THE POTENTIAL CONTRIBUTION OF MOBAND TO THE EPIDEMIOLOGY OF CEREBRAL PALSY

Nigel Paneth MD MPH
Departments of Epidemiology & Biostatistics and Pediatrics and Human Development
Michigan State University

NIEHS, Durham, NC
March 14, 2018
OUTLINE OF THIS TALK

- What is cerebral palsy (CP)?
  - Clinical picture
  - Frequency
  - Epidemiology
  - Preventability

- What is MOBAND?
  - What special features make it ideal for studying CP epidemiology?
  - Are there any limitations?
  - Some examples of where we might be heading
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
SPECIELLE
PATHOLOGIE UND THERAPIE
HERAUSGEGEBEN VON
HOFRATH PROF. DR. HERMANN NOTHNAGEL.
IX. BAND,
II. THEIL, II. ARTHÄLTERUNG.

DIE
INFANTILE CEREBRALLÄHMUNG.

VON
DR. SIGM. FREUD
PRIVATDOZENT AN DER UNIVERSITÄT WIEN.

WIEN 1897.
ALFRED HÖLDER
K. K. HOF- UND UNIVERSITÄTS-BUCHHÄNDLER
L. ROTHENHORNSTRASSE 16.
Preis für Abonnenten: 6 M. 40 Pf.  Einzelpreis: 8 M.
William Osler wrote the only 19th century monograph on CP published in the US.
AND FINALLY, A COMPREHENSIVE 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 / £190.00. www.mackeith.co.uk
WHY IS CEREBRAL PALSY IMPORTANT?

- CP is the commonest severe neurodevelopmental disability in children; prevalence about 1 per 300 school-age children in the US.

- 50% cannot walk; 50% have intellectual disability, half of it severe, 33% have epilepsy.

- Usual classification is by motor abnormality (spastic, dyskinetic, ataxic) and limb involvement (quadriplegia, hemiplegia, diplegia).

- Lifetime direct excess costs (medical, rehabilitative, educational) for each child with CP are estimated to be at least $1 million.

- CP prevalence increased modestly in the final quarter of the 20th century and now may be declining slightly.
PREVALENCE AND TIME TRENDS

- Population-based registries in Europe and Asia find CP prevalence at school age to be 1.5 – 2.5 cases per thousand live births.

- But recent CDC surveys in four US states show a prevalence rate of 3.0 - 3.5/1,000 school-age children.

- The prevalence of CP, especially severe CP appears to be higher in African-Americans in the US.

- Increased survival of very premature infants has outpaced reductions in survivor prevalence of CP, so a modest increase in the prevalence of CP was seen in CP registries. With stable survival since 1995 or so, and perhaps better outcomes, CP prevalence appears to have stabilized or declined in premature survivors.
NUMBER OF CHILDREN < 1,000 G SURVIVING TO AGE ONE IN THE US 1960-2010

Data for 1960 based on white population only
TRADITIONAL RISK FACTORS FOR CP

- **PREMATURE BIRTH**
  - 50 fold higher risk in infants < 28 wks.
  - In high-income countries, accounts for some 40% of CP cases. In low income countries, with rare survival in extreme prematurity, the proportion is much less.

- **FETAL GROWTH**
  - Moderate risk factor, especially at term. Not nearly as important as gestational age.

- **BIRTH ASPHYXIA**
  
  Long thought my many to be the basic cause of CP, with very expensive implications for obstetric malpractice lawsuits. But:
  
  - Some degree of birth asphyxia is very common, and most infants recover completely.
  - **Prenatally compromised** infants often respond poorly to the stress of labor; e.g. Down’s syndrome babies have low Apgar scores.
ON THE INFLUENCE OF ABNORMAL PARTURI-TION, DIFFICULT LABOURS, PREMATURE BIRTH, AND ASPHYXIA NEONATORUM, ON THE MENTAL AND PHYSICAL CONDITION OF THE CHILD, ESPECIALLY IN RELATION TO DEFORMITIES.

By W. J. Little, M.D.

Senior-Physician to the London Hospital; Founder of the Royal Orthopaedic Hospital; Visiting-Physician to Asylum for Idiots, Earlswood; Etc.

(Communicated by Dr. Tyler Smith.)

Pathology has gradually taught that the foetus in utero is subject to similar diseases to those which afflict the economy at later periods of existence. This is especially true if we turn to the study of the special class of abnormal conditions, which are termed deformities. We are acquainted, for example, with abundant instances of deformities arising after birth from disorders of the nervous system—disorders of nutrition, affecting the muscular and osseous structures, --- disorders from malposition and violence. Each of these classes of deformity has its representative amongst the de-
THE FIRST PROSPECTIVE STUDY OF CP: THE NATIONAL COLLABORATIVE PERINATAL PROJECT (NCPP)

- The NCPP recruited some 55,000 pregnancies in 12 US medical centers, mostly on the East Coast, 1959-1966 and followed some 45,000 of them to age 7 years.
- 189 cases of CP were diagnosed based on careful neurological evaluation.
- The study was designed to assess etiologic factors for CP, though it has been used to address many other research questions.
- Blood was collected in pregnancy and has been archived since then.
FATE OF THE BIOLOGICAL COLLECTION

- The NCPP was developed by NINDS, but in the 1970’s, NINDS, to save money, planned to destroy the prenatal serum collection.
- NICHD stepped in and took over the collection.
- Since then, the collection has been used to study pregnancy issues such as fetal growth, with a special focus on environmental contaminants.
- Information on CP is housed at NINDS and the biological collection is at NICHD. The connections are not being made, and the biological collection has never been used to study CP!
CP RISK IN RELATION TO LABOR COMPLICATIONS IN BABIES > 2,500 G
(Data from the NCPP, births 1959-66)

- NO LABOR COMPLICATIONS (49%) 0.3%
- ANY LABOR COMPLICATION (51%) 0.3%

- COMMON COMPLICATIONS
  - NUCHAL CORD (18%) 0.3%
  - MECONIUM (25%) 0.4%
  - 2ND STAGE ≥ 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%
BIRTH ASPHYXIA AND CP IN THE NCPP

45,449 CHILDREN

189 CHILDREN WITH CP

40 CHILDREN WITH ANY ASPHYXIA INDICATOR

23 CHILDREN WITH OTHER REASONS FOR CP
12 < 2KG, 14 NON-CNS ANOMALY
1 MICROCEPHALY, 7 PRENATAL RISK

149 CHILDREN WITH NO ASPHYXIA INDICATOR

17 CHILDREN "PURE" ASPHYXIAL DAMAGE
<10% OF ALL CP
1 PER 2,700 BIRTHS
SOME RECENTLY HYPOTHESIZED RISK FACTORS FOR CP

- **COAGULATION**
  - Perhaps as much as 5-10% of CP is from perinatal stroke. It is plausible, but not proven, that some may have polymorphisms of the coagulation system.

- **THYROID HORMONES**
  - Low thyroxine after birth a risk factor (not certain if causal) in preterm; possibly also at term. A syndrome which is a form of CP (neurologic cretinism) linked to iodine deficiency in endemic goiter areas.

- **INFECTION/INFLAMMATION**
  - Increasing evidence for a role of antepartum infection, especially in preterm birth (Fetal Inflammatory Response Syndrome - FIRS)
Genes only a modest factor in CP

Recurrence risk in siblings is about 1-2%, a 5 to 10-fold elevation in risk, similar to many polygenic birth defects.

Most consistent molecular genetic finding:
- **Apolipoprotein E** - A modest association with CP (odds ratios of 2-4) in most (but not all) studies with presence of epsilon 2 or 4 allele, in contrast to having the epsilon 3 allele.
PREVENTION

1. HEAD COOLING IN BIRTH ASPHYXIA
<table>
<thead>
<tr>
<th>Study</th>
<th>Death RR</th>
<th>Disability RR</th>
<th>Combined RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azzopardi (2005)</td>
<td>0.94</td>
<td>0.76</td>
<td>0.86</td>
</tr>
<tr>
<td>Gluckman (2005)</td>
<td>0.87</td>
<td>0.75</td>
<td>0.82</td>
</tr>
<tr>
<td>Jacobs (2011)</td>
<td>0.64</td>
<td>1.13</td>
<td>0.77</td>
</tr>
<tr>
<td>Shankaran (2005)</td>
<td>0.66</td>
<td>0.84</td>
<td>0.73</td>
</tr>
<tr>
<td>Simbruner (2010)</td>
<td>0.62</td>
<td>0.47</td>
<td>0.57</td>
</tr>
<tr>
<td>Zhou (2010)</td>
<td>0.70</td>
<td>0.54</td>
<td>0.63</td>
</tr>
<tr>
<td>Zhu (2009)</td>
<td>0.76</td>
<td>0.49</td>
<td>0.52</td>
</tr>
<tr>
<td>POOLED</td>
<td>0.75</td>
<td>0.73</td>
<td>0.74</td>
</tr>
</tbody>
</table>
PREVENTION

2. MAGNESIUM SULFATE IN PRETERM LABOR
OBSERVATIONAL STUDIES OF RECEIPT OF MgSO₄ IN PREMATURE LABOR

- TWO CASE-CONTROL STUDIES, INTERPRETED AS SHOWING A STRONG PROTECTIVE EFFECT.
    - OR = 0.11, p< .05
    - OR = 0.15, p< .05

- ONE COHORT STUDY INTERPRETED AS NOT CONFIRMING THE ABOVE RELATIONSHIP*
    - OR = 0.63, NS

*“The hypothesis that MgSO₄ use reduces the risk of...CP in low birth weight infants was not statistically supported in this study, although a modest reduction in risk of DCP cannot be excluded.”
RANDOMIZED TRIALS OF LABOR MgSO$_4$

- Three randomized trials in premature labor
  - **RR = 0.83 NS** (< 30 weeks) Crowther 2003
    [mortality OR = 0.83, NS]
  - **RR = 0.63 NS** (< 33 weeks) Marret 2008
    [mortality OR = 0.79, NS]
  - **RR = 0.55 p < .05** (24-31 weeks) Rouse 2008
    [mortality OR = 1.12, NS]
- One randomized trial in pre-eclampsia.
  - **RR = 0.51 NS** Magpie 2007
    [mortality OR = 1.12, NS]
Odds Ratios relating Magnesium and CP: seven studies

MORAL OF THIS STORY: TRUST THE ODDS RATIO MORE THAN THE P VALUE
MOBAND

A COMBINATION OF THE TWO LARGEST PREGANCY COHORTS IN EXISTENCE CREATED TO STUDY CP

1. Mothers and Babies in Norway (moba)
2. The Danish National Birth Cohort (DNBC)

Key reference: Tollanes et al: BMJ Open 2016 Sep 2;6(9):e012777
MOBAND CHARACTERISTICS

- Some 210,000 children, among whom 438 cases of CP were ascertained in the two national CP registries.
- CP prevalence is just over 2/1,000 live births
- N of births nearly 4 times and N of cases of CP nearly 2.5 times that of the NCPP
MOBAND DATA

- **DNBC**
  - Brief questionnaire at 6-10 weeks
  - Telephone interviews at 16, 31 weeks
  - Nutritional questionnaire at 25 weeks

- **MoBa**
  - Questionnaire at 13-17 weeks
  - Nutritional questionnaire at 22 weeks
  - Questionnaire at 30 weeks
MOBAND SPECIMENS

- **DNCB**
  - Blood at 6-10 weeks
  - Blood in mid-pregnancy
  - Cord blood

- **MoBa**
  - Blood and urine at 13-17 weeks
  - Cord blood
WHAT CAN MOBAND TEACH US ABOUT CP?

- MOBAND is by far the largest cohort study initiated in pregnancy and linked to CP cases.
- Virtually all recent studies of CP etiology are from administrative data sets and contain no information obtained in pregnancy in real time from mothers except what is recorded on medical records.
- There is virtually no information on CP in relation to either maternal interviews obtained during pregnancy or biological specimens obtained in pregnancy, other than a few studies of data collected at birth, such as cord blood.
- To use MOBAND data, approval is needed from MOBAND steering committee and from each of the two cohorts.
CONSIDERATIONS ABOUT APPROPRIATE USE OF MOBAND DATA

- Among the many kinds of associations worth exploring, I would suggest focusing on those that are most likely to lead to an inexpensive or easily implemented intervention.

- These might include nutritional, hormonal, infectious, environmental etiologies

- I suspect that finding a new genetic polymorphism for CP will not lead to a cost-effective intervention, at least in the short term.

- How might we set about to think about the best use of MOBAND to lead to CP prevention?
LEARNING FROM THE INTERVENTIONS

1. MgSO₄

- **32% reduction in CP < 32 weeks** (Crowther et al PLoS Med 2017; 14(10): e1002398)

- **1.6% of births are < 32 weeks** (US birth data, 2015) and their risk of CP is **3.2%** (Tronnes et al, 2014. op cit).

- In the Norwegian data, CP prevalence was 1.8/1,000 live births, but our best estimate in the US is 3-3.5/1,000.

- Above numbers indicate that full use of MgSO₄ might lead to a reduction in CP of about **1,200 cases** of CP per year in US, or a reduction of **10%**.
2. HEAD/BODY COOLING

- 25% reduction in CP in term births with hypoxic-ischemic encephalopathy (HIE)
- Birth prevalence of HIE is about 1.5/1,000 births
- Their estimated risk of CP is 15% - 20%
- Above numbers indicate that full use of head/body cooling might lead to a reduction of from 225 - 300 cases of CP per year in US, or a reduction of 2-3%.
SMALL EFFECTS ARE WORTH KNOWING ABOUT, BUT

- The two interventions we know of together reduce CP by 12-13%, or by 1,200-1,600 cases a year in the US.

- MOBAND cannot reliably detect such small effects. It can just detect a RR of 1.4 for all CP for an exposure found in 20% of the population.

- In part this reflects a relatively low CP prevalence in the Danish and Norwegian CP registries.

- And it is likely that effects will be specific to exposure categories (e.g. preterm birth, HIE) or, less likely, CP sub-types, further limiting power.
IMPLICATIONS FOR CP PREVENTION RESEARCH

- I think CP will be prevented, like heart disease, a little bit at a time.

- In heart disease, several clinical syndromes were aggregated – angina, heart attack, sudden death – and risk factors were examined for the aggregated clinical picture.

- Similarly, I suspect that to find important, intervenable risk factors, it will be more productive to focus on risk factors clusters (e.g. prematurity, term birth with labor problems) rather than on clinical sub-types (e.g. diplegia, hemiplegia).
MOBAND ILLUSTRATION #1

Tanja Gram Petersen et al: Maternal thyroid disorder in pregnancy and risk of cerebral palsy in the child: A population-based cohort study (in submission)

Examines CP in relation to thyroid disorders

- Self-reported thyroid disorders at 13-17 weeks of pregnancy. Question did not distinguish hypo from hyperthyroidism

- Thyroid medication use at 13-17 weeks in MOBA and at 31 weeks in DNBC

Some weak relationships found.

Next step – INVESTIGATE THE SERUM SAMPLES!

* Graduate student in epidemiology, University of Copenhagen
Diana Haggerty* proposes to investigate a nutritional-inflammatory interaction. She hypothesizes that an interaction between unbalanced maternal intake of two polyunsaturated fatty acids and perinatal exposure to an inflammatory event increases the risk of CP in offspring.

Both variables will be obtained from the maternal interviews about health and diet conducted during pregnancy in DNBC and MoBa.

Next step – INVESTIGATE THE SERUM SAMPLES!

* Graduate student in epidemiology, Michigan State University
FURTHER IMPLICATIONS

- It will be key to move quickly from suggestions emerging from examination of questionnaire data to examination of biological specimens.

- Especially important to focus on term births, where less is understood than in preterm births, because CP in preterm births has been the subject of considerable research in prospective cohorts, and we have identified some risk factors.

- If one topic ought to be explored in depth to identify risk factors in clinical, interview and biological data with high potential for intervention, I would recommend infection and inflammation.
THANKS FOR LISTENING

I’M HAPPY TO TAKE QUESTIONS

(This presentation will be posted at http://www.epi.msu.edu/faculty/paneth.htm)
EXTRA SLIDES IF NEEDED
### THREE LARGE STUDIES OF TRANSIENT HYPOTHYROIDINEMIA (THOP) IN PREMATURES AND NEURODEVELOPMENT

<table>
<thead>
<tr>
<th>CITATIONS</th>
<th>Sample size</th>
<th>THOP definition</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENGLAND</strong></td>
<td>Lucas et al Arch Dis Child 1988;63:1201 &amp; BMJ 1996;312:1133.</td>
<td>226 &lt; 1,850 g</td>
<td>T&lt;sub&gt;3&lt;/sub&gt; &lt; 0.3nM/L</td>
</tr>
<tr>
<td><strong>HOLLAND</strong></td>
<td>Meijer et al Arch Dis Child 1992; 67:944. Den Ouden et al Pediatric Res 1996; 39:142.</td>
<td>944 &lt;1,500g or &lt;32 weeks</td>
<td>T&lt;sub&gt;4&lt;/sub&gt; &lt; 3 SD’s below mean</td>
</tr>
<tr>
<td><strong>NEW JERSEY</strong></td>
<td>Reuss New Eng J Med 1996;334:821</td>
<td>466 &lt; 2,000g</td>
<td>T&lt;sub&gt;4&lt;/sub&gt; &lt; 2.6 SD’s below mean</td>
</tr>
</tbody>
</table>
QUINTILES OF HYPOCAPNIA AND ODDS RATIO FOR DISABLING CP IN NBH STUDY

Quintiles of PCO2

Q1 - HIGH
Q2
Q3
Q4
Q5 - LOW
Which column produced the most Children with CP?