An Epidemiologic Enterprise: from Fluoride to Folate

J David Erickson
Centers for Disease Control and Prevention
(Retired)

I have no financial or other interests that are relevant to the subject of this presentation.
The expectation (fantasy)

The problem

The solution

Too often the reality

The problem

The solution
What about prevention?

Promote individual behavior change……
- oral hygiene
- avoiding cariogenic foods
- “topical” fluoride treatments

What else could be offered?

Fluoride Added to Community Water Supplies

Increasing consumption of a natural dietary element. Caries preventive effect discovered from studies of mottled enamel associated with some drinking waters.

In paired city interventions, found to be remarkably effective in reducing caries.

Inexpensive
Evidence of safety
That was it for me. I would enter public health.
Prevent dental diseases through community actions
MPH - University of Minnesota
PhD - University of Washington

Important people I met in Seattle
**CDC Disease Prevention Framework**

- **Surveillance**
  - prevalence rates, trends
  - registry and classification of cases
  - monitor prevention efforts

- **Epidemiological Studies**
  - risk factors, gene-gene and gene-environment interactions
  - protective factors
  - public health concerns

- **Prevention Programs**
  - prevention strategies
  - public policy
  - education

**Metropolitan Atlanta Congenital Defects Program**

“MACDP”

A collaborative effort of CDC, Emory University, Georgia Department of Health since 1967

- Case ascertainment focused on health care system
- Births to residents of five counties in metro Atlanta
- Standard methods for case finding, data collection
- Case classification by clinical geneticists
- Numerators for rate calculations from vital records
### “Mongolism” Related to Water Fluoride*

<table>
<thead>
<tr>
<th>Water Fluorine mg/l</th>
<th>Total Births</th>
<th>Number Cases of “Mongolism”</th>
<th>Rate per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 - 0.2</td>
<td>196,186</td>
<td>67</td>
<td>0.34</td>
</tr>
<tr>
<td>0.3 - 0.7</td>
<td>70,111</td>
<td>33</td>
<td>0.47</td>
</tr>
<tr>
<td>1.0 - 2.6</td>
<td>67,053</td>
<td>48</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*Birch and cases from Illinois cities of maternal residence, 10,000-100,000 populations, 1950-1956

- Rapaport, Bull Acad Nat’le de Medicine (Paris) 1959
- Data obtained from fluoridealert.com, June 2012

### Down Syndrome Rates in Metropolitan Atlanta by Water Fluoridation Status, White Only, 1960-1973

<table>
<thead>
<tr>
<th>Age</th>
<th>Fluoridated Areas</th>
<th>Nonfluoridated Areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>166,186 Births</td>
<td>101,639 Births</td>
</tr>
<tr>
<td>DS</td>
<td>Rate per</td>
<td>DS</td>
</tr>
<tr>
<td>Age</td>
<td>Births</td>
<td>1000 Births</td>
</tr>
<tr>
<td>&lt; 19</td>
<td>19</td>
<td>0.77</td>
</tr>
<tr>
<td>20-24</td>
<td>41</td>
<td>0.69</td>
</tr>
<tr>
<td>25-29</td>
<td>34</td>
<td>0.68</td>
</tr>
<tr>
<td>30-34</td>
<td>25</td>
<td>1.13</td>
</tr>
<tr>
<td>35-39</td>
<td>15</td>
<td>18.5</td>
</tr>
</tbody>
</table>
Vietnam War Service and Birth Defects

The herbicide “Agent Orange” - a mixture of 2,4-D and 2,4,5-T (contaminated with “dioxin”) - was sprayed widely over Vietnam as a tactical maneuver to deprive the enemy the cover of jungle.

In the aftermath of the war, many veterans’ alleged that their health had been harmed by Vietnam service. Much of the blame was directed at exposure to Agent Orange.

One of the most frequently mentioned alleged ill-effects was birth defects in Vietnam Veterans’ offspring.

The surveillance data collected by the MACDP made CDC uniquely positioned to mount an epidemiologic study of the issue.

Vietnam Veterans’ Risk for Fathering Babies with Birth Defects Study

4929 Cases – families of babies born with major structural birth defects, ascertained by MACDP 1968-1980

3029 Controls – families of babies born without birth defects, ascertained from State of Georgia live birth certificates

Interviews with mothers and fathers

96 birth defect categories,

4 major hypotheses tested for each defect category:

• Veteran status
• Vietnam veteran status
• AO Exposure Opportunity Index (scores by DoD)
• Self Report of AO Exposure
### Risks for All Defects, Veterans and Vietnam Veterans

**All Veterans Risk, All Birth defects**

<table>
<thead>
<tr>
<th></th>
<th>Veteran Fathers</th>
<th>NonVeteran Fathers</th>
<th>Total</th>
<th>O.R.</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case</strong></td>
<td>1659 (38)</td>
<td>2727 (62)</td>
<td>4386</td>
<td>0.94</td>
<td>0.85 – 1.04</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>1047 (39)</td>
<td>1652 (61)</td>
<td>2699</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Risks for Spina Bifida, Vietnam Veterans

**Vietnam Veterans Risks, Spina Bifida**

<table>
<thead>
<tr>
<th></th>
<th>VietnamVet Fathers</th>
<th>All Other Fathers</th>
<th>Total</th>
<th>O.R.</th>
<th>C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case</strong></td>
<td>19 (9)</td>
<td>182 (91)</td>
<td>201</td>
<td>1.05</td>
<td>0.63 – 1.73</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>247 (9)</td>
<td>2434 (91)</td>
<td>2482</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A.O. Exposure Opportunity Index
Regression Beta 0.20 (p<.05) implies:

<table>
<thead>
<tr>
<th>Index</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>O.R.</strong></td>
<td>1</td>
<td>1.2</td>
<td>1.5</td>
<td>1.8</td>
<td>2.2</td>
<td>2.7</td>
</tr>
</tbody>
</table>
In 1996 Update, IOM Committee concluded that “…..there is limited/suggestive evidence for an association between exposure to herbicides used in Vietnam and spina bifida in offspring.” (Based on findings from the CDC Birth Defects and Vietnam Experience studies, and the Air Force’s Ranch Hand study.)

As a result, Congress authorized the Veterans Administration to provide benefits to Viet Vets’ children with spina bifida, including lifetime health care for the defect and related disabilities.

In 2008 the law was amended to provide ALL health care for the children for life.
Periconceptional Multivitamin use and the Risk of selected birth defects
Vietnam Veterans Study 1968-1980

- Choanal atresia
- Preaxial polydactyly
- Spina bifida
- Anencephaly
- Total ASB
- All CNS defects
- ASD
- VSD
- CL +/- CP
- Limb defects
- Omphalocele
- Reduction deformities

Risk Ratio With 95% Confidence Intervals

Folic Acid (multivitamins) and the risk for neural tube defects, 1980-1999

- '80-Smithells
- '81-S. Wales
- '88-Atlanta
- '89-W. Australia
- '89-CA/Illinois
- '89-Boston
- '90-Cuba
- '91-UK-MRC
- '92-Hungary
- '93-New England
- '95-California
- '99-P.R. China

Randomized trials
Non-randomized trials
Observational studies

Risk Ratio With 95% Confidence Intervals
China Folic Acid Community Intervention
(Good Compliance)

Intervention = 400 mcg folic acid supplement daily

2012 is the 20th Anniversary of the USPHS Folic Acid Recommendation

- 400 micrograms (0.4mg) folic acid daily,
- for all women capable of becoming pregnant,
- to prevent spina bifida and other NTDs.
- Increase consumption of folic acid/folate:
  • Improve dietary habits
  • Consume fortified foods
  • Take a daily folic acid supplement
43 Members in 37 Countries, and one Centre in Rome

International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)
- Network of surveillance programs (members)
- Executive Committee, program coordinator, and work Committees
- Funded mainly through Annual Dues
- Annual and Quarterly Surveillance
- Special Projects and studies
- Since 1974

International Clearinghouse Centre (ICBDSR Centre)
- Head office of Clearinghouse
- Director and research staff
- Appointed by Clearinghouse
- Funded through grants
- Currently in Rome, Italy (previously in Bergen, Norway)
- Supports, conducts many of the Clearinghouse studies, analyzes surveillance data, produces reports
- Since 1989

NTD Prevalence by Fortification Status
25 States, National Birth Defects Prevention Network
1995-2006

Prevalence per 10,000


Before Optional Mandatory fortification
Wheat Flour Fortification Status May 2012
68 Countries Fortifying with at least iron and/or folic acid

Flour Fortification Initiative, Emory University School of Public Health
**Hypothesis**

A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis

Joel B. Mason,1,2 Aaron Dickstein,2 Paul F. Jacques,3 Paul Haggarty,3 Jacob Selhub,3 Gerard Dalal,1 and Irwin H. Rosenberg1,2

1USDA, Agricultural Research Service; 2Harvard University; 3Tufts University School of Medicine, Boston, Massachusetts

Data for 2000 added since publication.

Data for 2000 is from January through September.

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**Percentage of Serum Folate Values ≥ 20 ng/mL, by Fortification, and by Year, 1994-2000.**

Kaiser Permanente Southern California Patients

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Data for 2000 added since publication. Data for 2000 is from January through September.
Age-adjusted Colorectal Cancer, United States 1986-2002


SEER Age-Adjusted Total US Mortality Rates for Colon and Rectum Cancer, All Ages, for 1969-2004 by Sex, Age-Adjusted to the 2000 US Std Population
http://seer.cancer.gov/faststats/

Kaiser Folate

<table>
<thead>
<tr>
<th>Year</th>
<th>Median µg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>12.6</td>
</tr>
<tr>
<td>1995</td>
<td>12.7</td>
</tr>
<tr>
<td>1996</td>
<td>11.7</td>
</tr>
<tr>
<td>1997</td>
<td>14.9</td>
</tr>
<tr>
<td>1998</td>
<td>18.7</td>
</tr>
</tbody>
</table>
Colon Cancer and Folic Acid in Chile

Hirsch, 2009

Colon cancer in Chile before and after the start of the flour fortification program with folic acid
Sandra Hirsch, Hugo Sanchez, Cecilia Albala, María Pía de la Maza, Gladys Barrera, Laura Leiva and Daniel Bunout

Outcome was number of hospital discharge diagnoses


Potential Adverse Outcomes:
Cancer (cont’d)

*Crude CRC mortality rate Chile 1990-2003*

Donoso, AD et al. *Rev Med Chile* 2006;134:152-8
Cognitive Issues

Morris presents data from NHANES showing poorer performance on cognitive tests if one has low serum B12 and high serum folates.

Berry shows that the only people with high serum folates are people who take supplements with have 6 or 25 micrograms of B12.

Morris has likely identified those with pre-clinical, early clinical pernicious anemia that need treatment with vitamin B12.

It is not a folic acid issue but a B12 issue that needs to be solved.

Proportion of participants who used supplements containing folic acid by serum folate quintiles and dietary sources of folic acid in non-Hispanic white seniors aged ≥60 y. NHANES, 2001–2002.

Berry, RJ et al. AJCN 2007;85:265-7
But pediatrics has always aimed at prevention and prevention of congenital malformations seems as necessary as prevention of contagious and alimentary disorders.”

- Warkany, Notes
Economic Evaluation of Folic Acid Fortification in the United States

- Through 2006, 37% reduction in NTDs
- Program costs
  - Fortification of flour: $3 million/year
  - Direct cost averted: $145 million/year
  - For every $1 invested there are >$45 in medical costs averted/year
- Lifetime medical costs per child with spina bifida are $461,000

Grosse et al. AJPH 2005

Neural Tube Defects
Other Risk Factors: 5%-10%

- Previous NTD-affected pregnancy
- Genetic variants
- Maternal diabetes
- Obesity
- Hyperthermia, fever
- Antiepileptic medications
- Lower socioeconomic status
- Race/ethnicity: Hispanic > white > black
A Challenge

How will we know when we have eliminated all folic acid-preventable NTDs?

- When all women reach a specified consumption or blood level?
- When NTD rates stabilize at some specified level?
- When we understand the underlying biology of NTD prevention? (wouldn’t it be ironic if it turns out to have something to do with methylation / epigenetics!)

Issues & opinions impeding widespread increases in consumption of folic acid:

General, related to supplements or fortified foods
- Doesn’t work
- Not important, even if it does work
- Lack of firm evidence about additional benefits
- Not needed, diet is good; termination of pregnancy available
- Not natural (“medicalization” of food, pregnancy, “single nutrient nutrition”)
- Difficult to change behavior (esp. supplements)
- Might cause harm, eg cancer, epigenetics
- Insufficient monitoring for safety concerns
Issues & opinions impeding widespread increases in consumption of folic acid:

Specifically related to fortified foods
- Lack of centralized food distribution system
- No culture for / experience with fortification (esp. Europe)
- Exposes whole population
- Loss of choice for individuals

But there has been a lot of progress, and Things could be worse!
Fortification of wheat flour with folic acid is a cost-effective intervention in Chile, a middle income country in the post-epidemiological transition. This result supports the continuation of the Chile fortification program, and constitutes valuable information for policy makers in other countries to consider.


<table>
<thead>
<tr>
<th>Fortification of wheat flour in Chile</th>
<th>(mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Since 1955</td>
<td></td>
</tr>
<tr>
<td>Iron (ferrous sulfate)</td>
<td>30.0</td>
</tr>
<tr>
<td>Thiamine</td>
<td>6.3</td>
</tr>
<tr>
<td>Riboflavine</td>
<td>1.3</td>
</tr>
<tr>
<td>Niacine</td>
<td>13.0</td>
</tr>
<tr>
<td>Since Jan. 2000</td>
<td></td>
</tr>
<tr>
<td>FOLIC ACID</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>(220ug/100g)</td>
</tr>
<tr>
<td>= consumption of ≈ 400 μg/day</td>
<td></td>
</tr>
</tbody>
</table>
Folic Acid consumption.

98% of women consume bread on daily basis

89% consume more than 180 g of bread/daily
(2 units, ~370 ug of FA)

No consumption of other folic acid fortified foods

No consumption of folic acid supplements

Folic acid contents of wheat flour in Chile-2005

n samples=338

80.8% are fortified

Median = 2.14 mg/kg
Range = 0.0 - 8.0 mg/kg

*Quantitation limit 0.019 mg/kg
Estimated folic acid intake from bread

Mean = 427 ug/day

Serum Folate pre & post Fortification


N=605
RBC Folate distribution of pre & post Fortification


- Pre Fortification (128±45)
- Post Fortification (312±79)

N=605

Serum B12 distribution pre & post Fortification


- Pre Fort (341±162)
- Post Fort (364±226)

N=605
Surveillance of NTD in Chile

Cost for the milling industry / year:

US$ 275,000

Averted cost from spina bifida cases prevented in one year:

US$ 9 million

Averted cost of nearly 33 dollars / 1 dollar spent in fortification.

A Llanos et al., Cost effectiveness of a folic acid fortification program in Chile. Health Policy (2007) healthpol 2007.01.011
### Changes in stillbirth and multiple births prevalence*

**Before** N=120,636 births (1999-2000)

**After** N=117,704 births (2001-2002)

<table>
<thead>
<tr>
<th></th>
<th>Before Fort*</th>
<th>After Fort*</th>
<th>RR (95% IC)</th>
<th>% reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>76.4</td>
<td>61.8</td>
<td>0.81 (0.73-0.89)</td>
<td>19.6</td>
</tr>
<tr>
<td>Multiple births</td>
<td>83.6</td>
<td>88.2</td>
<td>1.06 (0.96-1.15)</td>
<td>-5.5</td>
</tr>
</tbody>
</table>

* Prevalence per 10,000 total births

### Folic Acid and NTD, ECLAMC Data

**Chile, Argentina & Brazil, thru 2007**

<table>
<thead>
<tr>
<th></th>
<th>Chile</th>
<th>Argentina</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year 1st Fortified Births</strong></td>
<td>2001</td>
<td>2005</td>
<td>2005</td>
</tr>
<tr>
<td><strong>Monitored Births (After FA)</strong></td>
<td>243624</td>
<td>147853</td>
<td>92843</td>
</tr>
<tr>
<td><strong>FA In Flour, mg/kg</strong></td>
<td>2.2</td>
<td>2.2</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Est. Daily FA intake, µg</strong></td>
<td>499</td>
<td>486</td>
<td>264</td>
</tr>
</tbody>
</table>

### Folic Acid Fortification and NTD
Chile, Argentina & Brazil, Data thru 2007
Before vs. After Risk Ratios*

<table>
<thead>
<tr>
<th></th>
<th>Chile</th>
<th>Argentina</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>0.54</td>
<td>0.59</td>
<td>0.57</td>
</tr>
<tr>
<td>Spina Bifida - Total</td>
<td>0.43</td>
<td>0.59</td>
<td>0.99</td>
</tr>
<tr>
<td>Spina Bifida - Cephalic</td>
<td>0.17</td>
<td>0.27</td>
<td>0.49</td>
</tr>
<tr>
<td>Spina Bifida - Caudal</td>
<td>0.55</td>
<td>0.75</td>
<td>1.12</td>
</tr>
</tbody>
</table>


### Folic Acid Fortification and NTD
Chile, Argentina & Brazil, Data thru 2007*
Before, After Rates/1000 Births

<table>
<thead>
<tr>
<th></th>
<th>Chile</th>
<th>Argentina</th>
<th>Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anencephaly</td>
<td>0.63, 0.37</td>
<td>0.86, 0.37</td>
<td>1.12, 0.69</td>
</tr>
<tr>
<td>Spina Bifida - Total</td>
<td>1.02, 0.46</td>
<td>1.27, 0.66</td>
<td>1.45, 1.42</td>
</tr>
<tr>
<td>Spina Bifida - Cephalic</td>
<td>0.26, 0.05</td>
<td>0.37, 0.05</td>
<td>0.33, 0.14</td>
</tr>
<tr>
<td>Spina Bifida - Caudal</td>
<td>0.72, 0.38</td>
<td>0.88, 0.60</td>
<td>1.04, 1.23</td>
</tr>
</tbody>
</table>

Folic Acid-Preventable SBA in 2006
300,000 affected babies worldwide

Need to Find
- Causes
- Not Prevented
- Prevented

Worldwide SBA

Neural Tube Defect Surveillance Worldwide 2006

**Wheat Flour Fortification Status May 2012**

68 Countries Fortifying with at least iron and/or folic acid

People who have helped me with this presentation

RJ Berry, CDC Atlanta
Joe Mulinare, CDC Atlanta
Godfrey Oakley, Emory Atlanta
Pierpaolo Mastroiacovo, ICBD Rome
Sonja Rasmussen, CDC Atlanta
I hope that this interdisciplinary composition will remain a characteristic of our Society. There is a great need for a common language, mutual understanding, and cross-fertilization in this area where students in the basic sciences, clinicians, sociologists, and public health workers should meet.

Neural tube defects

Serious birth defects
  – spina bifida and anencephaly
> 1 of 1000 pregnancies
> 300,000 yearly worldwide

Increased consumption of folic acid can prevent 50-80%

Comprehensive, robust data
  – Randomized controlled trials
  – Consistent case-control studies
  – Occurrence and recurrence
  – Both multivitamins and folic acid alone
  – Consistent genetic findings (MTHFR)