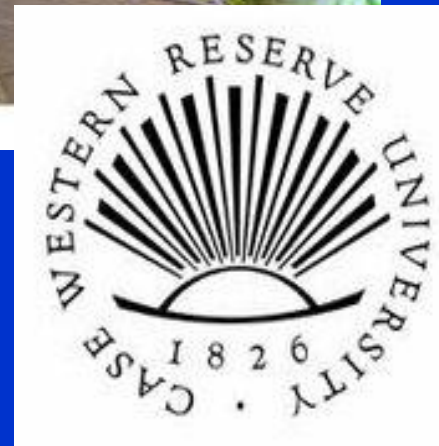


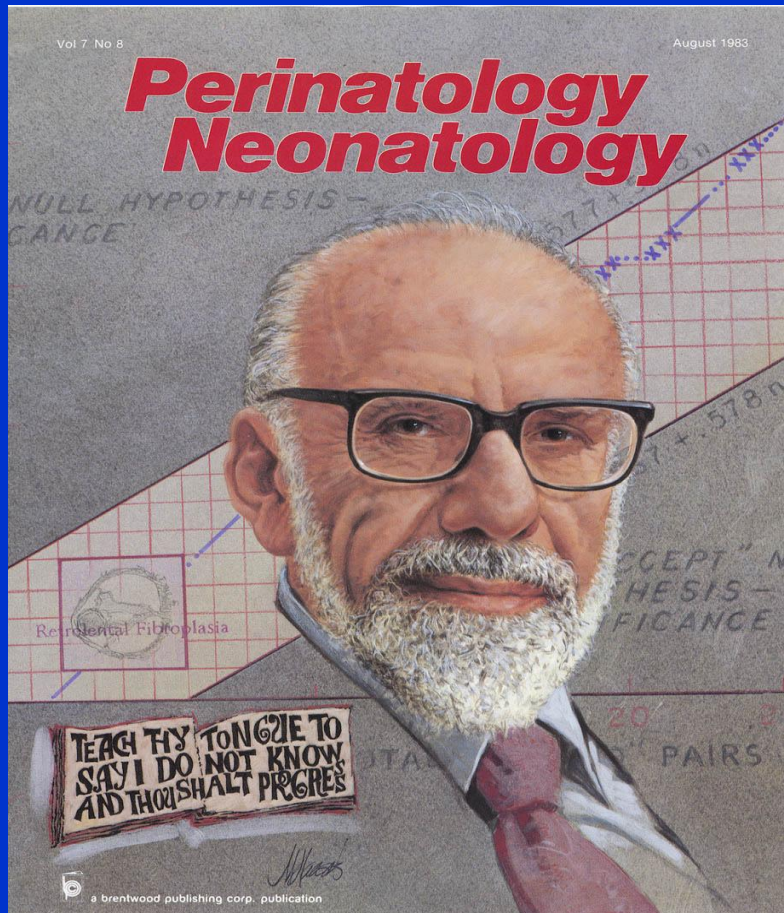
TRIUMPHS AND TRAGEDIES IN NEONATOLOGY: LESSONS LEARNED?



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Bill Silverman



“ We cannot always make our patients better but we can always make them worse!”

Milestones in Neonatology

- 1890-1920 Development of incubator
- 1920-1940 Era of nutrition
- 1940-1950 Era of antibiotics
- 1950-1960 O₂ therapy



MARTIN COONEY'S PREMATURE BABY EXHIBIT





TRIUMPHS



- PREVENTION
- INTERVENTION
- INVENTION – TECHNOLOGY
- CONVENTIONS – GUIDELINES;
CARE PATHWAYS; QUALITY
IMPROVEMENT
- RETENTION – BENCH MARKING
BEST PEOPLE AND PRACTICES

TRIUMPHS- PREVENTION

- *Blindness - Ophthalmia neonatorum- antibiotic eye ointment*
- *Hemorrhagic disease – Vitamin K*
- *Retardation – neonatal screening*
- *Rh disease – Rhogam*
- *Liver cancer – Hepatitis B Immunization*
- *Infections– Intrapartum antibiotics/cord care*
- *Birth defects – folic acid and periconceptual glucose control in diabetics*
- *Deafness – hearing screening*

MAJOR THERAPEUTIC TRIUMPHS

- Total parenteral nutrition
- Antenatal corticosteroids
- CPAP/ mechanical ventilation
- Surfactant
- Prostaglandins
- Nitric oxide
- Cryotherapy/Laser therapy for ROP
- ECMO
- HYPOTHERMIA
- Pulse oximeter screening for CCCHD

Exchange Transfusions

1946 Wallerstein

Sagittal sinus - out;

Superficial vein - in

1947 Diamond et al

First to introduce umbilical
vein catheterization

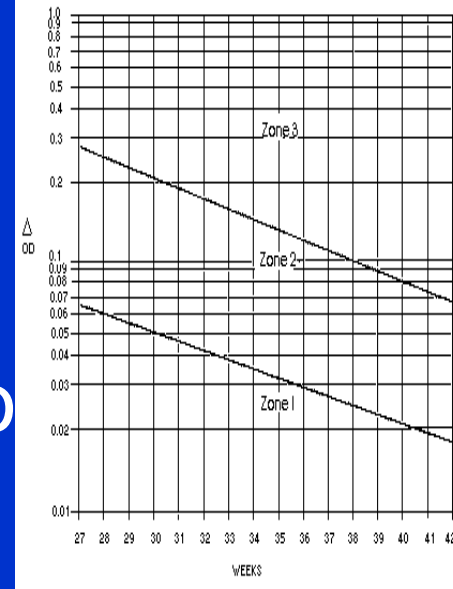
Alternate
removal and transfusion.



**HERALDS MODERN
ERA OF NEONATOLOGY**

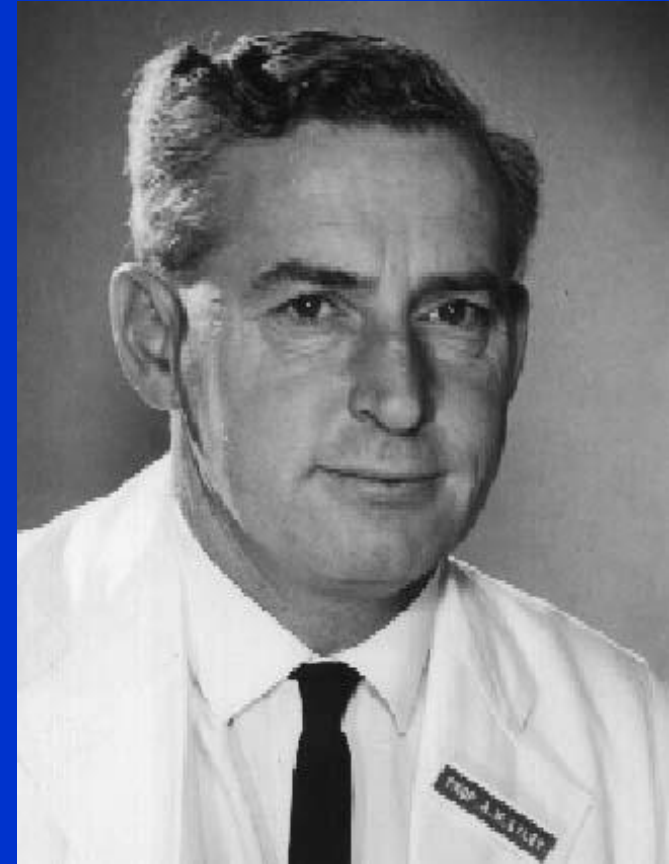
Erythroblastosis Fetalis

- 1952 Bevis Amniotic fluid analysis for severity of EBF
- 1963 Liley Intrauterine transfusion
- 1964 Fried Anti Rh gamma globulin for prevention of Rh disease
- 1965 Woodrow et al
- Today -Rh sensitization is almost totally eradicated in developed countries



RATIONALE FOR INTRAUTERINE TRANSFUSIONS

- "a young English lady, a geneticist, who had been working in Nigeria on sickle cell disease, visited Auckland.....with her she had some beautiful blood slides from neonates and infants homozygous HbS, who had been given normal cells intraperitoneally.
- There were floods of normal cells in their peripheral blood, and this was good enough evidence for us that cells could be taken up from the peritoneum in massive quantity and at a relatively rapid rate".
- Liley, A, 1965, *Pediatrics*, Vol. 35: 836-846).



Sir William Liley 1929-1983

**KCMG, DSc *Vict* PhD ANU MB ChB B Med Sc
Dip Obs FRSNZ FACOG FRCOG**

INTRAUTERINE TRANSFUSIONS

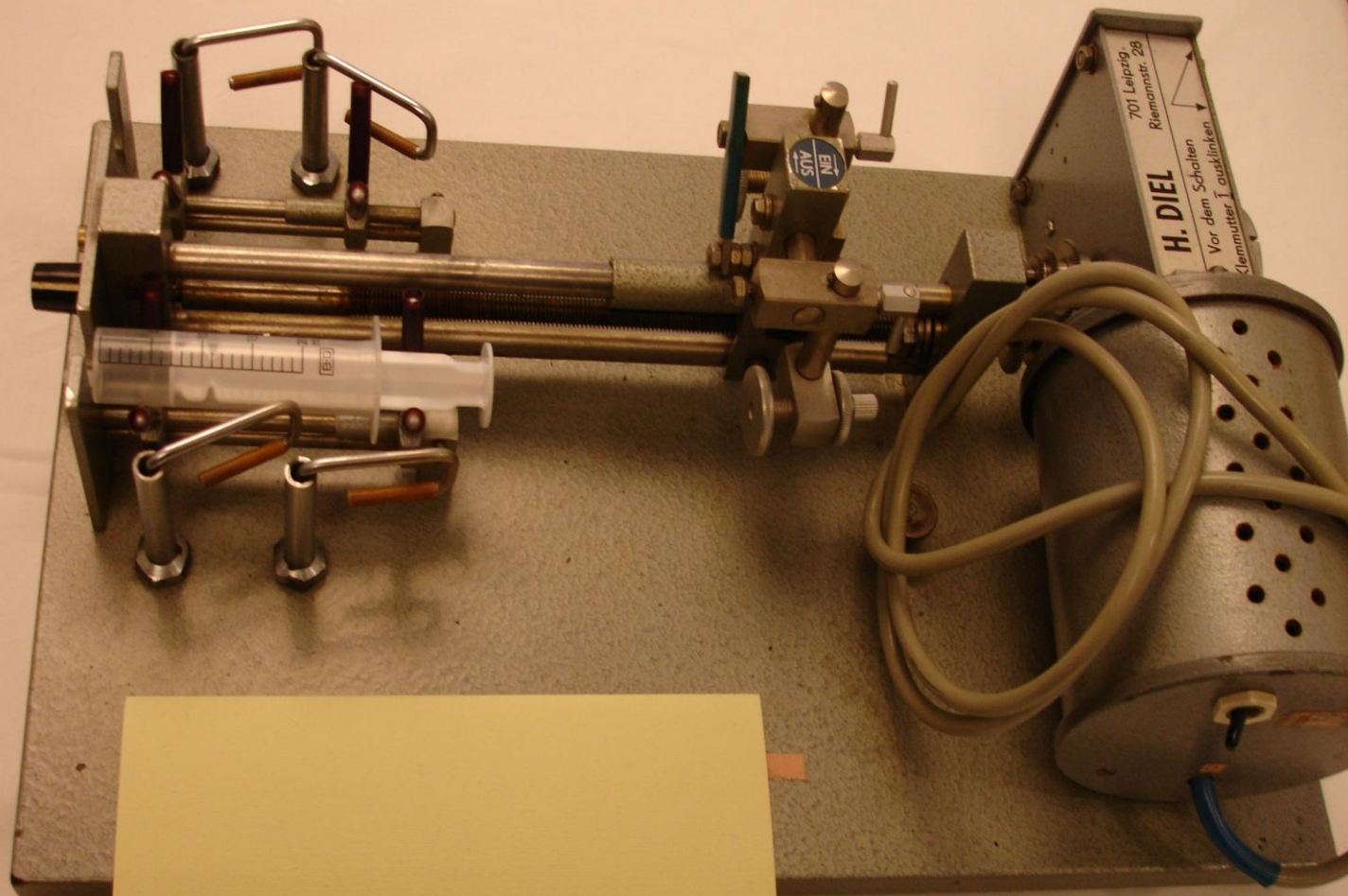
- As in many areas of science, major advance results from what is loosely termed serendipity.
- However, it is not luck which determines these major advances, **but rather the presence of a disciplined prepared mind** which can capitalize upon an observation, the significance of which would be ignored by others.
- During one amniocentesis, Liley "accidentally needled the distended fetal abdomen. Instead of getting deep yellow, cloudy, amniotic fluid I got brilliant, golden, clear fluid which was obviously ascitic fluid; this windfall was easily confirmed by injection of contrast medium.it occurred to me that if we could needle the fetal peritoneum without even trying then we could perhaps do it deliberately and put it to some good use".
- (Liley, A., *Pediatrics*, 1965; 35: 836-846)

-
- Bilirubin Management Guidelines For Healthy Term Infants**
- The chart displays bilirubin management zones and curves for healthy term infants. The y-axis represents bilirubin levels in mg per 100 ml (0 to 30), and the x-axis represents age in hours (0 to 168).
- Management Zones (from top to bottom):**
- Exchange Transfusion:** Red zone, highest bilirubin levels.
 - Very Intensive Phototherapy (27-30 h):** Orange zone.
 - Intensive Phototherapy:** Pink zone.
 - Moderate Phototherapy:** Blue zone.
 - Active Intake - Supportive Phototherapy:** Green zone.
- Curves (from top to bottom):**
- Breast Fed:** The highest curve, peaking around 15 mg/100 ml at 72 hours.
 - Pregnancy Associated:** The middle curve, peaking around 12 mg/100 ml at 72 hours.
 - Pregnancy Associated + Breast Fed:** The lowest curve, peaking around 8 mg/100 ml at 72 hours.
- Other Labels:**
- Zone B:** Located in the yellow area between 10 and 15 mg/100 ml at early ages.
 - Zone A:** Located in the red area at very high bilirubin levels.

WORLD WIDE IMPACT OF FAILURE TO ESTABLISH Rh immunization with RHOGAM

“Currently the missed opportunity for the preventative provision of an effective Rh globulin is the direct cause of 41,000 stillbirths, 90,000 neonatal deaths and 41,000 children with severe and permanent brain damage (kernicterus) each year.





Spritzenpumpe
1960

PREMATURE CARE IN THE 1950's- An interview with Dr. William Silverman, father of neonatal intensive care - Helen Harrison

“I was disturbed by how long it took to recognize the harmful effects of specific treatments. I began to advocate increased use of the randomized controlled trial to find out if treatments were beneficial and discover any unexpected risks”

PREMATURE CARE IN THE 1950's- An interview with Dr. William Silverman, father of neonatal intensive care by Helen Harrison

“I began to witness a series of **disasters** accompanying this rapid introduction of new drugs and procedures.

The liberal use of oxygen was associated with **blinding of infants.**

Some of the drugs that appeared so promising proved to be **lethal**, some led to **brain damage or other handicaps.**”

1950' S ERA OF BENIGN NEGLECT AND DISASTROUS INTERVENTIONS

- ❑ High mortality and morbidity
- ❑ Retinopathy/Oxygen/ACTH
- ❑ Restricted use of oxygen
- ❑ Efforts to prevent infection –
Kernicterus and Gray baby
syndrome

1950' S ERA OF BENIGN NEGLECT AND DISASTROUS INTERVENTIONS

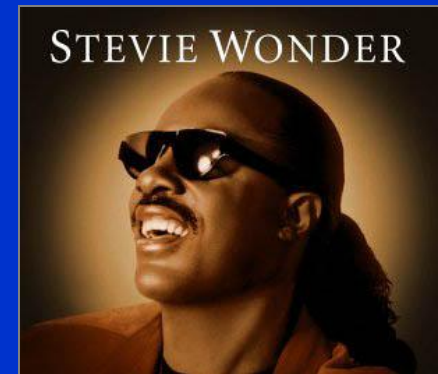
- ❑ *Prolonged starvation of immature infants- the lighter the infant the longer they were NPO*
- ❑ *Failure to promote breast feeding for preterm infants*

1950' S ERA OF BENIGN NEGLECT AND DISASTROUS INTERVENTIONS

- ❑ No intensive care/ No parents in nurseries- resulted in abuse and abandonment
- ❑ Apgar scoring system introduced
- ❑ Thermal regulation (NTE) reduced mortality

1940' s-1950' s: Recognition of Oxygen Toxicity

- Terry reported retinal detachment that appeared to occur frequently among premature infants who received 100% oxygen over prolonged periods of time
- The pathological findings of oxygen toxicity were termed retrolental fibroplasia (RLF), now known as retinopathy of prematurity (ROP)



OXYGEN- POTENTIALLY HARMFUL?

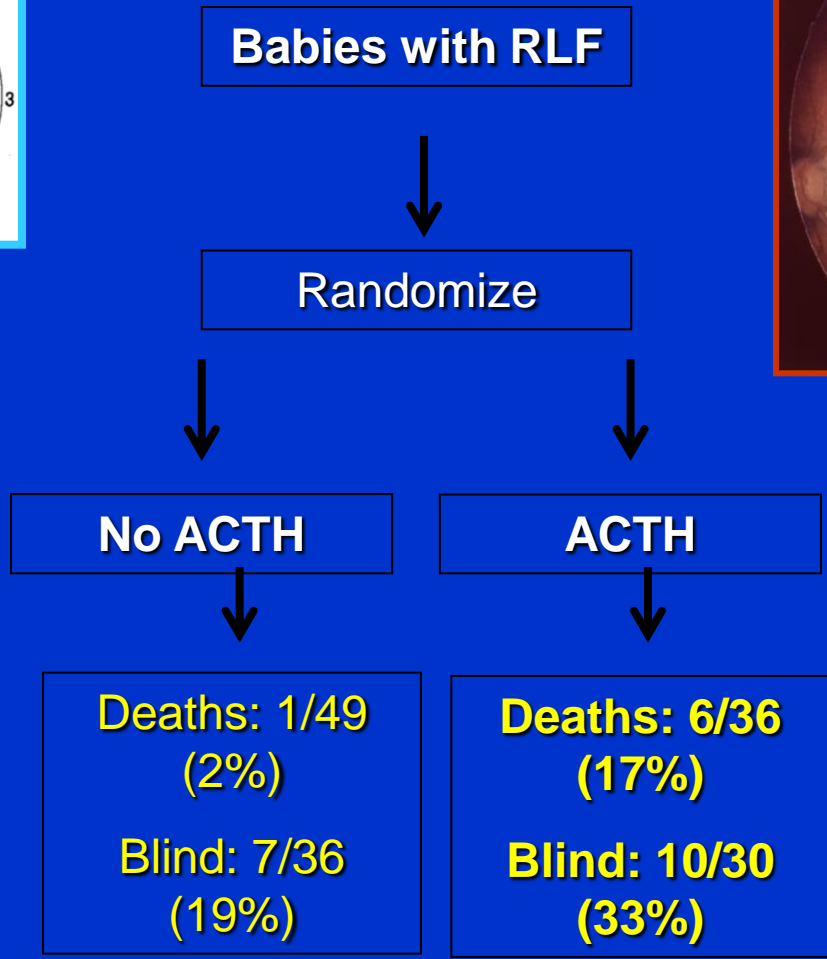
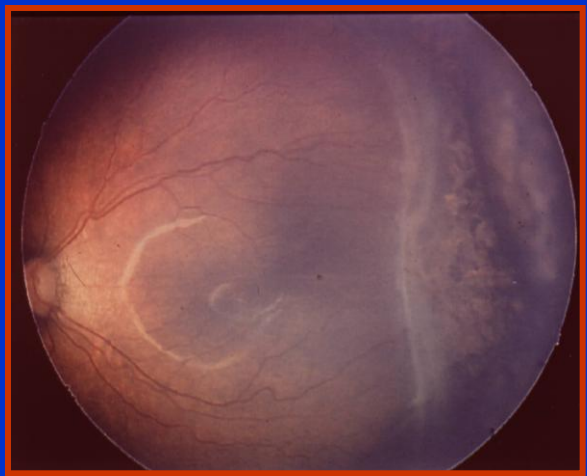
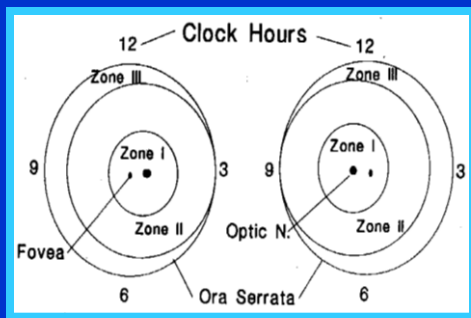
- Clinical trial
 - babies < 3.5 lb were assigned alternately to treatment (conservative O₂) or control (high O₂)
 - **trial difficult to conduct since some doctors/nurses questioned the wisdom of curtailing the O₂ for premature babies**
 - 6 of 37 (16%) of conservative O₂ group developed RLF
 - 17 of 28 (61%) of high O₂ group developed RLF
 - *Patz A, Hoeck.L De La Cruz E Studies on the effect of high oxygen administration in retrolental fibroplasia. American Journal of Ophthalmology 1952; 35, 1248-53*

ACTH FOR ROP – HELP VS HARM ?

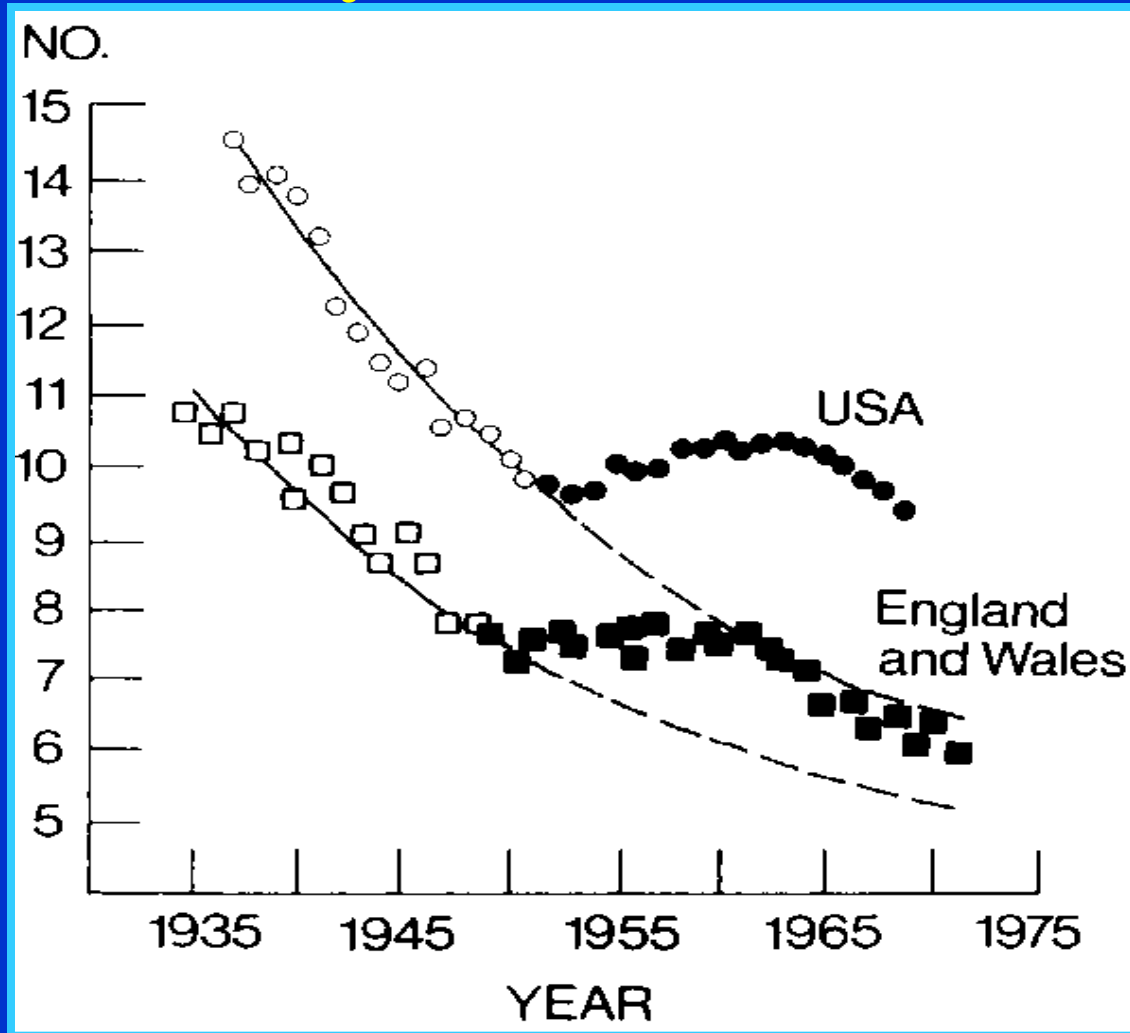
- Early treatments
 - increase in vascularisation might be a response to hypoxia – liberal use of O₂ in premature infants might then be justified
 - premature infants had low adrenal corticosteroid levels and the pathology of RLF was reminiscent of connective-tissue disease in adults – use of adrenocorticotrophic hormone (ACTH) might be useful
 - Blodi et al. (1951): of 25 out of 31 babies receiving ACTH appeared to respond with reversal of changes and preservation of eyesight
 - Laupus (1951), Pratt (1951) reported treatment failures

Blodi, F., Silverman, W., Day, R., Reese, A., 1951, Experiences with corticotrophin (ACTH) in the acute stage of retrolental fibroplasia. American Journal of Diseases of the Child 1951, 242 - 243.

**Reese, A., Blodi, F., Locke, J., Silverman, W., Day, R., 1952,
Results of use of corticotrophin (ACTH) in treatment of retinal fibroplasia.
Archives of Ophthalmology 47, 551 - 555.**

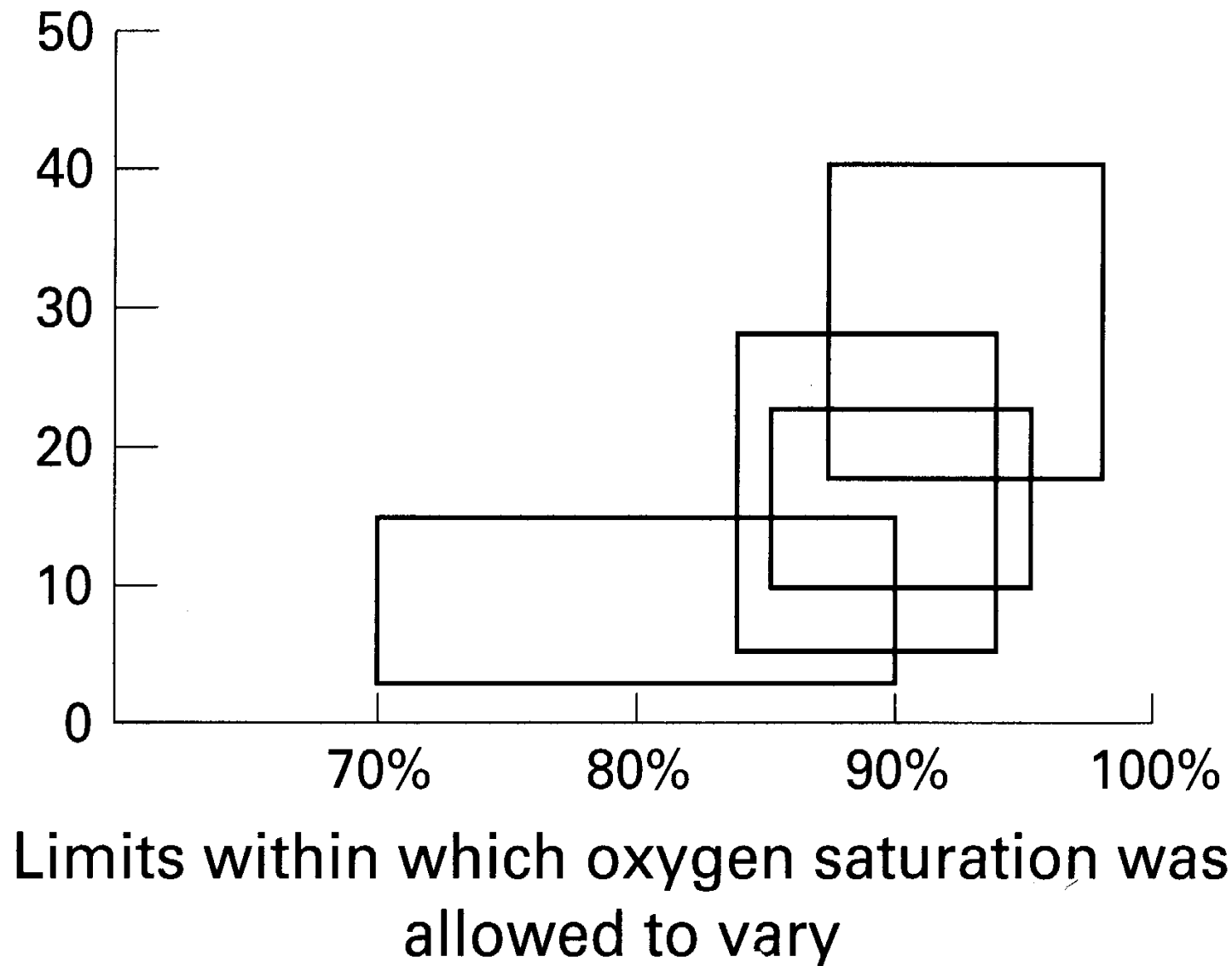


Deaths on day of birth /1000 live births



Mortality on the first day of life in the United States and in England and Wales before (open circles and squares) and after (closed circles and squares) oxygen restriction. (Redrawn from Bolton and Cross, 1974).

Percentage of babies developing
threshold retinopathy (and 95%
confidence intervals)

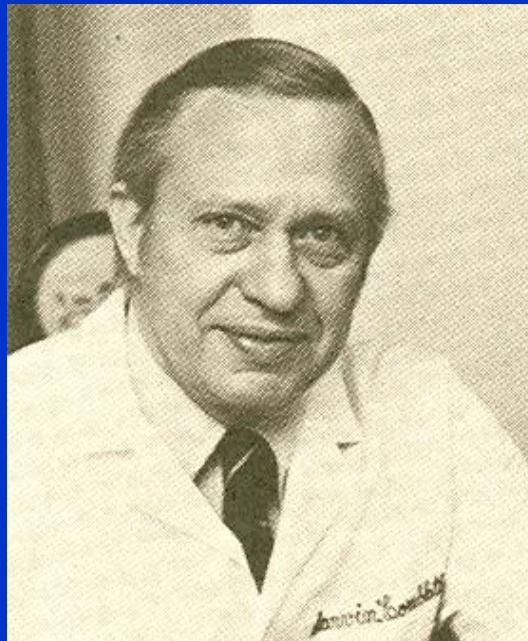


MORTALITY - SATURATIONS 85-89% VERSUS 91-95%

	Lower Saturation Group 85-89%	Higher Saturation Group 91-95%	
SUPPORT	19.9%	16.2%	1.27 * (1.01, 1.60)
BOOST	23.1%	15.9%	1.45 *(1.15- 1.84)
COT	15.3%	16.6%	1.11 (0.80- 1.54,)

A TRAGEDY AVERTED

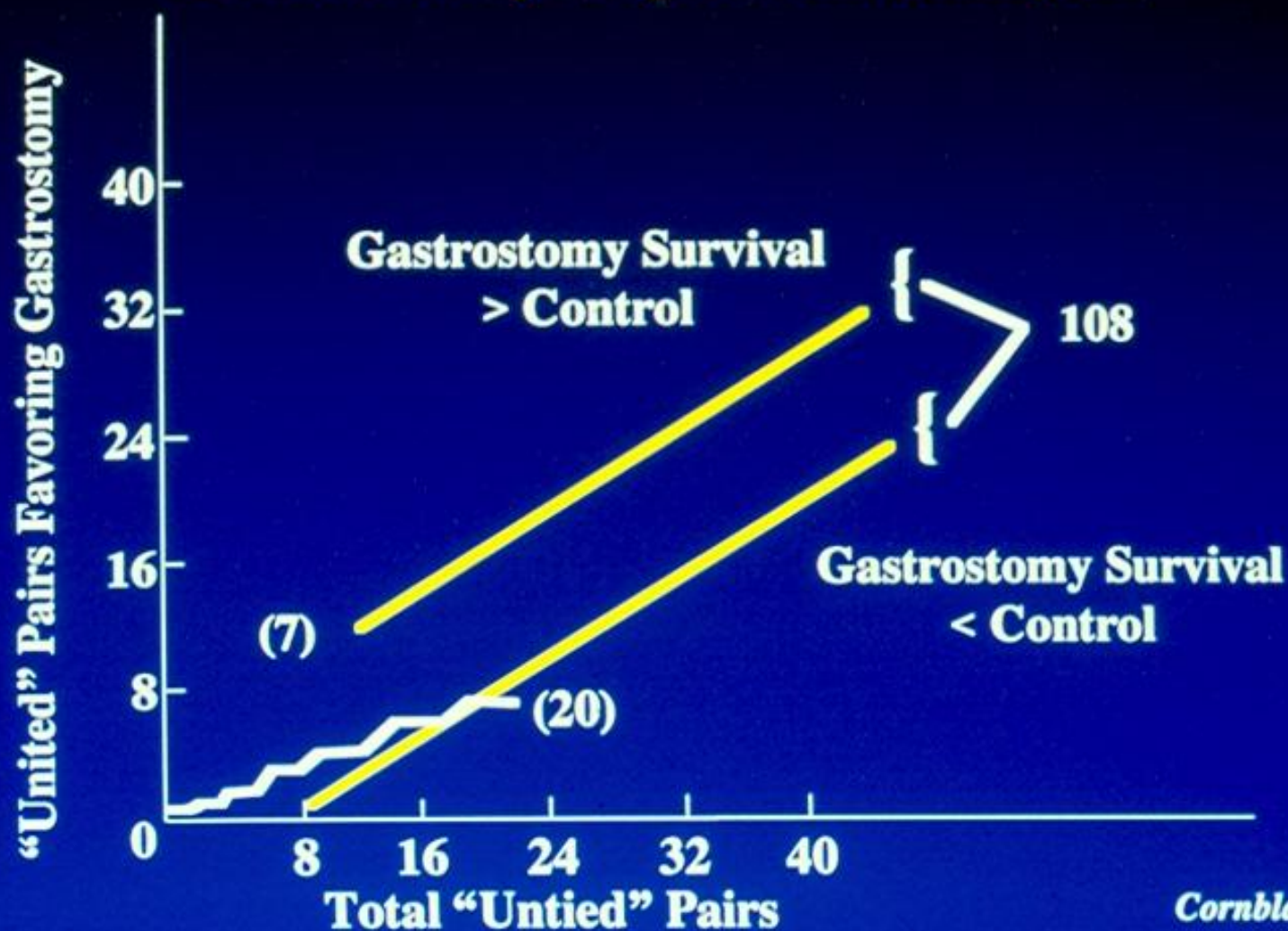
FEEDING GASTROSTOMY FOR
LOW BIRTH WEIGHT INFANTS



CONTROLLED STUDY OF FEEDING GASTROSTOMY IN LBW INFANTS - OUTCOMES

	Matched Pairs 54			
	Tied (34)		Untied (20)	
	<i>Lived</i>	<i>Died</i>	<i>Lived</i>	<i>Died</i>
Gastrostomy	31	3	7	13
Controls	31	3	13	7

Gastrostomy Sequential-Analysis



Controlled Study of Feeding Gastrostomy In LBW Infants

“During the 14-month period of this study, the over-all mortality among infants with birth weights between 750 and 1250 grams in the premature nursery of the Cook County Hospital dropped by 13 percent from that of the previous two years. Had this study lacked concurrent controls, the improvement in survival would have been ascribed to the feeding gastrostomy.”

Cornblath, M.



USHER REGIMEN

- Supplemental Oxygen $> 40\%$ if cyanosed
- Stimulate if apneic
- Glucose and sodium bicarbonate infusion according to pH –
 - 5meq/100 ml if arterial pH > 7.3 ;
 - 10 meq/100ml if pH 7.2-7.3;
 - 15 meq/100ml if pH 7.1-7.2
 - 25 meq/100 ml if pH < 7.1
- Feed enterally when spontaneous activity

USHER REGIMEN

Editors Note:” This interesting and informative paper should be read with care not only because of the new information presented, but also because it contains many unsupported or categorical statements with which a number of workers in the field of the newborn will take issue”

J. McKay

Unproven Therapies

DES & Pregnancy Outcome

	<i>Odds Ratio</i>	<i>95% CI</i>
Miscarriage	1.2	0.89-1.62
Stillbirth	0.95	0.50-1.83
Neonatal Death	1.31	0.74-2.34
All Three	1.38	0.99-1.92
Prematurity	1.41	1.08-2.00

Goldstein

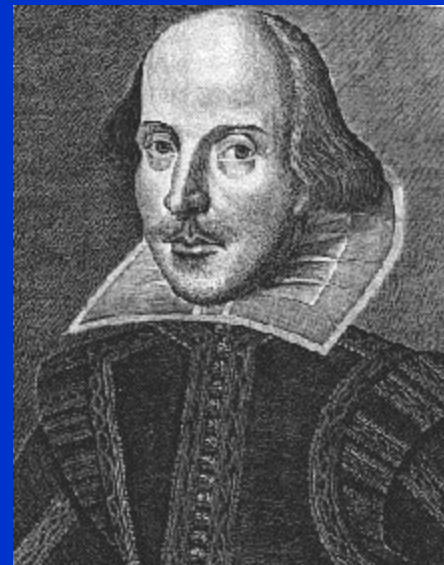
NEONATAL TRAGEDIES

IATROGENESIS ASSOCIATED WITH PREVENTION OF INFECTION

- Sulfisoxazole
- Chloramphenicol
- Novobiocin
- Hexachlorophene
- Kanamycin
- Diaper laundering, and
- Equipment cleaning.



HAMLET



IGNAZ SEMMELWEIS

- Semmelweis realized that the number of cases of puerperal fever was much larger at one of his wards than at the other. After testing a few hypotheses, he found that the number of cases was drastically reduced if the doctors washed their hands carefully before dealing with a pregnant woman. Risk was especially high if they had been in contact with corpses before they treated the women. The germ theory of disease had not yet been developed at the time. Thus, Semmelweis concluded that some unknown "cadaveric material" caused childbed fever.

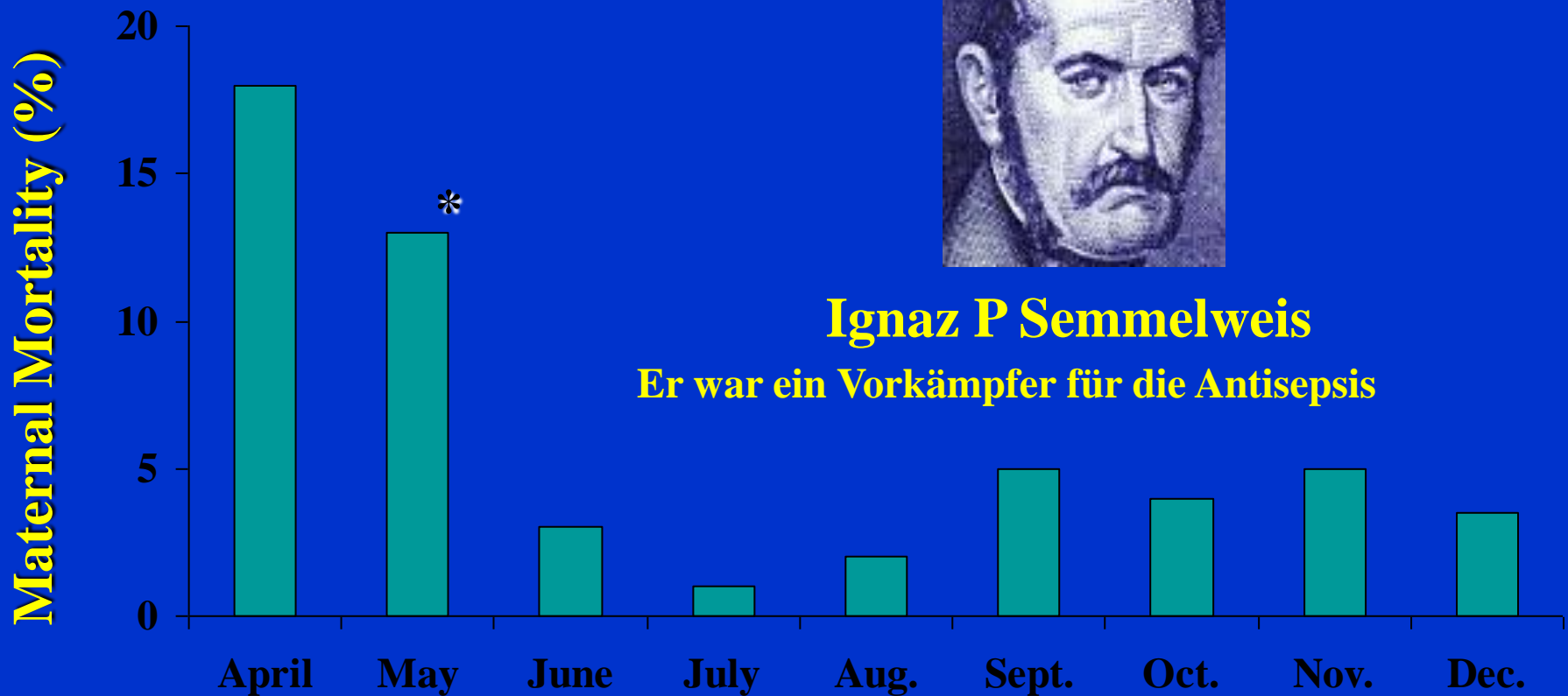


Vienna Lying-in, 1847



Ignaz P Semmelweis

Er war ein Vorkämpfer für die Antisepsis



* = *Introduction of chlorine hand washes*



SEMMELWEIS



- Semmelweis spent 14 years promoting his ideas and wrote a book in 1861
- The book received terrible reviews
- He had a nervous breakdown and was committed to a mental institution where he developed “blood poisoning” and died
- Only after his death was the germ theory recognized and he is recognized as a pioneer of antiseptic policy and prevention of nosocomial sepsis.

HEXACHLOROPHENE



If you could
see the germs,
you'd wash
your hands

Prevention of Neonatal Sepsis

4 Groups: 2 Antibiotics + 2 Humidities

- “Routine administration of antibiotics reduces neonatal mortality for premature newborns”
- Difficulty in recognizing neonatal sepsis justifies prophylactic treatment with antibiotics
- Ideal combination of antibiotics – uncertain
 - Groups 1, 2: Penicillin/sulfisoxazole +
Humidity high or Humidity moderate
 - Groups 3, 4: Oxytetracycline +
Humidity high or Humidity moderate

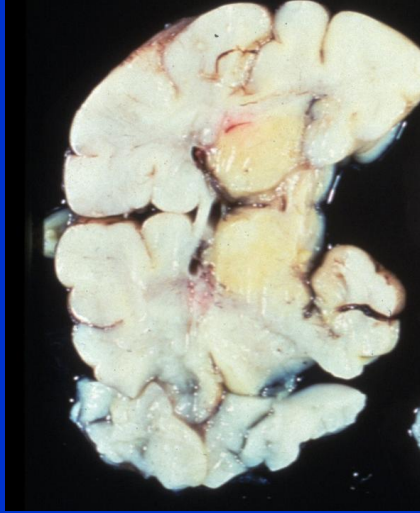
Silverman et al: Pediatrics
1956;18:614

Prevention of Neonatal Sepsis

Results

	Pen/Sulfa	Oxytetracycline
Mortality	72%	80%
Sterile at Autopsy	96%	69%
Kernicterus – died during study	36%	6%
Kernicterus – died after study	64%	0%

Pediatrics 1956;18:614

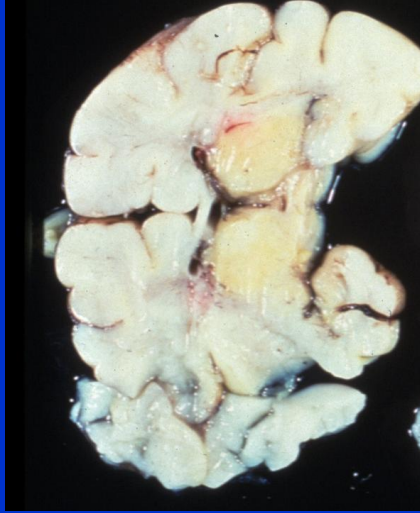


RESULTS



- The results of the study turned out to be deeply disturbing (Silverman et al. 1956).
- **First-5-day mortality was strikingly higher** among infants allotted to the arm of the trial treated with the widely accepted agents for prophylaxis (penicillin/sulfisoxazole) compared to the group receiving the proposed replacement (tetracycline).

•



RESULTS



- A previously unknown and subsequently demonstrated effect of sulfisoxazole was responsible for the startling and completely unexpected result: **the drug displaced albumin-bound bilirubin in the serum of jaundiced neonates with the result that they sustained fatal brain damage from a condition known as kernicterus.**

LESSONS LEARNED

- “We realized immediately that the trial would have been stopped sooner if we had 'peeked' at the results during the course of what we regarded as a very mundane exercise, instead of waiting until all infants had been enrolled.
- This horrific experience convinced us of the need to find a method of 'controlled peeking' at the accumulating results in randomized trials that were still recruiting.”

Silverman

Mortality Increased with Chloramphenicol

	<u>Mortality</u>
No antibiotics (n=32)	19%
Chloramphenicol (n=30)	60%
Penicillin + Streptomycin (n=33)	18%
Penicillin + Streptomycin + Chloramphenicol (n=31)	68%

Burns et al: New Engl J Med
1959;261:1318

CURRENT GOALS

- ✓ *Practice evidence based medicine*
- ✓ *Apply best practices and reduce center variability*
- ✓ *Avoid medical errors*
- ✓ *Prevent prematurity*
- ✓ *Prevent birth defects*

CURRENT GOALS

- ✓ *Prevent infection and major morbidities*
- ✓ *Optimize nutritional support – enhance and promote use of human milk*
- ✓ *Minimize invasive procedures and provide humane pain relief*

REPORT CARD NEONATAL PERINATAL MEDICINE

- Prevent prematurity
- Reduce asphyxia
- Eliminate GBS & nosocomial infections
- Reduce IVH
- Prevent BPD
- Avoid iatrogenesis
- Avoid medical errors
- MINIMAL progress but enhanced survival
- MINIMAL ↓+COOLING
- GBS ↓ Nosocomial ↓
- Accomplished
- Some progress
- High priority
- High priority

CURRENT GOALS

- ✓ *Provide stimulating and nurturing environment for patients and staff*
- ✓ *Support and educate nursing and ancillary staff*
- ✓ *Communicate with, inform, educate and support the parents/family and encourage them to visit and participate in care. Be truthful, attempt to be optimistic but always realistic.*
- ✓ *ATTEMPT cost-effective care*

Problems to Solve

- Prevention of major morbidities
 - Neuro-developmental impairment
 - chronic lung disease
 - NEC
 - growth failure
 - nosocomial sepsis
- Preservation of brain function including vision and hearing and monitor neuro-development

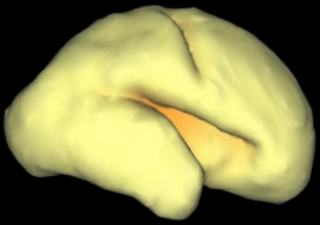


***Be
optimistic
and
prepared***

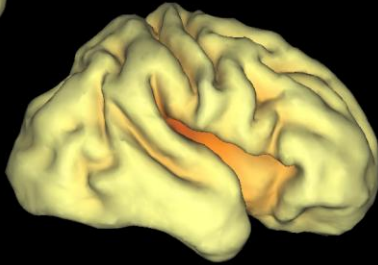


***Take your
shots!***

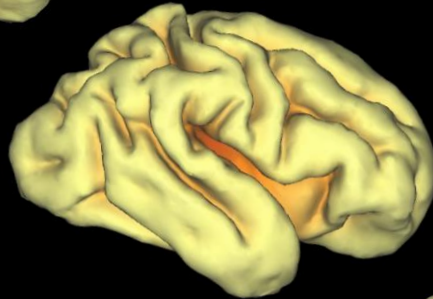
Cortical folding



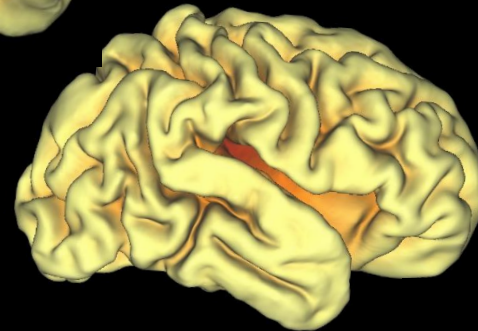
25 week



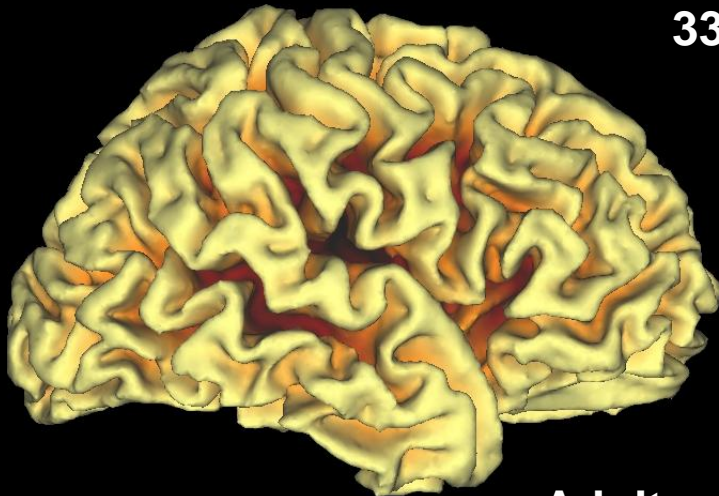
30 week



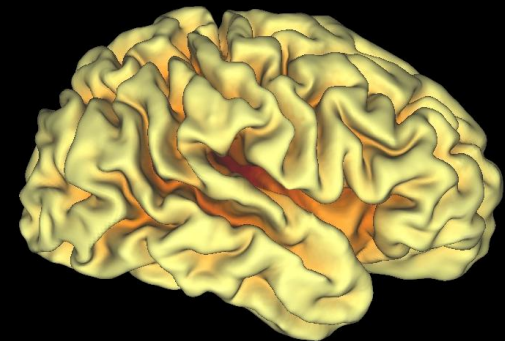
33 week



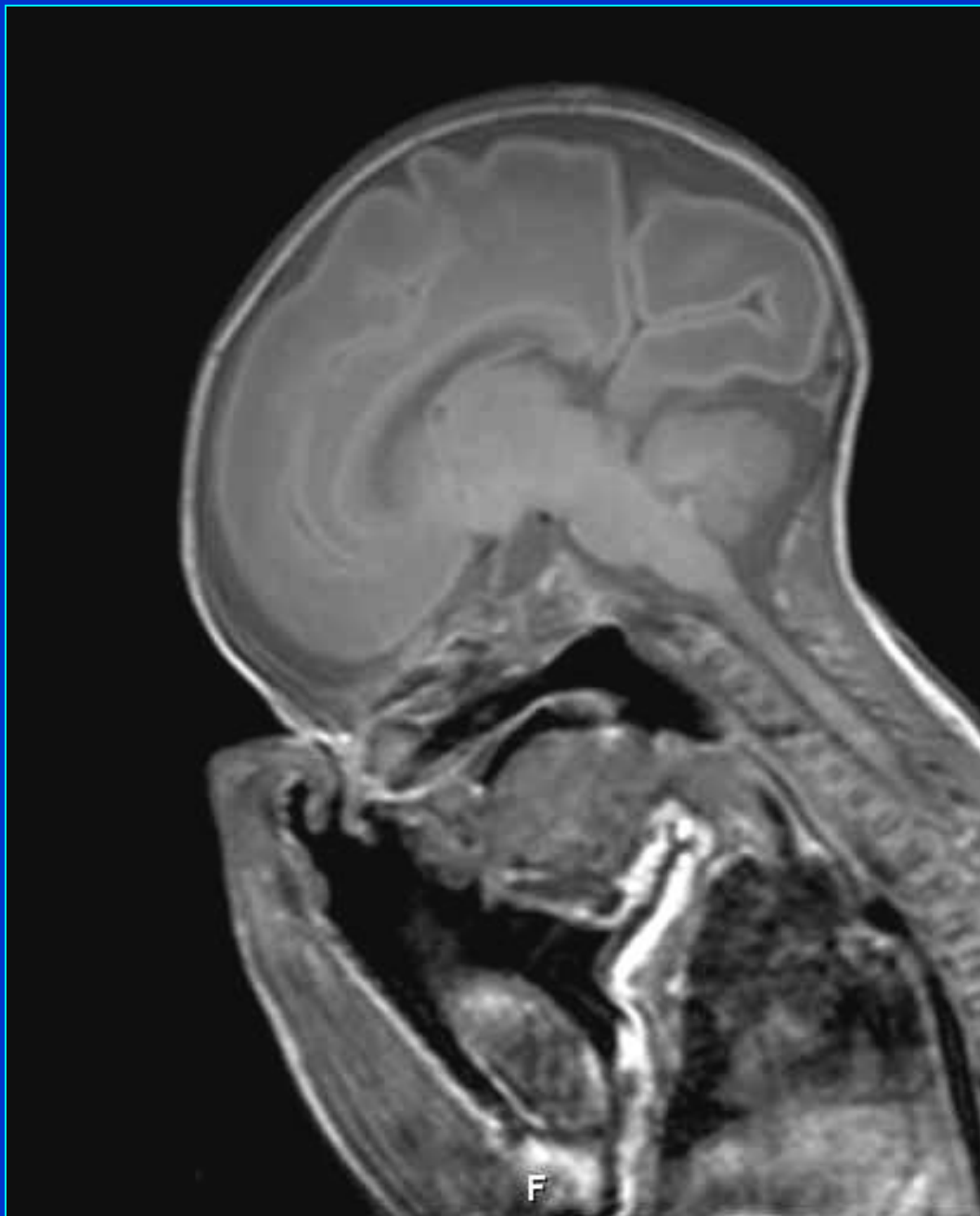
Term equivalent
(37 weeks)



Adult



Term control



Courtesy of Linda deVries