posterior cortical cataract may develop, however, and increase the opacity so that the blood vessels in the fibroplastic tissue become obscured. In some instances we see a dramatic clearing of the opaque tissue in the vitreous humor, and it is evident that a considerable amount of vision is present. This improvement is most obvious in the eyes which have grown appreciably and have anterior chambers of nearly normal depth. When a bright red reflex can be seen and fundus detail made out, retinoscopy is performed. The eyes of 2 infants were found to be extremely hypermetropic; one was myopic. In 2 instances glasses were prescribed; these the children tolerated well.

With favorable development, the searching nystagmus, so typical early in the disease, tends to abate and even disappear, and internal strabismus develops frequently. In most of the patients the improvement has been only moderate. Although it is apparent that these infants are conscious of light stimulation, and that some of them see relatively

large objects which present a great contrast, in those whose eyes are severely involved there is no evidence of ability to judge distance, because these infants never reach for the objects, as do seeing infants of the same age. In an attempt to determine whether or not the fovea has developed and is functioning even moderately well, the parents have been asked to use 2 or 3 different colored lights, each having a specific meaning—indicating feeding time, bath time, and rest time—varying the schedule sufficiently so that the color of the light will eventually establish a conditioned reflex. This has failed, but its failure may be the matter of improper establishment of the conditioned reflex rather than an indication that color perception is entirely lacking. If it were possible to show that color discrimination is present, the prognosis should be better.

All these premature infants at birth appear to have a gray-blue iris. For this typical color I have used the term "fetal blue." In cases where the eyes grow rapidly and the depth of the anterior chambers becomes relatively normal, this fetal-blue color is quickly lost, but even in the most severely involved eyes, which grow little or none, there is eventually a definite but incomplete change of color. In brunette infants the iris becomes an abnormally dull brown.

As only 3 of these patients show mental abnormalities, there seems to be no correlation between retrolental fibroplasia and retardation in mental development of the premature infant. Mental retardation does occur in about 12 per cent of all premature infants.[4]

Of the cases originally reported,[1, b] Case 7 must be disregarded. The pathologic examination of the left eye gave evidence that an unyielding tissue had pulled the retina and optic nerve toward the crystalline lens, thus indicating the method by which retinal folds and retinal separations originate in retrolental fibroplasia. Although this may still be a true concept of how retinal separation develops in many of the infants with typical fibroplasia, the reason for remov-

ing this case from consideration is that a younger sister, born at full term, has the same type of eye disease as observed clinically in Case 7. This must, then, represent a hereditary eye defect. The prematurity of the older child was the factor that led to its original inclusion in this study.

The eyes of the infants in this series treated with x-ray show no benefit. Dr. Pelham Glover,[3] of Altoona, Pa., had 2 patients whose eyes he felt improved after the implantation of radon seeds. A repetition of his treatment was given in 2 cases here; in both, the eyes not only showed no improvement but also shrank into typical phthisis bulbi.

It has already been pointed out that at birth all extremely premature infants have a functioning tunica vasculosa lentis. The venous drainage for this vascular system is through the pupillary portion of the tunica vasculosa lentis, the so-called pupillary membrane, to the anterior surface of the iris. In all infants, including those who later develop retrolental fibroplasia, the pupillary portion of the tunica vasculosa lentis, as seen grossly, undergoes involution. It is possible, however, for small vessels of about capillary size to persist at the extreme edge of the pupillary margin of the iris, thus furnishing an invisible drainage for the still functioning tunica vasculosa lentis. It is possible and even probable that in some cases the tunica vasculosa lentis behind the pupillary membrane persists without any venous drainage, just as at times the hyaloid artery persists, ending blindly near the lens. As embryonic connective tissue can develop in the meshwork of the tunica vasculosa lentis behind the crystalline lens, so also connective-tissue elements may develop around these blood vessels. This new tissue would be inflexible and unyielding, binding the pupil down at these points, thus giving rise to posterior synechia. Before the appearance of the fibroplastic overgrowth, however, the blood vessels circling around the pupillary margin were delicate and elastic enough to permit relatively normal dilatation and contraction of the pupil. Posterior synechia do develop frequently in infants with

retrolental fibroplasia without any evidence of an inflammatory process. The development of fibroplastic tissue around these blood vessels would account, in part at least, for the persistence of the fetal-blue or the dull brown color of the irides.

The development of glaucoma is common enough to warrant careful attention; 5 cases have been observed. This does not necessarily mean that these eyes are producing aqueous humor in sufficient amounts to induce this complication. Lack of development of the iris-angle meshwork and Schlemm's canal would induce glaucoma even where there is an extremely small production of aqueous humor. In these 5 cases the eyes remained microphthalmic. In only one instance, a case that Dr. Georgiana Theobald showed me, was hydrophthalmos present. Pilocarpine 1 per cent has been used daily in this series in an attempt to prevent the development of glaucoma, and no new cases have occurred. In the examination of the few pathologic specimens of retrolental fibroplasia, each show a poorly developed iris-angle meshwork. It seems reasonable to presume that hydrophthalmos would invariably arise in these cases if aqueous humor were elaborated in sufficient amounts.

It has already been pointed out that there is a strong tendency toward the development of posterior synechia. In an attempt to prevent this a mydriatic* which is effective for only a few hours has been used once each week. This prophylactic measure has been less successful in preventing posterior synechia than the prophylaxis to prevent the glaucoma. The effectiveness of these treatments can be determined only through further study. The infants soon resist the use of all collyria as energentically as they can, and such medication is to be avoided where it is really safe to do so. Nevertheless,

* ℞ Homatropine HBr..... 0.15
Epinephrine Bitartrate..... 0.30
Cocaine HCl..... 0.075
Paredrine HBr 1%.....15.000

I have not felt justified in giving it up until either the failure of prophylaxis has been proved or the eyes have shown definite evidence of growth and a deepening of the anterior chamber.

Continued clinical study of this disease has shown that one of the physical findings was incorrectly interpreted. The toothlike processes at the periphery of the opaque tissue were originally called "dentate processes" or "gothic arches." These were thought to represent a serration at the edge, resulting from the insertion of the opaque tissue in the ciliary processes. It was noted that the color of these arches, presumed to correspond to the ciliary valleys, was usually red, like the normal fundus reflex. Sometimes the color was dark brown, a finding not feasible on the basis of the original interpretation. In one recent case, observed when the infant was under ether anesthesia and with the pupil fully dilated, a transilluminator was applied to the sclera for the purpose of determining whether or not a massive intra-ocular hemorrhage had occurred—a complication that has arisen in some cases. The eye transilluminated well, and from one side a clear view was obtained of this region of "dentate processes." It was obvious at a glance that these red or dark brown areas were in reality the ciliary processes themselves, with the opaque connective tissue of the fibroplasia extending behind them. A study of the ciliary processes under these conditions showed that there was considerable variation in the amount of pigment in this organ. In some cases, the processes were red at their extremities, but nearer their bases there was a gradual change to a dark red, and then to the dark brown of the normally pigmented processes.

The eyes of 2 infants who did not have fibroplasia were examined during ether anesthesia. One of these had unilateral microphthalmus and the other retinoblastoma. It was possible to see the ciliary processes through dilated pupils even though the anterior chambers were of normal depth (Figs. 1 and 2 A). In spite of blue-colored irides, the processes were a

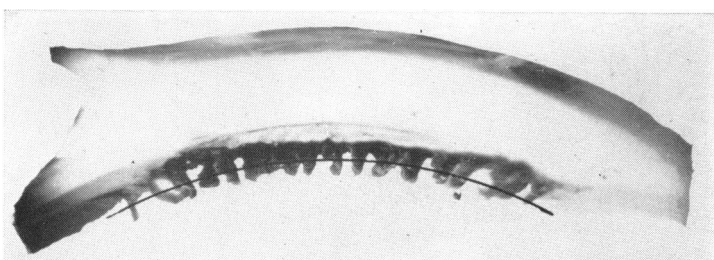

Fig. 1.—Adult human ciliary processes as seen in an "end piece" removed when globe was opened for microscopic sectioning. Portion of cornea is seen cut through obliquely. Note relation of ciliary process width to that of ciliary valley. Black line indicates the extent to which the tips of the processes can be seen through the dilated pupil in the newborn infant's eye.

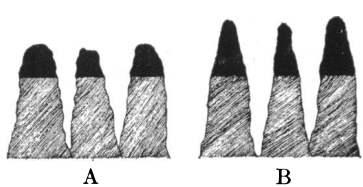

Fig. 2.—Diagram showing variations in thickness and length of ciliary processes in (A) normal infant eye, and (B) infant eye containing fibroplasia. The solid black tips represent the part visible in clinical examination with the ophthalmoscope or by means of transillumination. *A* is consistent with the normal ciliary process relation as shown in Fig. 1.

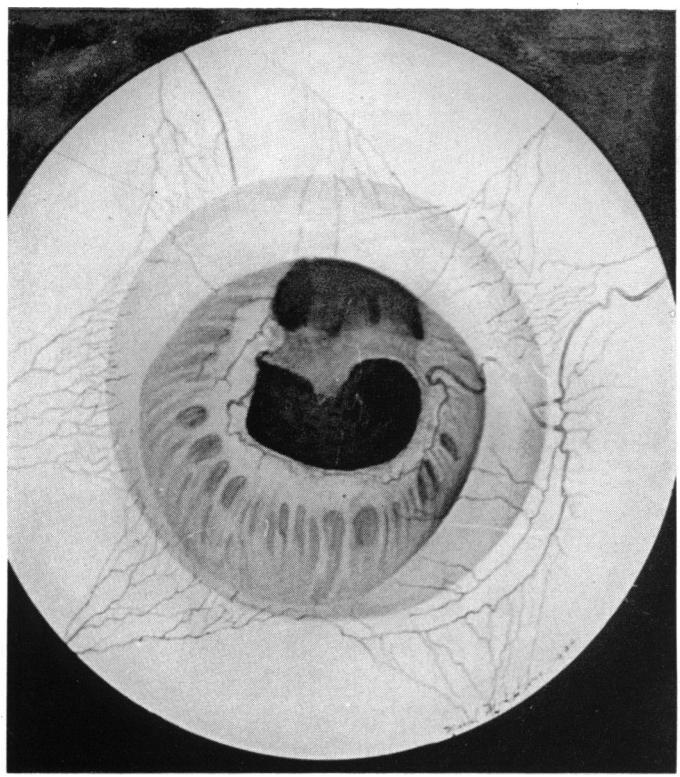

Fig. 3.—Artist's drawing of an eye in which vascular connection between iris and episcleral net is shown extending along scar of cataract incision. If need for a newly formed vascular connection exists, this shows that such a connection can be established along an operative wound.

dark brown color and were fully twice as wide as infants with fibroplasia. In an infant of 4½ months with retrolental fibroplasia in which the membrane was absent in one quadrant, the ciliary processes were longer and narrower in the region where the fibroplasia was most noted (Fig. 2 B). The ciliary processes were wider and shorter in the quadrant where fibroplasia was lacking (Fig. 2 A). The ratio of the width of the ciliary process to the width of the intervening ciliary valleys was 1:3 in the region of fibroplasia, and 1:1½ in the quadrant where fibroplasia was lacking. If the wider, shorter process is the true appearance of normal ciliary processes, then those seen in fibroplasia, often appearing red or pigment free, are indeed definitely undeveloped—strong evidence that the ciliary body is maldeveloped. A further study of ciliary processes at various times as the infants grow may prove of value in showing the variation in development rate, in pigmentation, and in size.

The original concept, that the disease arose through hypertrophy of the intra-ocular vascular system because of a precociously high blood pressure resulting from premature birth, seems less tenable as the factors are examined more minutely. Thoma[5] pointed out that the effect of increased blood pressure is to keep a vascular system open as well as to cause it to hypertrophy. This is indeed quite the case in instances of abnormal arteriovenous communication, in which the arteries, relieved of considerable pressure because of the fistula, atrophy and become veinlike, whereas the veins, now subjected to a pressure almost arterial in amount, hypertrophy and become artery-like. In addition there is an actual increase not only in the width of the capillaries but also in the number of capillaries in this bed.[6] At no stage in normal development is the future need for blood vessels anticipated. The blood vessels, considered to be the most adaptable tissue in the embryo and fetus, are not developed at any stage of embryonic and fetal life beyond the needs of the organism at that time. Thus, the blood vascular system is constantly

meeting the demand for oxygenated blood from the ever-changing tissue as growth and development proceed. High blood pressure *per se* does not cause widespread new capillary growth, as might be expected from Thoma's hypothesis. The cornea becomes vascularized not because people have high blood pressure, but because there is a local need for blood in response to an inflammatory process or an injury. If this reasoning can be used in relation to retrolental fibroplasia with persistence of the tunica vasculosa lentis and hyaloid artery, then the cause of the disease is not a precociously high blood pressure, but lies in the fact that there is a need for this vascular system.

Of course, until the cause of this disease process is definitely known, we must continue to consider all possible etiologic factors. In experimental work, attempts were made either to produce the disease or to cause a precocious involution of the hyaloid artery and tunica vasculosa system in hundreds of opossums and young rats. Although the disease was not produced, it appeared that repeated dilatation of the pupil and the examination of the eyes of these animals with an ophthalmoscope did tend to delay the time at which this vessel system disappeared. In the earlier study it seemed highly improbable that precocious exposure to light was an etiologic factor, especially in its effect on the retina *per se*, despite observation that the process of myelination of the optic nerve appeared to be accelerated in the prematurely born infant.[7] Consideration of the possible effect of pupillary response and even of accommodation in the premature infant seems to lead to a more plausible cause of the development of fibroplasia. The pupil does contract and dilate in the most premature infant in response to exposure to light and to use of a mydriatic, but the possibility of accommodative or other activity of the ciliary muscle is only theoretical.

It is probable that active pupillary responses could embarrass the venous drainage of the tunica vasculosa lentis by stretching and tending to kink the vessels as they extend

from the posterior surface around the pupillary margin to the anterior surface of the iris. Should this cause a closure of the vessels at the pupillary margin, then we would have perhaps a persistence of the hyaloid artery and the tunica vasculosa lentis with considerable passive congestion in them. Passive congestion, in itself, is not presumed to cause fibrosis, but the edema associated with it can produce fibrosis such as is seen in the so-called pulmonary osteo-arthropathy.[8]

Again the pupillary response without, or more likely with, some muscular activity of the ciliary body may tend to open the iris-angle meshwork region. From the appearance of the ciliary body in the fetal eyes one can conclude that aqueous humor is formed before Schlemm's canal and the iris-angle meshwork are developed sufficiently to take away any or all of this fluid, thus producing a higher intra-ocular pressure—a temporary physiologic "glaucoma." In fact, the mechanism by which congenital glaucoma develops may, for a while, be active in all eyes as a normal process, being relieved by the development of an adequate drainage of aqueous humor from the eye, a development which fails to occur in hydrophthalmos. If the iris-angle meshwork is opened in a form capable of physiologic activity through the pull of the uveal-tract musculature on the scleral spur, then precocious exposure of the eye to light and optical imagery in the prematurely born infant would open the angle and drain aqueous humor from the eye, thereby circumventing the occurrence of the transitory physiologic glaucoma. This lack of aqueous humor would result in an extremely shallow anterior chamber and a decrease in intra-ocular pressure which would fail to stimulate the growth of the eye, thus giving rise to microphthalmus. The crystalline lens and the cornea in part obtain their nutrition from the aqueous humor. If nutrition is inadequate, we have an explanation for the formation of cataracts and corneal opacities which later occur in retrolental fibroplasia. Until this aqueous humor is developed in the fetal eye, these organs are nourished by the tunica vasculosa lentis system.

If aqueous does not develop, then the need for nourishment of the lens and cornea could be supplied by a persistence of the hyaloid artery and tunica vasculosa lentis. Thus, lack of aqueous humor accumulation explains many but not all of the findings in retrolental fibroplasia; the occasional occurrence of glaucoma as a complication needs some further explanation.

Another view is that the ciliary body fails to elaborate aqueous humor. Whether the absence of aqueous humor formation is the result of lack of permeability of the capillary walls and the ciliary epithelial layers separating the capillaries from the posterior chamber, or of lack of an adequate vascular supply to the ciliary processes, is purely conjectural. A microscopic study of the few specimens of fibroplasia available show abnormal ciliary processes in the disease. These are distorted and stretched out but are not connected to the fibroplastic mass in every case. Thus, morphologic evidence of abnormality of the ciliary body does exist.

If the ciliary body is at fault because of improper vascular development, it is probable that a more adequate vascular connection could be produced surgically. In considering these possibilities one recalls the proposal made by Sonderman[9] regarding a certain type of glaucoma. He felt that glaucoma could arise from an overproduction of aqueous humor in relation to an increasing stricture of the vortex vein at the region of the ampulla, and substantiated this theory with pathologic specimens. Sonderman said that such glaucoma could be detected by observing fluorescein in the anterior chamber in an extremely short time after an intravenous injection as compared with the time in a normal eye. He believed that there is occasionally a "secretory" glaucoma. He attempted to establish a new vascular drainage of the ciliary body by performing a trephining of the sclera over the ciliary body so that the scar-tissue repair of this lesion and the newly formed blood vessels along this tract could connect the ciliary-body circulation with that of the episclera. In Sonderman's hands

this operation seems to have been effective. Provided a better arterial blood supply or a better venous drainage of the ciliary body is needed and can be surgically established, it is possible that this type of operation could be of value in retrolental fibroplasia.

After careful consideration of possible complications, this operation was tried on one infant who had unilaterally a marked persistence of functioning pupillary membrane, a shallow anterior chamber, a fetal-blue iris, and an opacity deep in or behind the crystalline lens. Three weeks after the operation the blood vessels in the pupillary membrane had ceased functioning, the color of the iris improved, the anterior chamber deepened, and the eye was growing—a dramatic result.

Other similar operations have been performed on 18 infants. In 2 cases the eyes showed so much improvement that each mother requested that the operation be done on the other eye also. Six other eyes have shown improvement after this operation. In one instance glaucoma was relieved and did not recur. If the operation is really responsible for the improvement noted, it is possible that the benefit may be derived from some factor in the operation not now obvious. This operation may have possible therapeutic value for these infants, but this statement is made with hesitation, since the operation has yet to completely prove its value. In this series, however, no complications have arisen. It should by no means be performed routinely on all these infants until it has proved its worth in carefully selected cases, where there is little chance of harm and great chance of improvement. This method of determining the effectiveness of surgical treatment must necessarily be slow, especially when we consider that many of the eyes operated on show considerable deterioration and would not improve even after an operation of proved value.

The justifiable indications for an operation on such insecure basis have been in infants with one eye severely involved

and the other eye showing little or no involvement, or in infants with severe bilateral fibroplasia in which complications such as glaucoma, posterior synechia formation, development of corneal opacities, or a combination of these are beginning to appear.

The technic of the operation is as follows: The conjunctival flap is turned down toward the limbus from some 4 mm. behind. Care is taken to cleanse the sclera thoroughly; a 1-mm. trephine is applied at a distance approximately 2 mm. from the limbus. In these cases, where there is practically no anterior chamber, the danger of entering the iris angle is very small. In no operation has this happened. A reduction in resistance is usually noted when the sclera has been completely penetrated, but inspection from time to time is the safest guide to knowing when one is approaching the ciliary body. The button is easily removed by gentle dissection, and the flap is replaced. The wound is reclosed with a continuous suture, the lower end of which is left relatively long so that it can be easily removed without another anesthetic. No dressing is applied to the eye, and on the fifth day the suture is removed.

No eyes that have had this operation performed on them have been obtained; it is impossible to state whether or not new vascular connections are actually produced. In one instance, however, I have seen a vascular connection between episcleral vessels and newly formed vessels on the iris along the tract of a cataract incision in a patient with severe glaucoma (Fig. 3). This demonstrates that new vascular connections large enough to be seen without magnification can be and are established along an operative wound between the interior and exterior of the eye if the need is strong enough.

SUMMARY

Approximately 10 per cent of all premature infants weighing 3 lbs. or less at birth develop retrolental fibroplasia, of which 160 cases have been collected.

Partial resolution of the fibroplastic tissue in the eyes in which growth does occur when no complications arise rarely results in improvement sufficient to permit really good vision.

Occasionally, cataractous development may obscure deeper ocular changes.

Inability of the infants to judge distance is a common characteristic.

The "fetal-blue" color of the iris persists longer, its speed of disappearance being a direct proportion to the rapidity of growth of the involved eye.

One atypical case originally reported must now be excluded. The full-term birth of a younger sister, with the same lesion, indicated a probable heritary factor not evident in any other cases.

Mental retardation in infants with retrolental fibroplasia is less frequent than mental retardation of normal premature infants.

Radiation therapy has proved to be valueless—in fact, more damaging than beneficial.

Glaucoma, a complication of some frequency, rarely gives rise to hydrophthalmos and appears to be preventable by daily use of miotics. On the other hand, mydriatics having short duration used once a week are less successful in preventing posterior synechia.

The "dentate processes" originally improperly interpreted are actually brown (pigmented), or red (unpigmented) ciliary processes, observable through dilated pupils, extending in front of the opaque tissue. These processes in infants with fibroplasia are narrower, often less pigmented, and perhaps more elongated when contrasted with the ciliary processes observed in the same manner in infants with normal eyes.

The more tenable theory of the cause of this disease is the failure of aqueous humor production or accumulation which may be caused by the effect of precocious exposure to light activating pupillary and ciliary body musculature before the hyaloid vascular system has disappeared. This failure leaves

the crystalline lens dependent upon the hyaloid artery and tunica vasculosa lentis, thereby causing a persistence of this vascular system.

Surgical attempt to establish new vascular connections between the ciliary body and the episclera by a scleral trephining over the ciliary body appears to produce some improvement.

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DISCUSSION

DR. E. V. L. BROWN, Chicago, Ill.: I have operated on one case—each eye, as advised by Dr. Terry. It is too early to determine the results. I am extremely interested in the subject because for years back we have been taking out such eyes, fearing glioma. After seeing the patient, Drs. Bothman, Kronfeld, Kraus, Stough, Fralick and I would each write down separately what we thought the diagnosis should be. I do not know who was wrong most of the time but I guess we were all wrong many times. We have been mistaking many cases of retrolental fibroplasia for gliomas. Four or 6 enucleated eyes seen between 1935 and 1940 were really cases of retrolental fibroplasia.