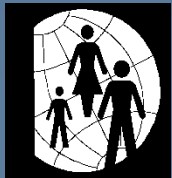


THE CAUSATION AND PREVENTION OF CEREBRAL PALSY

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Michigan State University

<http://www.epi.msu.edu/faculty/paneth.htm>

TERATOLOGY SOCIETY
MONTREAL
JULY 1, 2015



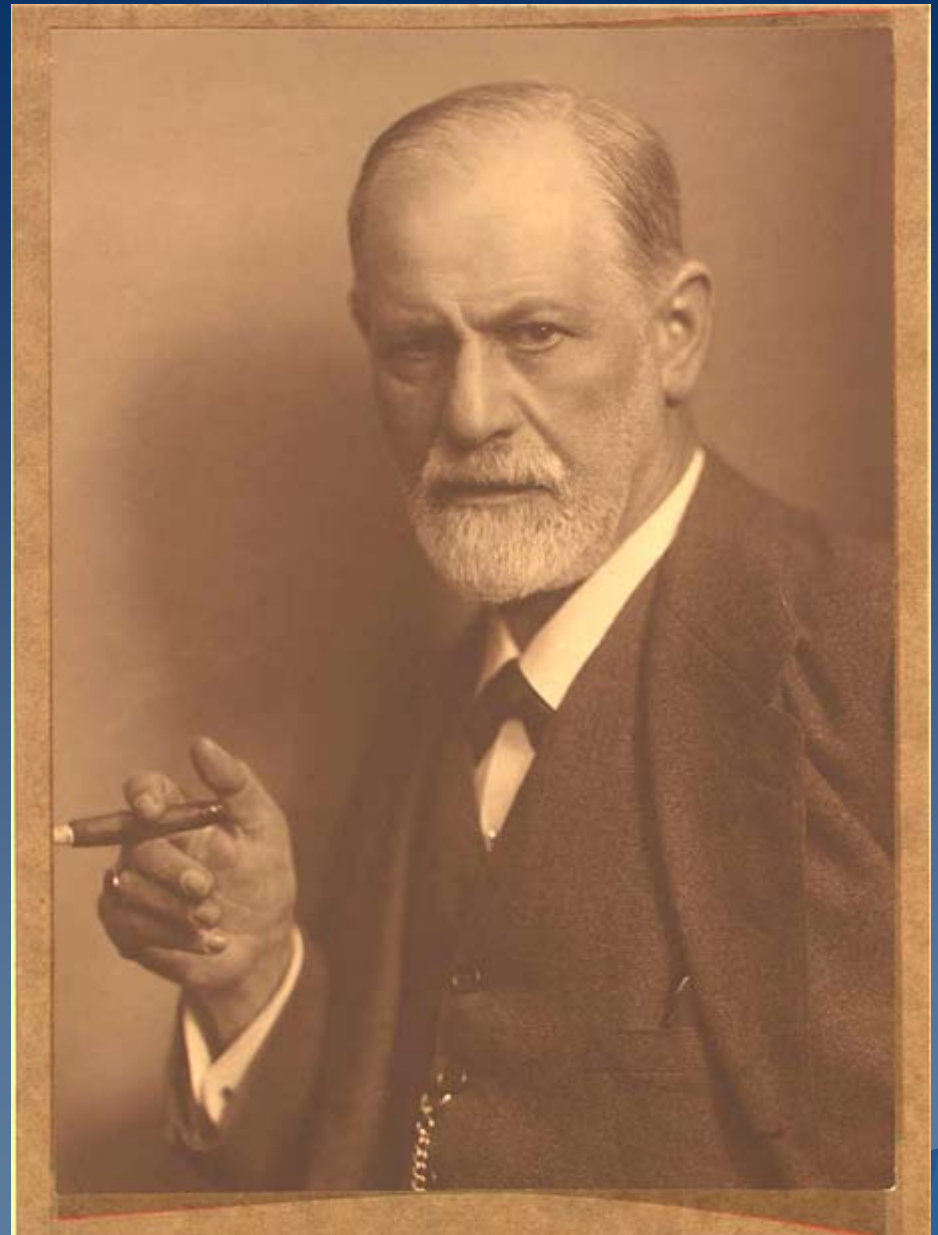
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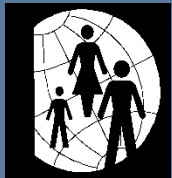
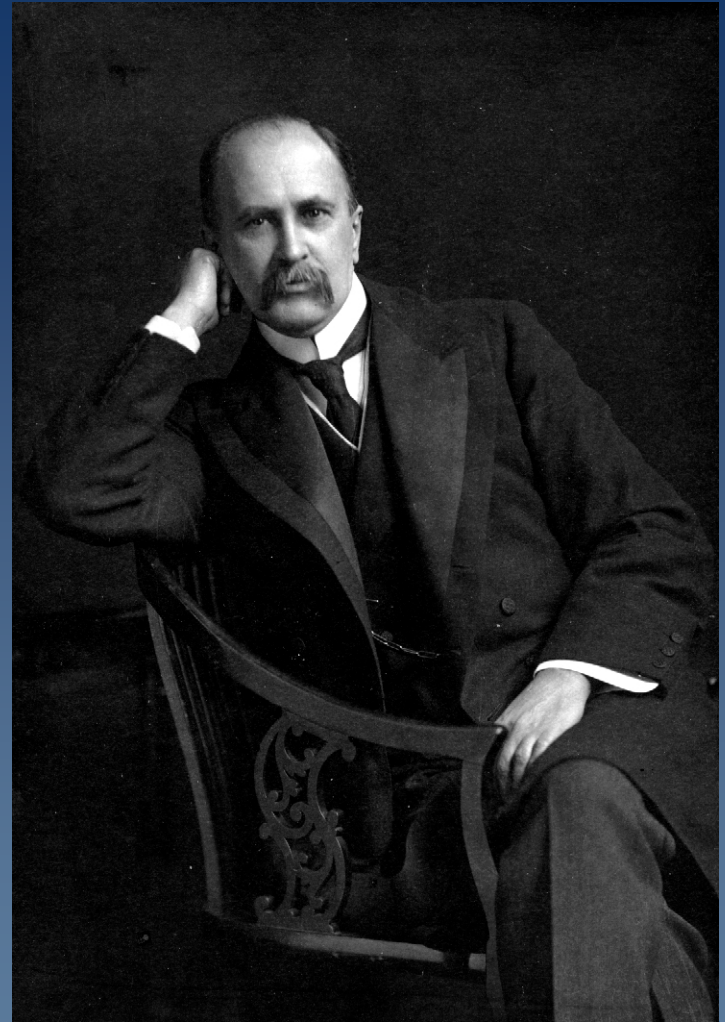
SOME IMPRESSIVE
PEOPLE HAVE
STUDIED CP

Sigmund Freud was the leading European authority on CP of the late 19th Century.

He authored three monographs on CP in the 1890's



William Osler wrote the
only 19th century
monograph on
CP published in the US



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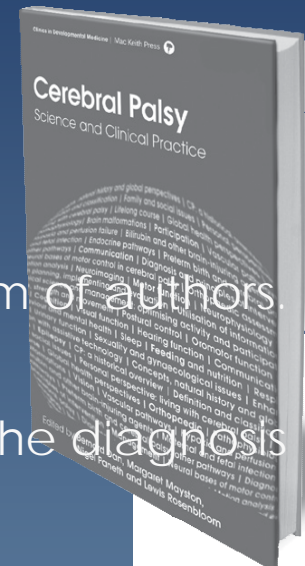
AND NOW, A 21ST CENTURY TEXTBOOK

Cerebral Palsy

Science and Clinical Practice

Edited by **Bernard Dan, Margaret Mayston,
Nigel Paneth, and Lewis Rosenbloom**

- A major new publication from an eminent international team of authors.
- The only comprehensive reference book on CP.
- Scientific foundations and principles that form the basis for the diagnosis of CP, and support the range of available interventions.



280 x 205mm / 692 pages / Hardback / October 2014 / 978-1-909962-38-5 /
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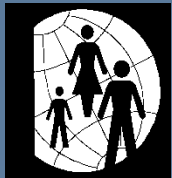
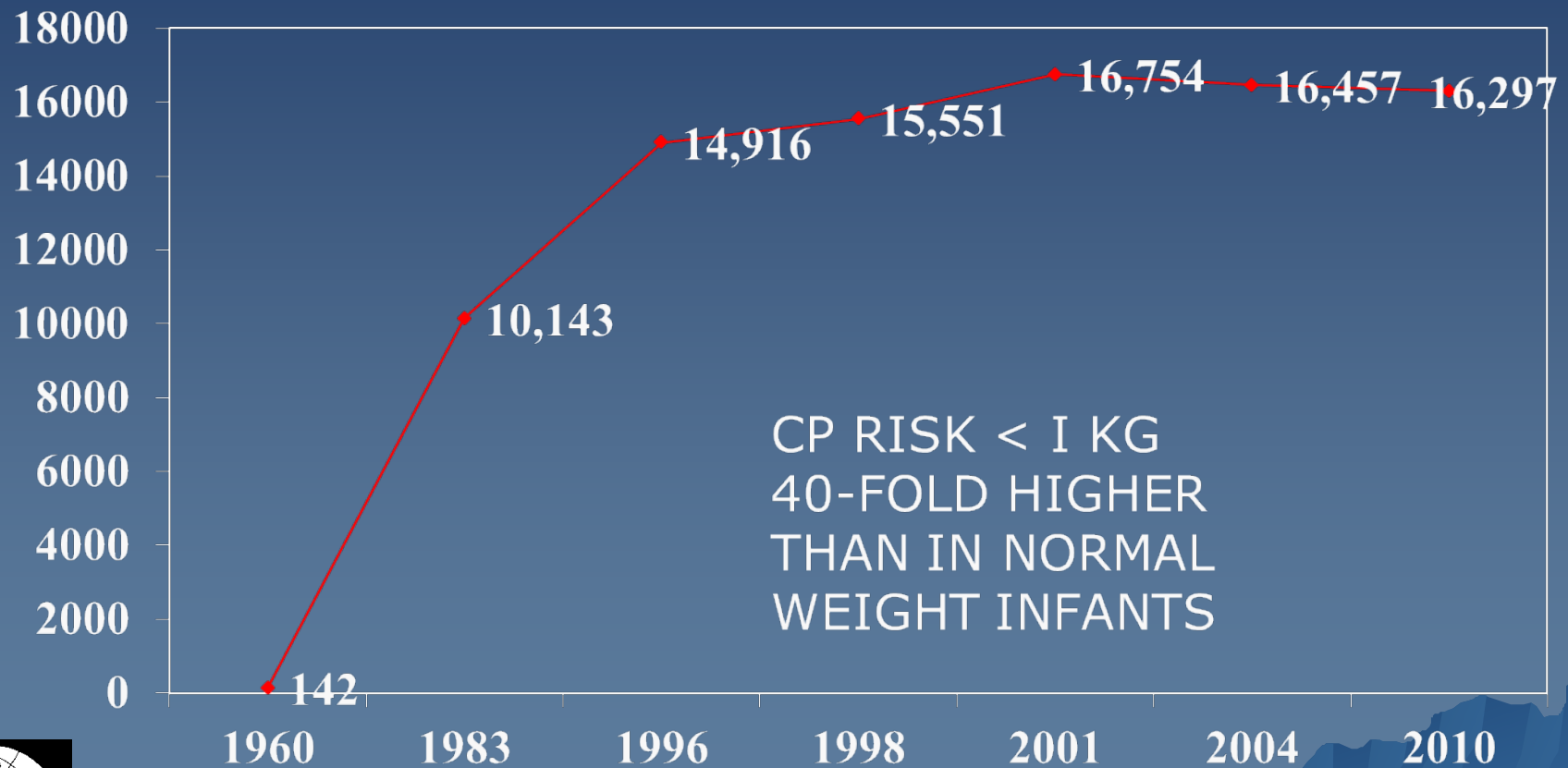
T: +44 (0)1234 243407 (Free phone, UK only or +44 (0)1234 843294 / F: +44 (0)1234 843296 / E: books@wiley.co.uk

PREVALENCE OF CP

- ◆ Population registries in Europe and Asia find CP prevalence at school age from **2.0–2.5 cases per thousand live births**
- ◆ No good population data in the US, as we have no ongoing population registries, but one recent 4-state study suggests that US prevalence might be as high as **3.0 - 3.5/1,000**
- ◆ This means that from **one in 300-500 children** has CP, or about **8,000–14,000 new cases** each year in the US.
- ◆ Each new birth cohort of CP is estimated to add **\$11.5 B** in direct and indirect costs to the economy.



IMPORTANT DEMOGRAPHIC SHIFT AFFECTING CP PREVALENCE: INCREASED SURVIVAL OF INFANTS < 1KG AT BIRTH



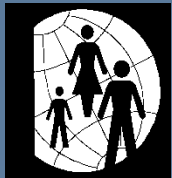


THE MYTH THAT WILL NOT DIE

CP IS ALWAYS DUE TO
OBSTETRICAL
MALPRACTICE

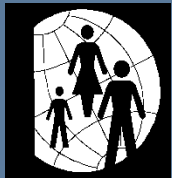
THE OLD CONSENSUS ON BIRTH ASPHYXIA

- ◆ Birth asphyxia is **the** major cause of cerebral palsy, and contributes in an important way to mental retardation and other cognitive and developmental problems.
- ◆ Careful monitoring, detection and treatment of asphyxia in labor will substantially reduce the morbidity burden from birth asphyxia.



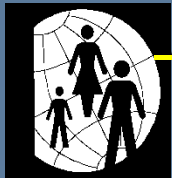
PROBLEMS WITH THE OLD CONSENSUS

1. Evidence linking measures or proxies of birth asphyxia to CP is weak, except in rare and extreme cases.
2. In spite of nearly universal electronic fetal monitoring in labor, and a **seven-fold rise in the cesarean section rate** in the US since 1970, there is no evidence of a decline in the prevalence of CP.
3. Other factors have emerged as significant in the background of children with CP



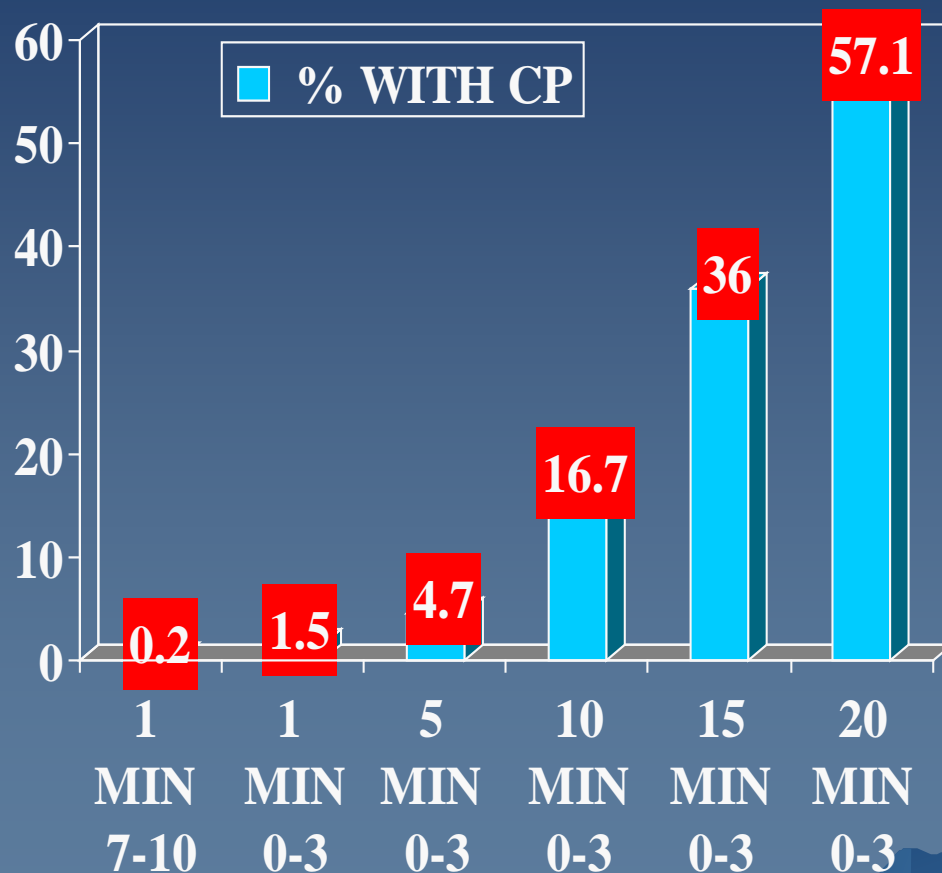
THE NATIONAL COLLABORATIVE PERINATAL PROJECT

- ◆ Some 55,000 pregnancies enrolled 1959-1966 at 12 major medical centers; > 45,000 children followed to age 7.
- ◆ PURPOSE: to study the relationship of pregnancy and labor events to CP.
- ◆ The key papers on asphyxia and CP, all by Karin B Nelson and Jonas Ellenberg:
 - Pediatrics 1979;64:225-32
 - Pediatrics 1981;68:36-42
 - JAMA 1984;251:1843-8
 - NEJM 1986; 315:81-6



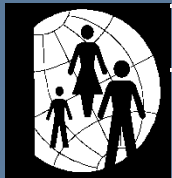
APGAR SCORES AND CEREBRAL PALSY IN INFANTS $\geq 2,500$ G

Which column produced the most Children with CP?

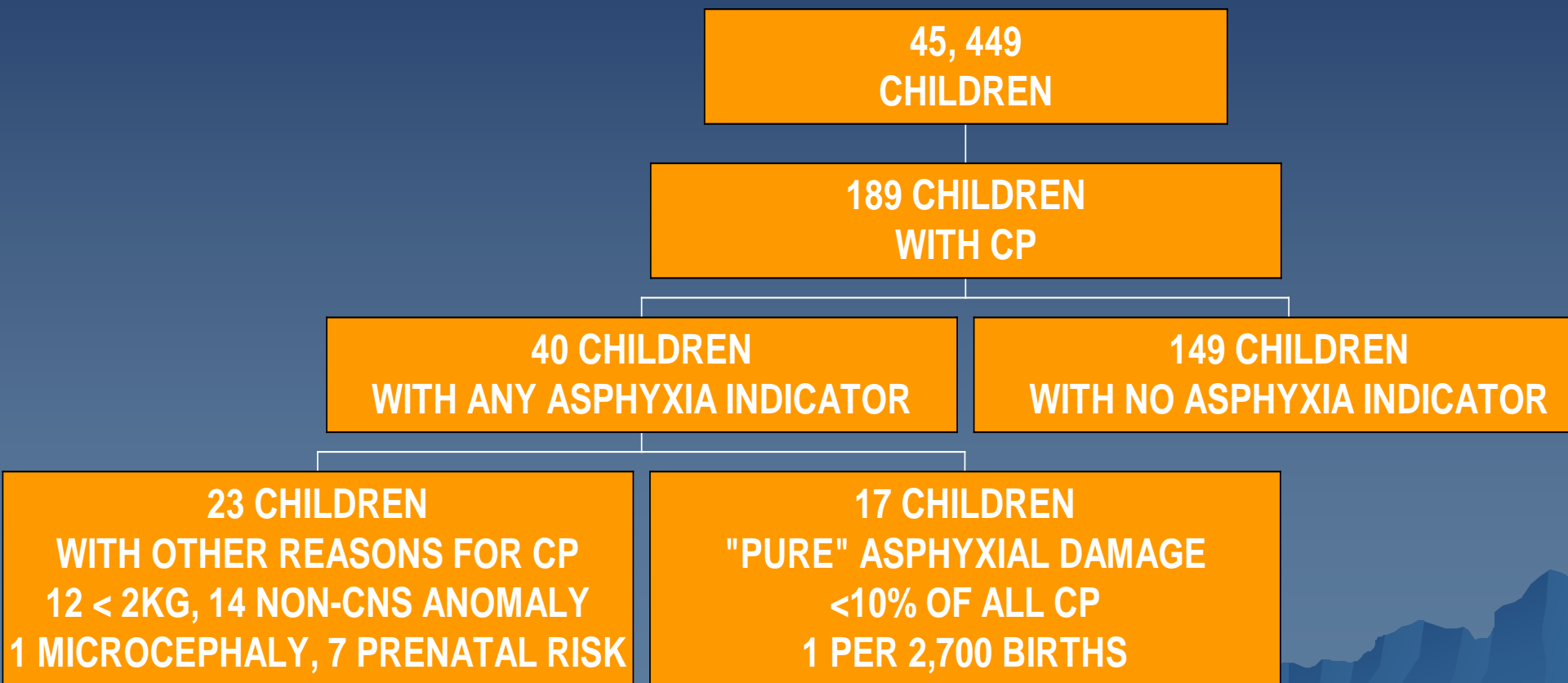


CP RISK IN RELATION TO OB COMPLICATIONS IN BABIES > 2,500 G

	<u>CP RISK</u>
◆ NO OBSTETRIC COMPLICATIONS (49%)	0.3%
◆ ANY OBSTETRIC COMPLICATION (51%)	0.3%
◆ COMMON COMPLICATIONS	
– NUCHAL CORD (18%)	0.3%
– MECONIUM (25%)	0.4%
– 2 ND STAGE \geq 1 HOUR (10%)	0.3%
– MID OR HIGH FORCEPS (8%)	0.4%
◆ LESS COMMON COMPLICATIONS	
– CORD PROLAPSE	0.4%
– PLACENTA PREVIA	0.6%
– BREECH POSITION	1.0%
– ABRUPTIO PLACENTAE	1.9%

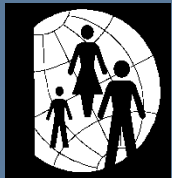


“ASPHYXIA” AND CP IN THE NCPP STUDY



SOME OTHER POSSIBLE RISK FACTORS

- ◆ PERINATAL INFECTION?
- ◆ THYROID HORMONES?
- ◆ VENTILATORY MANAGEMENT?



META-ANALYSIS FINDINGS FOR CHORIOAMNIONITIS AND CP

- ◆ Preterm infants pooled OR = 1.9
- ◆ Term infants pooled OR = 4.6

Wu et al Ment Retard Dev Disabil Res Rev. 2002;8:25-9.



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THREE LARGE STUDIES OF NEONATAL THYROID LEVELS IN PREMATURES ALL FOUND WORSE NEURODEVELOPMENT IN THOP BABIES

England

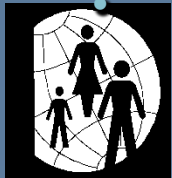
- Lucas et al Arch Dis Child 1988;63:1201-6
- Lucas et al BMJ 1996;312:1133-4

Holland

- Meijer et al Arch Dis Child 1992; 67:944-7
- Den Ouden et al Pediatric Res 1996; 39:142-5

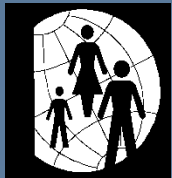
USA

Reuss et al New Eng J Med 1996;334:821-7



STEPWISE ADJUSTMENTS IN ASSESSING EFFECTS OF THOP ON NEURODEVELOPMENT

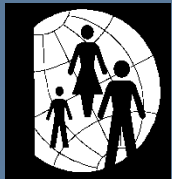
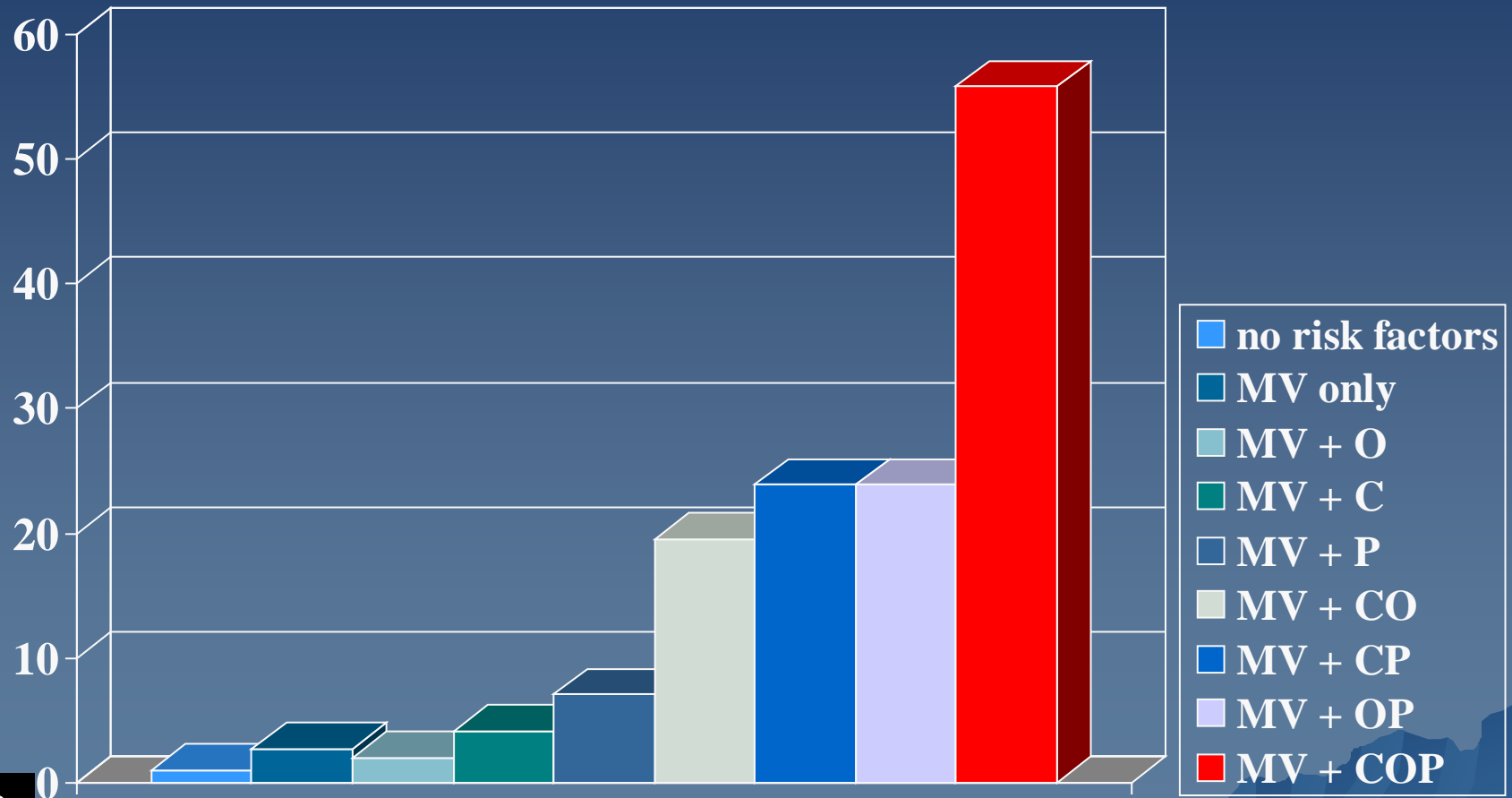
	ODDS RATIO FOR CP	MDI SCORE DIFFERENCES
Unadjusted	17.6	17.5
Adjusted for gestational age	10.8	15.4
Adjusted for GA and 15 other variables	3.5	9.9
Adjusted for GA and 21 other variables	4.4	6.8



From Reuss et al NEJM 1996;334:821-7

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ODDS RATIOS FOR DISABLING CP BY VENTILATORY RISK FACTORS: Children with up to four risk factors





TRIALS TO PREVENT CEREBRAL PALSY

FOUR PERINATAL INTERVENTIONS SHOWN IN AT LEAST ONE APPROPRIATELY-POWERED RANDOMIZED TRIAL TO SUCCESSFULLY REDUCE RISK OF CP IN SURVIVORS.

ESTABLISHED

- Therapeutic hypothermia in term infants (7 trials showing effectiveness)
- MgSO_4 administered in labor in infants < 32 weeks GA (4 trials showing effectiveness)

JURY STILL OUT

- Caffeine for apnea (one positive trial)
- Enriched infant formula (one positive trial)



INTERVENTIONS THAT HAVE NOT REDUCED CP IN APPROPRIATELY-POWERED TRIALS

- ◆ Indomethacin
- ◆ Repeat dose of betamethasone in labor
- ◆ More liberal blood transfusion
- ◆ Early hydrocortisone
- ◆ Inhaled nitric oxide
- ◆ Vitamin A
- ◆ Etamsylate
- ◆ Antenatal phenobarbital
- ◆ HIFI Ventilation

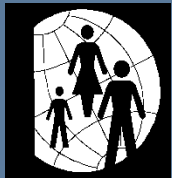
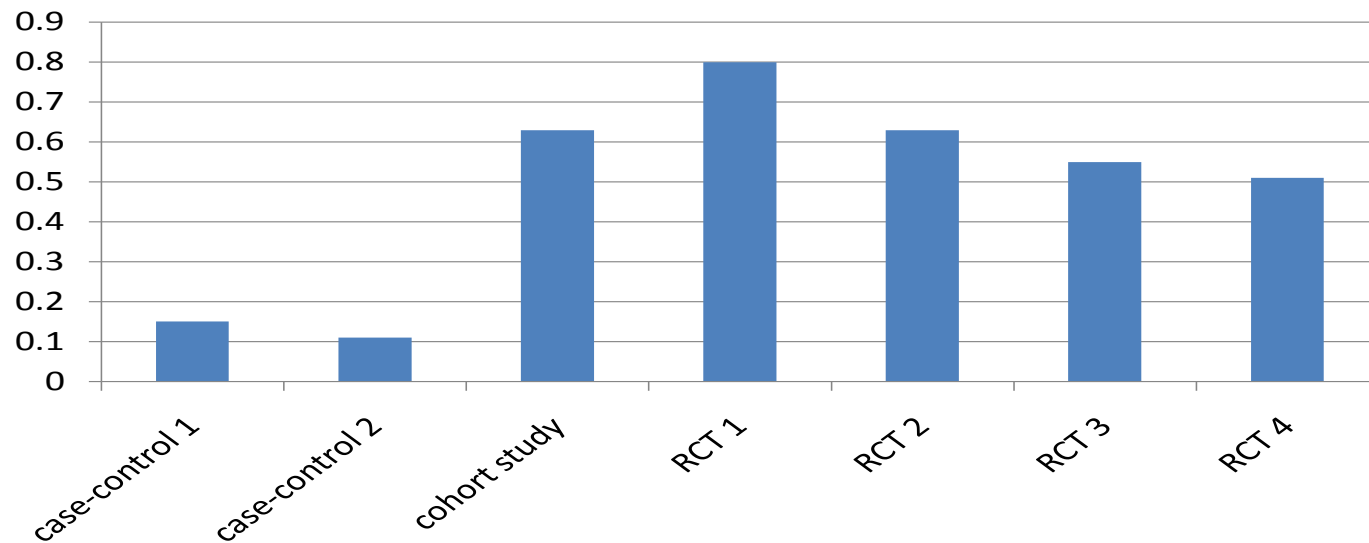


OUTCOMES OF 7 HEAD/BODY COOLING TRIALS FOR NEONATAL ENCEPHALOPATHY

	Death RR	CP/Disability RR In all randomized	Combined RR
Azzopardi (2005)	0.94	0.76	0.86
Gluckman (2005)	0.87	0.75	0.82
Jacobs (2011)	0.64	1.13	0.77
Shankaran (2005)	0.66	0.84	0.73
Simbruner (2010)	0.62	0.47	0.57
Zhou (2010)	0.70	0.54	0.63
Zhu (2009)	0.76	0.49	0.52
POOLED	0.75	0.73	0.74



Odds Ratios relating Magnesium and CP: seven studies



TO SUMMARIZE

- ◆ The myth that birth asphyxia causes all or most of CP is (or should be!) dead.
- ◆ About 25% of term CP “caused” by birth asphyxia might be preventable by newborn cooling. This effect might be seen even if encephalopathy was due to other causes.
- ◆ Perhaps a third of CP before 32 weeks might be preventable by MgSO₄ in labor.
- ◆ THOP should be a trial target
- ◆ Avoiding hypocapnea in preemies might prevent CP
- ◆ Infection may yet prove an important preventable cause of CP





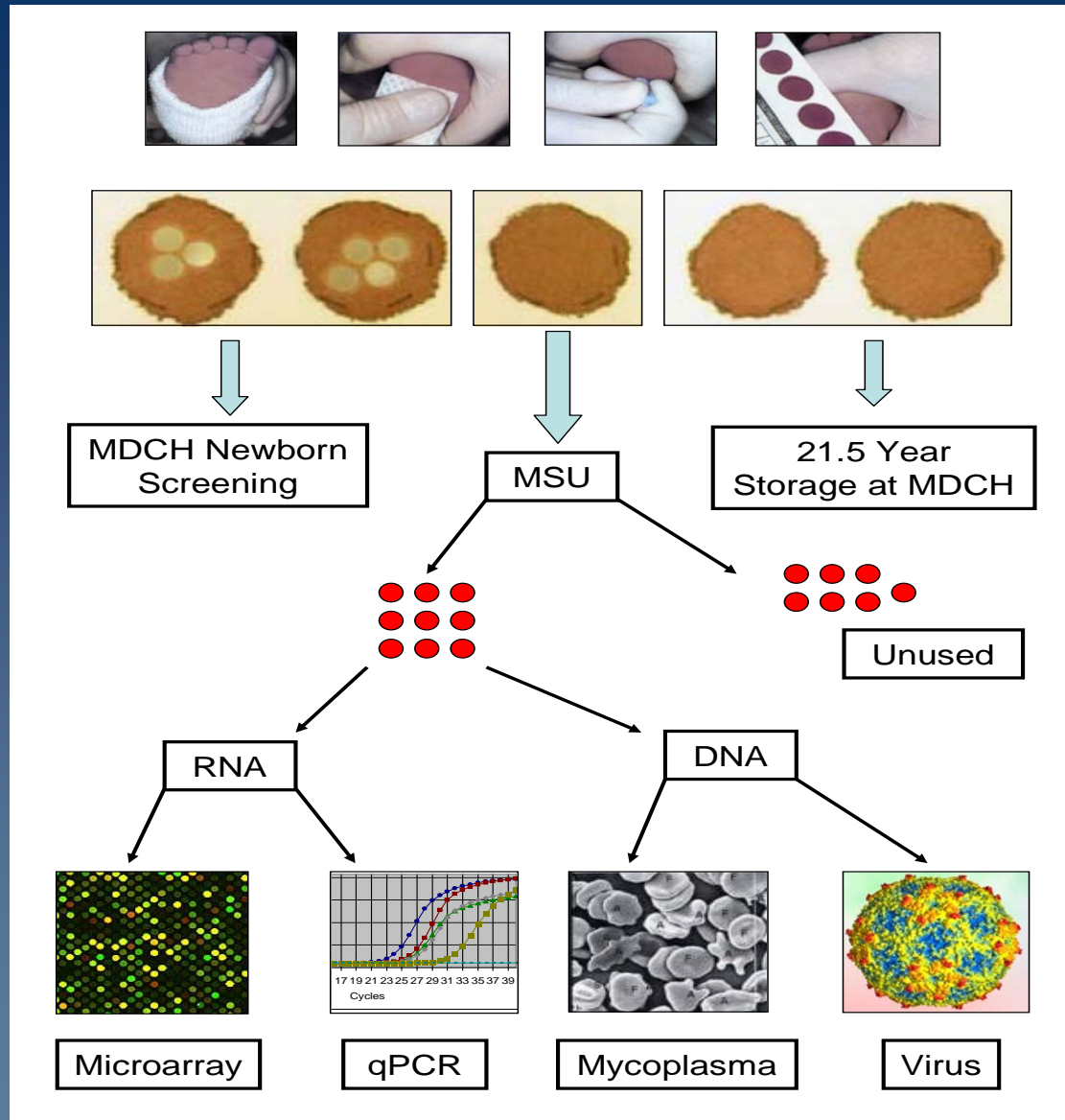
IF TIME

GENE EXPRESSION AT BIRTH AND CP

OWL CASE-CONTROL STUDY

- ◆ **CP cases:** Ages 2-16, born in MI, recruited from child neurology and CP clinics in Ann Arbor, Lansing and Grand Rapids
- ◆ **Matched controls:** birth year, gender, and gestational age (< 28; 32-34; 35-37; >37 weeks) principally from area primary care practices, and, for cases < 32 weeks, newborn follow-up programs.
- ◆ Exposure information: maternal interview, birth certificates and maternal and infant hospital discharge abstracts from birth
- ◆ Permission to obtain and study **archived newborn blood spots** from state.







SOME EARLY FINDINGS ON THE FIRST 53 SINGLETON PAIRS

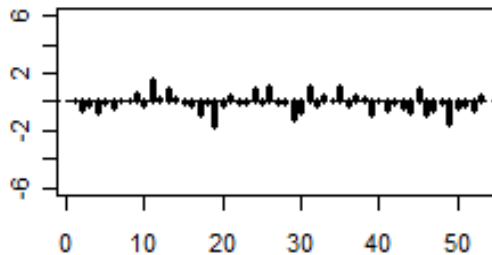
Ho NT, Furge K, Fu W, Busik J, Khoo SK, Lu Q, Lenski M, Wirth J, Hurvitz E, Dodge N, Resau J, Paneth N: Gene expression in archived newborn blood spots distinguishes infants who will later develop cerebral palsy from matched controls.
Pediatric Research 2012 Dec 26 (e-publication)

Microarray Findings for Up, Down Regulation and Both for the Seven Hypothesized Pathways

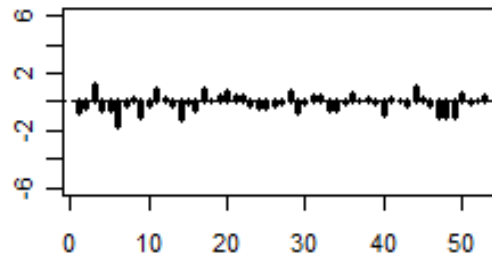
53 singleton case-control pairs

PATHWAYS	EFFECT SIZE (Δ/σ)	DOWN	UP	BOTH
Inflammatory				
Canonical	-0.10	NS	NS	NS
Empirical	-0.19	< .001	NS	NS
Thyroidal				
Canonical	-0.03	NS	NS	NS
Empirical	0.13	NS	<.01	NS
Asphyxial				
Canonical	0.18	NS	NS	NS
Empirical	-0.16	<.01	NS	NS
Coagulative				
Canonical	-0.08	NS	NS	NS

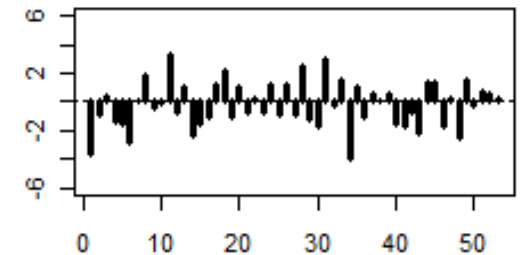


a

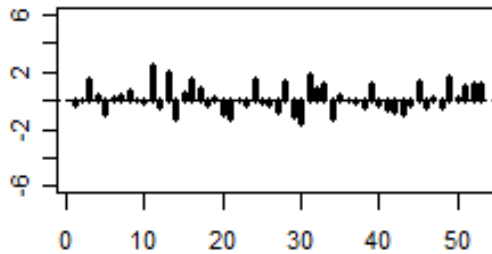
Coagulation - curated

b

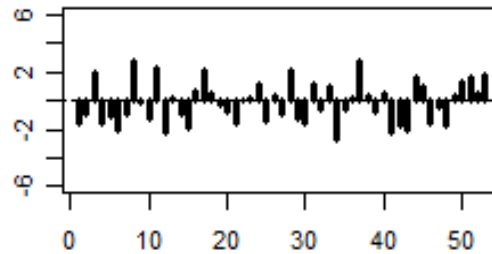
Inflammation - curated

c

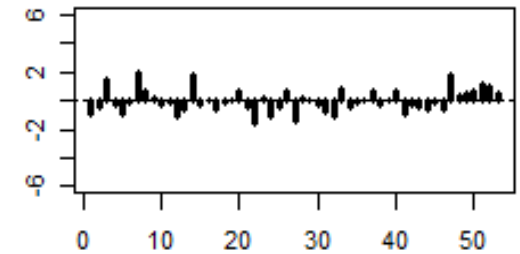
Inflammation - empirical

d

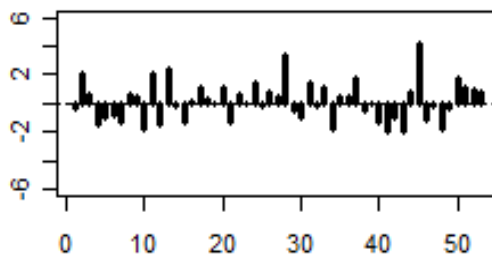
Hypoxia - curated

e

Hypoxia - empirical

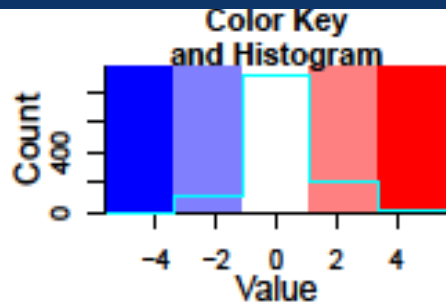
f

Thyroid - curated

g

Thyroid - empirical

Z-STATISTICS OF RELATIVE MRNA
EXPRESSION IN 53 CP CASE-CONTROL
PAIRS: Seven pre-hypothesized gene
sets reflecting four pathways.



FIRS in singleton cases vs. controls

\log_2 fold differences between case and control for each of 36 genes for each pair.

