I should like to ask Dr. Dotter if, in his experience, it is desirable or necessary to inject as much as 40 cc. of the contrast medium.

DR. LEO RIGLER, Minneapolis: After seeing this beautiful demonstration, I am reluctant to introduce any discordant note, but I wish to emphasize that, while angiocardiography certainly is a method of study which permits us to learn a great deal about congenital heart diseases and diseases of the pulmonary arteries, one must not be overwhelmed by the brilliant detail presented in these films and develop an inferiority complex about conventional methods of diagnosis. I think it is possible, particularly in the noncyanotic types of congenital heart disease, to make an accurate diagnosis without angiocardiography in the overwhelming majority of cases if all the diagnostic factors, including, of course, meticulous roentgenologic studies, are considered. In cyanotic heart disease, I believe that angiocardiography may well be necessary in a much larger percentage of the cases. I was most interested in Dr. Dotter's statement about pulmonic stenosis, and should be gratified to know the basis for his impression that isolated pulmonic stenosis is not rare. My only experience, in a large series of autopsies in cases of congenital heart disease of all kinds and descriptions, is that isolated pulmonic stenosis of the type found in the tetralogy of Fallot is very rare. This is of some importance in the question of whether true pulmonic stenosis, without associated defects and, at least, in its relatively early stages, actually can produce cyanosis. I should like to reemphasize Dr. Dotter's criticism of the criteria which have been given for the diagnosis of cor pulmonale. It has been my experience that the diagnosis of cor pulmonale can be made in a great many cases long before right heart failure has occurred. If one carefully studies cases of bronchial asthma, silicosis or tuberculosis, the enlargement of the right side of the heart, first indicated by enlargement of the pulmonic artery, becomes apparent long before the symptoms of actual failure, such as cyanosis and ascites, appear.

DR. J. E. MILLER, Dallas, Texas: Dr. Dotter has indicated that his cases of the Eisenmenger complex were not amenable to aortic-pulmonary anastomosis. I have 4 or 5 patients in whom I have made this diagnosis from angiocardiography, and the same may be true of them. In 1 of the patients, however, where most of the contrast material went into the pulmonary artery, instead of the aorta, the clinicians were not entirely satisfied that my impression of the Eisenmenger complex was correct. The patient was operated on, with the plan of measuring pressures in the pulmonary artery. The clinicians had indicated that anastomosis would be done provided the pressure was less than 350 mm. of water. The measurements indicated that the pressure was 300 mm. of water, plus or minus 20. The anastomosis was made, and the result was excellent. Since I have other patients with the same angiocardiographic diagnosis, there will be a clinical reevaluation; perhaps some of them will be operated on. We should not say that anastomosis is not applicable when the diagnosis of Eisenmenger's complex has been made angiocardiographically.

DR. CHARLES T. DOTTER: We have seen at least 2 cases of pulmonic stenosis in adults in whom we were unable to demonstrate any other cardiovascular lesion. We believe it a more common condition than formerly recognized and anticipate that studies employing catheterization of the heart will bear this out. In our experience, the diagnosis of Eisenmenger's syndrome should be made angiocardiographically only when a large, dilated, nonstenotic pulmonary artery can be demonstrated. The decision regarding operative intervention rests solely upon the shoulders of the surgeon. In closing, may I comment upon the undeserved reputation which angiocardiography has gained, namely, that it is a difficult procedure. It can be accomplished with very little special equipment, making use of a standard cassette with which one obtains only two films during an injection. All the films which you have seen today were made in that manner. For the other details of technic, may I refer you to the papers of Drs. Robb and Steinberg, published in 1938 and 1939.[2] The details have changed very little since then. I believe that angiocardiography will grow to be a commonplace method of examination, employed in all hospitals and in the hands of many radiologists.

RETROLENTAL FIBROPLASIA

Incidence in Different Localities in Recent Years and a Correlation of the Incidence with Treatment Given the Infants

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and
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Boston

Retrolental fibroplasia (R. L. F.) is an ocular disease usually associated with prematurity and usually affecting both eyes. The most conspicuous diagnostic sign is the presence of a membrane, often vascularized, situated behind the crystalline lens. The presence of blood vessels in the membrane serves to differentiate retrolental fibroplasia from congenital cataract. The affected eye may be smaller than normal, the anterior chamber shallow and the ciliary body abnormally serrated. Secondary changes, such as synechiae, glaucoma and iritis, frequently develop. The disease is rarely, if ever, seen at birth but develops when the infant is between 1 and 5 months of age. It has been seen to start as a dilatation of the retinal vessels followed by exudative retinitis and subsequent retinal detachment.[1]

Retrolental fibroplasia was first associated with prematurity by Terry[2] in 1942. Since then there have been indications that the incidence has increased more in some localities than in others. The apparent increase in the frequency of the disease in recent years cannot be explained by the statement that the condition in a significant number of cases was formerly undiagnosed and therefore missed[3] or that a significantly greater proportion of premature infants survives now than in 1942.[4] To date, no satisfactory theory of the cause of retrolental fibroplasia has been proposed. It seems likely, however, that if it were demonstrated that the incidence of the disease were actually increasing, or that the incidence varied significantly from place to place, the possible number of explanations would be greatly reduced. Moreover, it might be feasible, from a knowledge of the incidence in any one locality over a period of years, or in various localities, to correlate the incidence with some factor associated with mother or infant at one particular time or place. Accordingly, studies were made of the number of premature infants born in particular hospitals in various localities, in whom retrolental fibroplasia did or did not develop. The results to be reported show that the incidence, at least in some localities, has increased and that this increased incidence correlates positively with certain treatment given to the infant, although,

From the Departments of Ophthalmology and Obstetrics and the Howe Laboratory of Ophthalmology, Harvard Medical School; the Massachusetts Eye and Ear Infirmary; the Boston Lying-in Hospital, and the Providence Lying-in Hospital. Supported by a grant from the Foundation for Vision for the study of retrolental fibroplasia.

Mrs. Harriet D. Parish and the staffs of the record rooms and social service departments of the Boston Lying-in and Providence Lying-in hospitals gave assistance in this study; Drs. Stewart Clifford and Clement Smith gave advice and suggestions in reporting the results of the study and outlining the new vitamin and iron medication schedule to be used at the Boston Lying-in Hospital.

1. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Tr. Am. Acad. Ophth. **53**: 18-38 (Sept.-Oct.) 1948.

2. Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens, Am. J. Ophth. **25**: 203-204 (Feb.) 1942.

3. The fact that cases of retrolental fibroplasia were not recognized in former years cannot alone account for the present apparent rise in incidence, because the number of children born since 1942, in certain localities at least, whose vision is seriously impaired by retrolental fibroplasia far exceeds the number of cases of blindness occurring in former years which could possibly be attributed to this condition.

4. The survival rate of premature infants at the Boston Lying-in Hospital has not increased significantly during the past sixteen years. Values reported for other hospitals (Dunham, E. C.: Premature Infant, Children's Bureau Publication 325, United States Department of Labor, Children's Bureau, 1948) suggest that any increased survival rate is small compared with the apparent increase in incidence of retrolental fibroplasia.

as indicated later, this correlation does not constitute proof of causal relation between incidence and treatment.

PREVIOUS STUDIES

Previous reports of the incidence of retrolental fibroplasia (with the exception of the report of Owens and Owens [1] at the Johns Hopkins Hospital in Baltimore and that of Gilger [5] at the Cincinnati General Hospital, to which detailed reference will be made later) have been preliminary in nature. Ingalls,[6] quoting a personal communication from Clifford and Allers, stated that at the Boston Lying-in Hospital, between 1938 and 1945, the incidence of the disease for 254 infants, weighing less than 4 pounds (1,814 Gm.) at birth, is 13 per cent. He mentioned, however, that 4 of the infants with retrolental fibroplasia weighed more than 4 pounds at birth, in which case the incidence rate for infants weighing less than 4 pounds at birth appears to be approximately 11 per cent. He pointed out, also, that the estimate is probably conservative because of "missed" cases. The number of babies successfully investigated is not given, and Ingalls concluded that the stated incidence rate must be considered approximate.

Clifford and Weller [7] (quoting a personal communication from Allers) said that the incidence in the same nursery in Boston was 23 per cent for infants weighing between 2 and 3 pounds (907 and 1,361 Gm.) at birth. The number of infants on which this figure is based and the period of time covered are not given.

Others who have studied retrolental fibroplasia, including Krause [8] and Reese and Payne,[9] have not investigated the relative frequency of the disease in children born prematurely, although Krause reported that it has occurred in 1 out of 4,000 births at the Chicago Lying-in Hospital. The period covered by the data is not given.

METHODS

Inquiries [10] were sent to parents or guardians of all infants born at the Boston Lying-in Hospital and Providence Lying-in Hospital who weighed 4 pounds or less at birth, to establish the present condition of their eyes. Responses were obtained concerning 93 and 95 per cent of all infants in these two locations, respectively. When an ocular defect was reported, the children were seen by an ophthalmologist who gave the diagnosis in any cases of retrolental fibroplasia. The information used in correlating incidence of the disease and factors relating to the mothers and infants was taken from the hospital records, and frequently additional information was obtained from the mothers and pediatricians concerning the treatment of the infant after discharge from the hospital.

5. Gilger, A. P.: Retrolental Fibroplasia in Prematurely Born Children, Am. J. Ophth., to be published.
6. Ingalls, T. H.: Epidemiology of Encephalo-Ophthalmic Dysplasia, J. A. M. A. **138**: 261-264 (Sept. 25) 1948.
7. Clifford, S. H., and Weller, K. F.: The Absorption of Vitamin A in Prematurely Born Infants With Experience in the Use of Absorbable Vitamin A in the Prophylaxis of Retrolental Fibroplasia, Pediatrics **1**: 505-511 (April) 1948.
8. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, Arch. Ophth. **36**: 387-444 (Oct.) 1946.
9. Reese, A. B., and Payne, F.: Persistance and Hyperplasia of Primary Vitreous, Am. J. Ophth. **29**: 1-19 (Jan.) 1946.
10. The data for the New York Hospital were collected by Dr. Lewis Fraad, and the diagnoses were made under the supervision of Dr. John McLean of the Department of Ophthalmology of the Cornell Medical School. The information concerning the Cincinnati General Hospital and the Hartford Hospital was supplied by Dr. Anita P. Gilger and Dr. A. C. Unsworth, respectively, and will be reported by each in detail elsewhere. The study at the Johns Hopkins Hospital in Baltimore was made by Drs. William and Ella Owens. The data concerning the Colorado General Hospital in Denver were supplied by Dr. Lula O. Lubchenco and Dr. Harry H. Gordon; those for the Michael Reese Hospital in Chicago, by Dr. Julius Hess and Miss Evelyn C. Lundeen; those for Birmingham, England, by Dr. V. Mary Crosse of the Public Health Department of Birmingham.

RESULTS

The results of the study for the Boston Lying-in and Providence Lying-in hospitals and those of Gilger for Cincinnati are shown in a series of 9 graphs in which the data are presented for each year studied. The first figure for each place shows the birth weights of infants in whom retrolental fibroplasia developed, plotted as a scattergram. The second figure presents in percentage the incidence of the disease for all of the children and the incidence, separately, for those infants weighing less than 3 pounds and those who weigh between 3 and 4 pounds at birth. The third figure shows the actual number of cases of retrolental fibroplasia, the number of children in whom this disease did not develop and, indicated by a line above the blocks, the number of children about whom no information could be obtained.

TABLE 1.—*Incidence of Retrolental Fibroplasia (R. L. F.) in Various Localities*

	<3 Lb. (1,361 Gm.)			3-4 Lb. (1,361-1,814 Gm.)				
	Children with R.L.F.	Normal* Children	Incidence, Percentage	Children with R.L.F.	Normal Children	Incidence, Percentage	Years	Fraction Investigated, Percentage
Boston	9	35	20.5	1	105	0.95	1938-1942	85
Boston	10	28	26.3	33	129	20.2	1943-1947	97
Providence, R. I.	7	23	23.3	9	186	4.6	1941-1947	92
Baltimore	0	23	0	0	63	0	1935-1944	33 (est.)
Baltimore	4	29	12.1	1	38	2.5	1945-1947	?
Hartford, Conn.	4	3	57	4	24	14.3	1948	100
New York	5	60	7.7	1	141	0.7	1939-1946	83
Cincinnati	2	20	9.1	5	69	6.8	1943-1947	62
Birmingham, England	0	21	0	0	83	0	1945	100
	<3 Lb. (1,361 Gm. (est.)			3-3 Lb. 5 Oz. (1,361-1,500 Gm. (est.)				
Denver	2	8	20	0	4	0	1948	67
	<2.8 Lb. (1,260 Gm.)							
Chicago †	5	211	2.3	..	...	....	1922-1947	97

* Normal in all tables indicates simply the absence of retrolental fibroplasia.

† It will be observed that the data given for the Chicago hospital (Michael Reese Hospital) cover a twenty-five year period. The ages of the 5 patients with retrolental fibroplasia were 2, 3, 5, 7 and 16 years (4 females, 1 male), indicating that the incidence of the disease has been and still remains low.

The data from the other cities are not presented graphically because either the number of cases of retrolental fibroplasia was too small or the period of time covered in the studies was too short. They are included, however, in this report (table 1), since they represent the only available information at this time on the incidence of this disease.

Boston.—There were 372 infants weighing 4 pounds or less at birth and surviving six months or more, who were born at the Boston Lying-in Hospital during the years 1938 through 1947. Of these, it was found that retrolental fibroplasia had developed in 53 and had not developed in 298; 21 could not be located. In 44 of the cases of retrolental fibroplasia, both eyes were affected; in 9, one eye only was affected. From figures 1, 2 and 3 it is evident that the incidence of the disease had increased during the second five years of the period studied (1943 through 1947), and that this increase is accounted for chiefly by an increase in cases among the heavier infants (3 to 4 pounds). Figure 3 shows that only 1 case of retrolental fibroplasia occurred in 102 premature infants weighing

between 3 and 4 pounds at birth (1.0 per cent) prior to 1943, whereas in the same weight group there were 33 cases in 162 premature infants (20 per cent) in the years 1943 through 1947. The incidence during the same two periods in infants born in this hospital who weighed less than 3 pounds at birth (table 1)

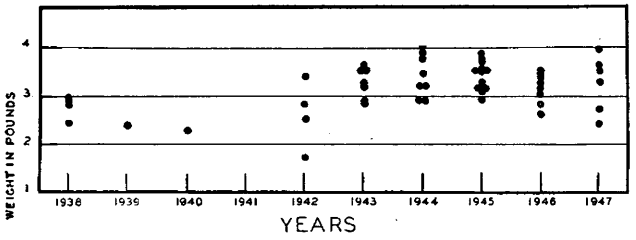

Fig. 1.—Birth weights of premature infants in whom retrolental fibroplasia developed who were born at the Boston Lying-in Hospital.

was 20.5 and 26.3 per cent, respectively. The year to year fluctuation in the incidence of the disease in the lighter group of infants (figure 3) may be explained by the small number of infants in this weight group.

Providence.—There were 246 infants weighing less than 4 pounds at birth and surviving six months or more, who were born at the Providence Lying-in Hospital during the years 1941 through 1947. Of these, it was found that retrolental fibroplasia had developed in 16 and had not developed in 218; 12 could not be located. In 14 of the cases of retrolental fibroplasia both eyes were affected; in 2, one eye only was affected. Figure 4 shows that, unlike the situation at the Boston hospital, the retrolental fibroplasia occurred in the 3 to 4 pound weight group with approximately the same frequency throughout the period of study. Figure 5 shows that the total incidence of the disease has not varied significantly throughout the eight year period. The high incidence observed in the light weight group during the years 1942 through 1944 is not significant because of the small number of infants in this group (fig. 6).

Cincinnati.—There were 156 infants weighing less than 4 pounds at birth, presumably living at the time the survey was made, who were born at the Cincinnati General Hospital during the years 1943 through 1947. Of these, it was found that retrolental fibroplasia had developed in 7 and not in 89; 60 could not be located.

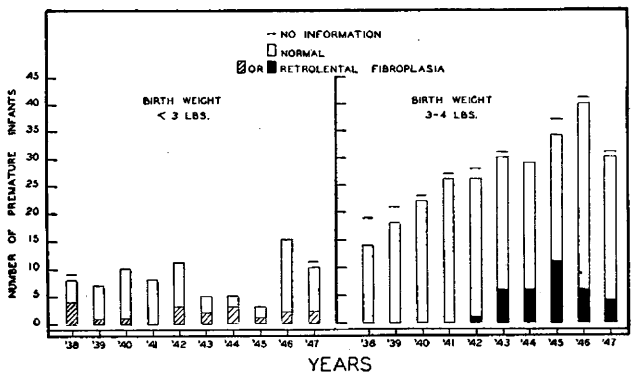

Fig. 2.—The number of premature infants born at the Boston Lying-in Hospital (top line), the number of cases of retrolental fibroplasia (cross hatch for the birth weight group under 3 pounds and solid blocks for the birth weight group 3 to 4 pounds) and the number of premature infants known to be normal with respect to retrolental fibroplasia (open blocks).

The number of cases of retrolental fibroplasia in children born at this hospital is too small to permit any conclusions with regard to distribution by years.

Other Cities.—The data regarding the incidence of retrolental fibroplasia for other cities are summarized and presented in table 1, along with a similar condensation of the data for the three cities already reported. The table shows that the incidence in the infants weighing less than 3 pounds at birth is higher in every location (where any cases of retrolental fibroplasia exist) than it is in the group weighing 3 to 4 pounds at birth. It shows also that there is a considerable variation in the incidence in different localities.

The data thus far presented suggest that the incidence of retrolental fibroplasia has increased in recent years, particularly in the 3 to 4 pound weight group in the Boston hospital. The question arises as to whether any particular factor or factors associated with the mothers or infants can be correlated with the increased

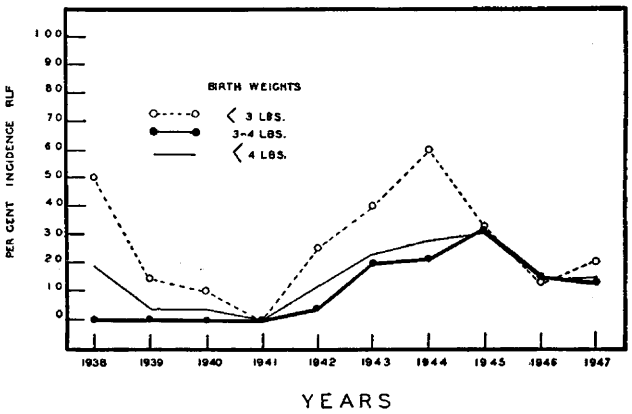

Fig. 3.—The incidence of retrolental fibroplasia in premature infants born at the Boston Lying-in Hospital.

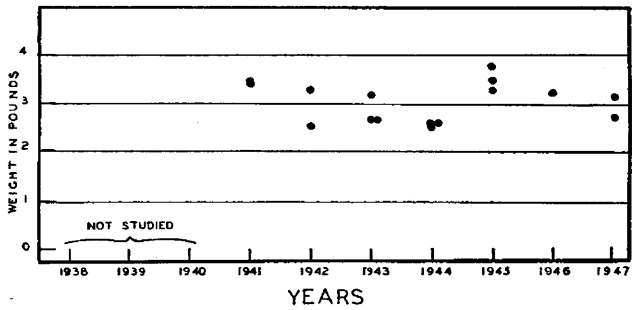

Fig. 4.—Birth weights of premature infants in whom retrolental fibroplasia developed who were born at the Providence Lying-in Hospital.

incidence of the condition. Those factors affecting the mothers or infants may be divided into two classifications. The first (tables 2 through 13) includes those factors affecting some mothers or some infants throughout the ten year period studied. The second includes those factors which either were absent entirely or varied significantly from one part of the study period to another, but which applied to all cases, once initiated.

In the first classification it is possible to determine whether the incidence of retrolental fibroplasia in any particular group is different from that in the total group. The factors considered are:

Parity (table 2)
Age of mother (table 3)
Rh type (table 4)
Type of delivery (table 5)
Analgesic administered (table 6)
Anesthesic administered (table 7)
Causes of prematurity (table 8)

Single or multiple births (table 9)
Sex of the infant (table 10)
Presence of congenital abnormalities (table 11)
General information (table 12)
Miscellaneous (table 13)

There appears to be a significant correlation between the incidence of retrolental fibroplasia and only two of the aforementioned factors. The first of these is seen in table 2, which shows that the incidence of retrolental fibroplasia in offspring of primiparous women (45 per cent of the total) was 9.5 per cent compared with 19.7 per cent in those of multiparous women. This difference in incidence may be said to be significant, since the probability that it would occur by chance is much less than 1 in 100. The number of cases involved in each parity group above 1, taken separately,

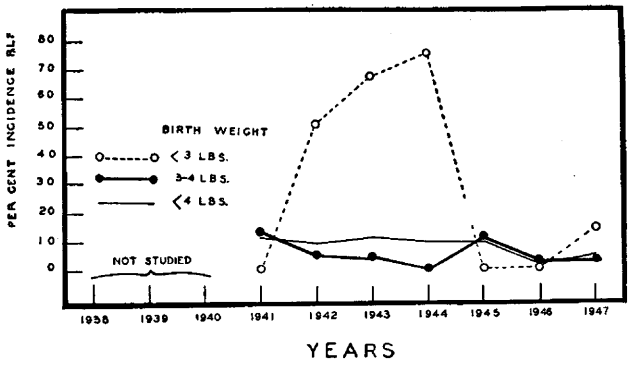

Fig. 5.—The incidence of retrolental fibroplasia in premature infants born at the Providence Lying-in Hospital.

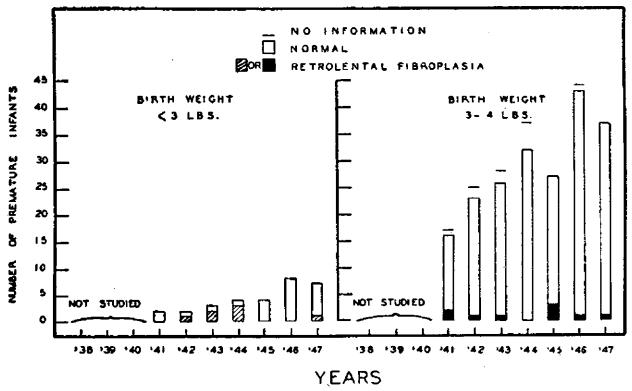

Fig. 6.—The number of premature infants born at the Providence Lying-in Hospital (top line), the number of cases of retrolental fibroplasia (cross hatch for the birth weight group under 3 pounds and solid blocks for the birth weight group 3 to 4 pounds) and the number of premature infants known to be normal with respect to retrolental fibroplasia (open blocks).

is too small to determine whether the incidence rises progressively with parity.

The second instance of possibly significant correlation is seen in table 12, which shows that infants in whom retrolental fibroplasia subsequently developed remained in the nursery, water jacket incubator and in oxygen for longer periods than the infants in whom retrolental fibroplasia did not develop. This suggests that the general health of the infants in whom retrolental fibroplasia subsequently developed may have been poorer than of those whose eyes remained normal, or possibly that the latter were larger infants requiring a shorter stay in the hospital.

The distribution of cases of retrolental fibroplasia according to sex is also of possible significance. Table 10 shows that the disease occurs more frequently in male (14.0 per cent) than in female (9.2 per cent) subjects. The probability that this distribution would occur by chance is between 1 in 10 and 1 in 20. The distribution by sex at the Boston hospital was approximately constant from year to year, except for 1945,

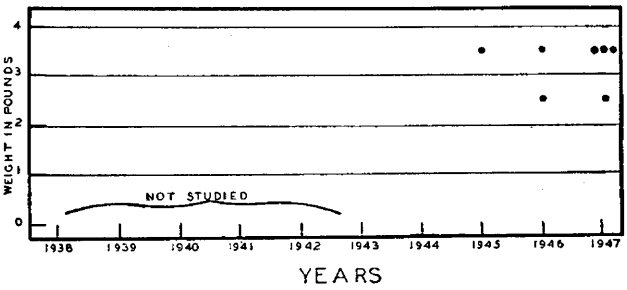

Fig. 7.—Birth weights of premature infants in whom retrolental fibroplasia developed who were born at the Cincinnati General Hospital.

in which year all 12 cases of retrolental fibroplasia occurred in male subjects. The probability that this would occur by chance, considering the average incidence in all of the years in male and female subjects in the Boston hospital, is less than 1 in 1,000,000. We are unable to account for the distribution by sex in

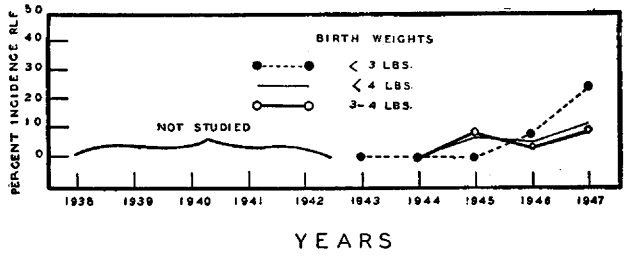

Fig. 8.—The incidence of retrolental fibroplasia in premature infants born at the Cincinnati General Hospital.

this year, or for the much higher incidence observed in 1945 compared with that in the years 1943, 1944, 1946 and 1947.

Gilger (Cincinnati), who has similarly attempted to correlate incidence with factors affecting mothers or infants, found no correlation between the incidence of

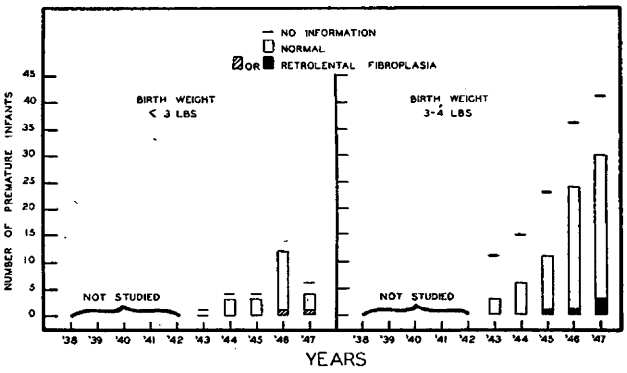

Fig. 9.—The number of premature infants born at the Cincinnati General Hospital (top line), the number of cases of retrolental fibroplasia (cross hatch for the birth weight group under 3 pounds and solid blocks for the birth weight group 3 to 4 pounds) and the number of premature infants known to be normal with respect to retrolental fibroplasia (open blocks).

the disease and the age of the mother, frequency of uterine bleeding, virus infections during pregnancy, chronic illness during pregnancy, causes of prematurity

or race. She found, as we did, a probable positive correlation between the parity of the mothers and the incidence of retrolental fibroplasia, since all 7 of the cases of the condition which she reports occurred in infants of multiparous mothers. The probability that this would occur by chance is 1 in 10. She did not investigate the length of stay in the hospital and other such factors.

The use of the analgesic meperidine hydrochloride was the only factor of those thus far considered in which there was any appreciable variation in frequency of administration in one part of the period investigated compared with another. This drug was used more frequently in the last five year period and was administered to 77 mothers in 166. The incidence of retrolental fibroplasia in infants born to mothers receiving meperidine hydrochloride was 23.5 per cent compared with an incidence of 19 per cent in infants whose mothers did not receive the drug. This difference is not significant.

The second classification, viz., the factors which changed from one part of the 1938 through 1947 period compared with another part, and which once initiated affected all infants, will now be considered. As mentioned previously, the most striking instance of

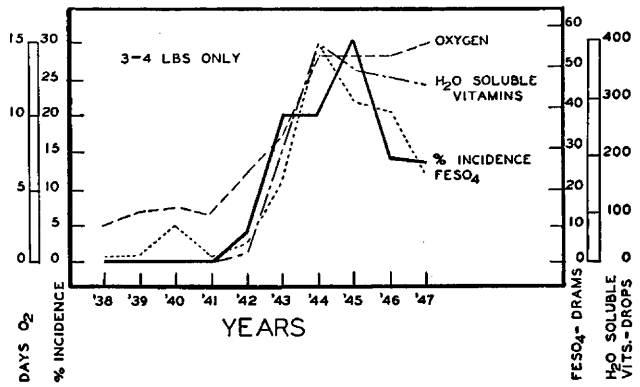

Fig. 10.—Correlation between the incidence of retrolental fibroplasia in premature infants born at the Boston Lying-in Hospital, and the administration of oxygen, ferrous sulfate (1 dram contains 1 grain, 65 mg. iron sulfate) and vitamin supplements given in a water-miscible form.

increased incidence (fig. 2) occurred during the second half (1943 through 1947) of the ten year period in infants weighing between 3 and 4 pounds. Since any correlation between treatment and incidence might be expected to be most evident in this group in which the increase in incidence was most apparent, the following data are concerned with this birth weight group only (3 to 4 pounds). Examination of the hospital records showed that the treatment of the infants varied significantly with time in three respects only: first, administration of a multiple vitamin preparation in which the fat-soluble vitamins are made miscible with water; secondly, administration of iron in greatly increased quantities, and thirdly, more frequent administration of oxygen.

To determine whether there was a significantly positive correlation between the increased incidence and the use of any or all of these three agents, the average actual amount administered per infant per hospital stay was plotted along with the incidence of the disease for the same period. This method of representing the data is necessarily arbitrary, but since all three forms of treatment were used for essentially all of the infants, this method of averaging seems to represent a valid method for comparing change in incidence with change in quantity of the agent administered. From figure 10 it may be seen that the incidence rises along with the total amount of the water-miscible vitamin preparation and the total amount of iron given. The graphs also show that the maximum

TABLE 2.—*Parity,* Boston Lying-in Hospital*

Para	Normal Children	Children with R.L.F.	Incidence, Percentage
1	143	15	9.5
2	67	13	16
3	33	13	28
4	20	4	17
5	13	4	24
6	5	0	0
7	1	1	50
8	5	1	17
9	4	0	0
10	1	0	0
Over 10	1	1	50
Unreported	5	1	17
Total multiparas	150	37	19.7
Total	298	53	15.1

* The percentage of the total group of premature infants whose mothers were primiparas does not differ significantly from the percentage of the total number of term babies born of primiparous mothers. This was true also for mothers who gave birth to their second and third, fourth and fifth, sixth child or more.

quantity of the water-miscible vitamin preparation and iron given and the maximum incidence of retrolental fibroplasia do not correspond precisely. The correlation between rise in incidence and dosage is less striking for oxygen than for the water-miscible vitamin preparation and for iron.

Additional information concerning the possible correlation between the three forms of treatment consid-

TABLE 3.—*Age of Mother, Boston Lying-in Hospital*

Years	Normal Children	Children with R.L.F.	Incidence, Percentage
16-25	89	14	14
26-35	146	27	16
36-45	52	10	16
Unreported	11	2	15
Total	298	53	15.1

TABLE 4.—*Rh Type,* Boston Lying-in Hospital*

Type †	Normal Children	Children with R.L.F.	Incidence, Percentage
Rh +	67	16	19
Rh −	13	5	28

* Years 1945, 1946 and 1947 only.
† In the white population the distribution according to Rh type is 85 per cent Rh positive and 15 per cent Rh negative. The distribution found here in normal persons is 84 per cent Rh positive and 16 per cent Rh negative, and the distribution in infants with retrolental fibroplasia is 76 per cent Rh positive and 24 per cent Rh negative. In this small sample there is no deviation from the normal either with respect to the normal infants or those in whom retrolental fibroplasia developed.

ered herein and the incidence of retrolental fibroplasia can be obtained by comparing the treatment with respect to these three items and the incidence of the condition in other localities where sufficient data regarding treatment are available.

Table 14 (3 to 4 pound weight group only) presents data concerning the administration of water-miscible

vitamins [11] and iron given infants in the hospitals studied in other cities in comparison with that given at the Boston hospital. For comparative purposes in the table, the quantities are listed as zero when not given, and higher or lower than the middle range of quantities used at the Boston hospital.

From this table it can be seen that the incidence is 1 per cent or less in those hospitals in which low doses of iron were given either without vitamins in water-miscible form (Boston 1938 through 1942, New York, Birmingham) or with vitamins in this form in low dosages (Baltimore). The incidence is intermediate (between 1 and 20 per cent) in those hospitals in which iron or the amount of water-miscible vitamin preparation used is high (Cincinnati and Providence, group 1, respectively). These data, therefore, show that in cities other than Boston there is also some degree

TABLE 5.—*Type of Delivery, Boston Lying-in Hospital*

Type	Normal Children	Children with R.L.F.	Incidence, Percentage
Breech	64	12	17
Transverse	7	5	42
Low forceps	84	6	7
Cesarian	37	10	21
Normal	153	22	13
Unreported	12	0	0
Average incidence			15.1

TABLE 6.—*Analgesic Administered, Boston Lying-in Hospital*

Analgesic	Normal Children	Children with R.L.F.	Incidence, Percentage
Amobarbital	29	4	12
Meperidine hydrochloride	78	23	22.8
Phenobarbital	51	8	13.5
Magnesium sulfate	46	6	12
Morphine	27	6	18
Pentobarbital sodium	35	2	5
Pantopon *	31	7	18
Paraldehyde	16	5	24
Scopolamine	147	29	16
"Seconal sodium" (sodium 5-allyl-5-[1-methylbutyl] barbiturate)	112	21	16
Average incidence			15.1

* A proprietary preparation containing the total opium alkaloids in the form of soluble hydrochlorides.

of positive correlation between the incidence of retrolental fibroplasia and the quantity of vitamins given in a water-miscible form or the amount of iron administered. A possible exception to this correlation may be seen from the second group at Providence, where no water-miscible vitamins were administered, but the incidence of retrolental fibroplasia was 4 per cent—an intermediate value.[12] In evaluating the results of such a comparison it is necessary to keep in mind that the regimen may be altered after the infant is sent home. Accurate information concerning home care is difficult to obtain.

We believe that, so far as the factors cited herein may operate to increase the incidence of retrolental fibroplasia, they do so indirectly and not through a direct toxic effect. This belief is supported by the observation that the incidence of the condition in infants under 3 pounds was much less influenced by the presence or absence of these factors from one locality to another, although the incidence was higher than in the heavier infants (3 to 4 pounds). One may suppose that, all other factors remaining constant, an added influence of some kind may be necessary before retrolental fibroplasia develops in any significant number of the heavier infants. The primary mechanism, however, presumably is the same in both weight groups.

TABLE 7.—*Anesthetic Administered, Boston Lying-in Hospital*

Type	Normal Children	Children with R.L.F.	Incidence, Percentage
Gas	52	14	21
Ether	107	18	14
Vinyl ether	13	7	35
Spinal	98	16	14
Average incidence			15.1

TABLE 8.—*Causes of Prematurity, Boston Lying-in Hospital*

Cause	Normal Children	Children with R.L.F.	Incidence, Percentage
Spontaneous delivery	178	32	15
Preeclampsia	76	10	12
Premature separation of placenta	31	8	20
Placenta previa	17	5	23
Premature rupture of membranes	44	7	14
Hydramnios	5	0	0
Unreported	13	0	0
Average incidence			15.1

TABLE 9.—*Single and Multiple Births, Boston Lying-in Hospital*

Type	Normal Children	Children with R.L.F.	Incidence, Percentage
Single	230	42	15.4
Twins	63	11	14.9
Triplets	5	0	0
Total	298	53	15.1

TABLE 10.—*Sex of the Infant in Various Localities*

	Male			Female		
	Normal Children	Children with R.L.F.	Incidence, Percentage	Normal Children	Children with R.L.F.	Incidence, Percentage
Boston	127	24	15.9	171	29	14.5
Providence, R. I.	95	11	10.3	114	5	4.2
Cincinnati	37	7	15.9	52	0	0
Total	259	42	14.0	337	34	9.2

Some comment is in order regarding the difference between the administration of vitamins in water-miscible form and in other forms. Lewis and his co-workers [13] and Clifford and Weller [7] have shown that the

11. Each drop of the standard preparation used at the Boston hospital provided on the average: vitamin A, 500 units; thiamine, 0.1 mg.; riboflavin, 0.1 mg.; ascorbic acid, 5 mg.; vitamin D, 100 U.S.P. units, and niacinamide, 0.5 mg.

12. Two of the 4 children with retrolental fibroplasia in Hartford (table 1) were also known never to have received iron or vitamins in a water-miscible form. Data are not available at present concerning treatment administered the children in this group in whom retrolental fibroplasia did not develop.

13. Lewis, J. M., Bodansky, O., Birmingham, J., and Cohlan, S. Q.: Comparative Absorption, Excretion, and Storage of Oily and Aqueous Preparations of Vitamin A, J. Pediat. **31**: 496-508 (Nov.) 1947.

absorption of vitamin A by premature infants when the vitamin is given in a water-miscible form is much higher than it is from an oil-soluble preparation.[14] An infant, therefore, may be capable of absorbing more vitamin A from a water-miscible preparation of 5,000 units of vitamin A than from an oil-soluble preparation of 15,000 units. The water-soluble vitamins presumably are equally well absorbed whether administered in water or accompanying vitamins A and D in the water-miscible form. If, then, the administration of vitamins in a water-miscible form plays a part in increasing the incidence of retrolental fibroplasia, vitamins A or D are probably the ones involved. Since the solvent of the water-miscible preparation used in Boston has been changed several times during the period in which it was used, without a significant change in the incidence of retrolental fibroplasia, it is presumably innocuous. In all the hospitals not using the water-miscible preparation, vitamin A was administered in doses of about 15,000 units per day in an oil preparation, except in Boston in the years 1938 through 1942 when no vitamin A was given.

TABLE 11.—*Presence of Congenital Abnormalities, Boston Lying-in Hospital*

Abnormalities	Normal Children	Children with R.L.F.	Incidence, Percentage
Hemangioma	12	2	14
Umbilical hernia	17	0	0
Congenital heart disease	12	0	0
Undescended testes	11	1	8
Hydrocephalus	3	0	0
Other head deformities	6	0	0
Malformed genitalia	8	3	27
Others	15	2	12
Average incidence			15.1

TABLE 12.—*General Information, Boston Lying-in Hospital*

Item	Days	
	Normal Children	Children with R.L.F.
Average period in nursery	46	56
Average period in water jacket incubator	12	19
Average period in oxygen	12	21

The use of cow's or breast milk for feeding in various localities is difficult to correlate with the incidence of retrolental fibroplasia, since in many hospitals the use of breast milk varies so much with the available supply. Nevertheless, from the data which are available the incidence of this condition does not appear to correlate with the differential use of cow's and breast milk.

CONCLUSIONS

In certain areas the incidence of retrolental fibroplasia has increased significantly in recent years. In Boston, where the data are most complete, the rise in incidence was found chiefly in the 3 to 4 pound (1,361 to 1,814 Gm.) weight group. The greater frequency of retrolental fibroplasia correlates with several changes in treatment of premature infants; i. e., use of vitamin supplements in water-miscible form and increased use of iron. While a positive correlation between rise in incidence of the disease and change in treatment does not constitute proof of any causal relation between the two, nevertheless it is suggestive that the medication used may be of etiologic significance.

To test this possibility, we, in conjunction with the staffs of the Boston Lying-in and certain other hospitals, are planning to investigate the effect on the incidence of retrolental fibroplasia of omitting the iron and also the multiple vitamin preparation in water-miscible form. It is planned to withhold the iron until the premature infant is between 2 and 3 months of age and substitute for the multiple vitamin preparation vitamin D alone, in a water-miscible form (1,000 units daily). In addition, the diet will be supplemented with 50 to 100 mg. of vitamin C daily. No vitamin A or vitamin B-complex will be given. The results of this study will be made available as soon as a sufficient number of infants has been tested to permit statistically valid conclusions concerning the true role of the aforementioned forms of treatment in producing retrolental fibroplasia.

This study has been concerned wholly with premature infants whose birth weights were less than 4 pounds (1,814 Gm.). The incidence of retrolental fibroplasia in heavier premature infants and in term babies has not been investigated, but, from the number of known cases of the disease in such infants, it must be extremely low. Before one draws inferences regarding possible harmful effects from the use of water-miscible vitamin preparations or iron in treating heavier premature infants or term babies, one should consider these facts.

TABLE 13.—*Miscellaneous Factors, Boston Lying-in Hospital*

Factor	Normal Children	Children with R.L.F.	Incidence, Percentage
Complete blood cell count (baby)	99	17	15
X-ray (baby)	67	13	16
X-ray (mother)	111	25	18
Transfusion (baby)	28	9	24
Clysis (baby)	32	8	20
Nonocular infection (baby)	56	13	19
Eye infection (baby)	35	6	15
Infection (mother)	74	16	18
Average incidence			15.1

TABLE 14.—*Correlation of Treatment with Incidence in 3-4. Pound Weight Group*

	Years	Multiple Water-Miscible Vitamin Preparation *	Iron *	ncidence of R.L.F., Percentage
Boston	1938-1942	0	L	0.9
Boston	1943-1947	H	H	20.2
Baltimore	1935-1947	L	L	1.0
New York	1939-1946	0	0	0.7
Cincinnati	1943-1947	0	H	6.8
Birmingham, England	1945	0	L	0
Providence, R. I.	1938-1947	H	L	5.2
Providence, R. I.	1938-1947	0	L	4.0

* The quantities are listed as zero when not given, and higher (H) or lower (L) than the middle range of quantities used at the Boston hospital.

14. The use of the vitamin supplement in water-miscible form was inaugurated at the Boston Lying-in Hospital in 1943 to increase the amount of vitamin A absorbed by the premature infant. This therapy was instigated as a result of studies by Warkany (Warkany, J.: Congenital Malformations Induced by Maternal Nutritional Deficiency, J. Pediat. **25**: 476-480 [Dec.] 1944) in which it was shown that a disease resembling retrolental fibroplasia in many respects could be produced in young rats born of mothers who were deficient in vitamin A.