APPENDIX A

"Causes" of RLF
First Ten Years (1942–1952)

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
A. *Parental Factors*		
1. Causes of premature birth		
a. Multiple birth	High frequency in twins Identical (monovular) —twins both usually affected Fraternal twins—one or both affected	
b. Toxemia of pregnancy		
c. Premature separation of the placenta		
d. Placenta previa		
e. Premature rupture of membranes		
2. Maternal infection		

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
a. Smallpox vaccination		
b. Mild clinical infections		
c. Subclinical infections		
3. Nausea of pregnancy		
4. Attempted abortion		
5. Diet during pregnancy		
6. Medication during pregnancy		
7. X-ray examination		
8. Onset of labor		
9. Weight gain during pregnancy		
10. Presentation of the infant		
11. Type of delivery		
12. Type of anesthesia and analgesia		
13. Age of parents		
14. Economic status		
15. Place of conception		
16. Place of residence during pregnancy		
17. Parity of mother	First born more frequently affected in one series; first born less frequently affected in another series	
18. Blood type (Rh)		

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
status of the mother		
19. Type or condition of the placenta	Placental deformities more frequent in RLF	
20. Uterine bleeding	Bleeding in pregnancy was more frequent in infants who subsequently developed RLF; another series found no association	
B. *Factors Relating To The Infant*		
1. Season		
a. Month of conception		
b. Month of occurrence of RLF		
2. Sex	RLF more common in males	
3. Malformations	Skin hemangiomas more frequent in RLF	
4. Condition of infant at birth		
a. Resuscitation		
b. Cyanosis (or asphyxia)		
c. Chest wall retractions		
d. Jaundice		
e. Diarrhea		
f. Body temperature		

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
g. Rate of weight gain		
h. Blood pressure (intra-atrial)		
i. Calcium, phosphorus, phosphatase-level in the blood		
j. Red blood cell resistance to break down		
k. General health	Infants with RLF appeared "weaker;" they remained in the incubators longer and received more transfusions and subcutaneous injections of fluid than others who did not develop the disease	
5. Medical management		
a. Prenatal exposure to X-ray		
b. Exposure to light		Five trials of light exposure vs. eyes covered: all failed to implicate light
c. Initial	RLF more frequent in	

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
thirsting and starving	nurseries which withheld feedings for 2 to 3 days after birth	
d. Milk feeding	High incidence of RLF in some nurseries using cow's milk-mixture No RLF in a large nursery using only cow's milk-mixture	
e. Blood transfusion	RLF in infants who received early and repeated transfusions; acute RLF frequently progressed following blood transfusion; on the other hand, RLF in many infants who were never transfused	
f. Vitamin A deficiency	Eye defects in Vitamin A deficient rats resemble RLF	Large doses of Vitamin A did not prevent RLF in a group of premature infants
g. Use of water-miscible vitamin supplements and iron	Variation in frequency of RLF correlated with use of water-miscible vitamins and iron (Fig. 3-2)	Frequency of RLF unchanged when multivitamins and iron were excluded from diet of a group of premature infants
h. Vitamin E	Human premature	Prophylactic and

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deficiency	infant has low levels of vitamin E as compared with mature newborns	therapeutic administration of vitamin E (orally) gave conflicting results: some observed decrease in severity of eye damage, others observed no effect
i. Anoxia and oxygen	Sublethal oxygen-lack leads to damage of vascular tissue—(including retinal vessels of rats)	New cases of RLF continued to develop after reduction in oxygen concentration
	Improper use of oxygen (too rapid removal from supplemental oxygen) in premature infants followed by progression of acute RLF	Formal prospective trials reported in late 1952 (see Chapt. 4
	Variation in frequency of RLF (Fig. 3-2) correlated with use of oxygen treatment of premature infants	
	Use of high concentrations of oxygen correlated with rise in frequency of RLF	
	No RLF in a large nursery in U.S. and	

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
	in a center in England where oxygen was used freely	
j. Infection (viral agent?)		
k. Hemorrhagic tendency of premature infant	Pre-retinal hemorrhages commonly precede RLF	
l. Delayed retinal coaptation (apposition of retina to underlying choroidal layer of the eye)	Half of small premature infants show delay in coaptation of the retina; RLF developed in many of these infants	
m. Miscellaneous speculations: Uncontrolled new-blood-vessel growth in the retina Uveitis (inflammation of iris, ciliary body and choroid) resulting from un-		

Factors Speculated as the Cause of RLF	Retrospective Correlations ("Passive Observations")	Prospective Clinical Trials (Experimental or Quasi-Experimental)
specified noxious agents		
Ocular hypertension		
Careless use of substances which influence growth		