The prevention of birth defects: a global problem requiring urgent action

Godfrey P. Oakley Jr. MD. MSPM
13th Wolfson Lecture
London
October 31, 2012

Disclaimer

• Co-inventor of a patent that could lead to marketing of contraceptive pills with folic acid in them

• Paid consultant to Ortho-McNeil on this issue
Take Home Messages

• Birth defects are preventable.
• Lack of mandatory folic acid fortification in Europe is a tragic failure in public policy that should be reversed immediately as mandatory fortification is completely safe.
• We can substantially improve the health of children by creating the political will for birth defects prevention.

Joy of Epidemiology

• Making causal associations
• Prevention before mechanisms
• Smallpox vaccine before micro-organisms known
• Two for me:
  – Valproic acid and spina bifida
  – Folate deficiency and spina bifida
Epidemiology Not Enough

• Must get the prevention done, too

• One enters policy (politics) where fun begins

Birth Defect Prevention: Child Survival Priority for the 21th Century

• Birth defects leading cause of infant mortality in China

• Birth defects will be come leading cause of infant mortality in almost all, if not all, countries in 25 years as infant deaths from infection decrease
Birth Defects Milestones

1930s  Vitamin A deficiency in pigs
1940s  Rubella in people
        High vitamin A in rats
        Maternal Diabetes
        Maternal Age/Down Syndrome
1960s  Thalidomide
1970s  Fetal Alcohol Syndrome
1980s  Valproic acid/spina bifida
        Accutane causes birth defect
1990s  Folic acid deficiency/spina bifida

Embryonic and Fetal Development
My Hero Bill Foege
House on Fire: The Fight To Eradicate Smallpox

• “Smallpox did not disappear by accident: smallpox disappeared because of a plan, conceived and implemented on purpose by people.”
• Science to prevent smallpox for 200 years
• “Social will must be transformed into political will.”

-William H. Foege 2011

http://www.polioeradication.org/

• Read this web site to see how much political will has been created

• See weekly up to date counts of polio in total and by country—surveillance par excellence
Wild Polio **Weekly** Update
24 October 2012
CDC, WHO, UNICEF, Rotary

<table>
<thead>
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<th>Total Cases</th>
<th>Year to Date 2012</th>
<th>Year to Date 2011</th>
<th>Total 2011</th>
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<tr>
<td>Globally</td>
<td>175</td>
<td>489</td>
<td>650</td>
</tr>
<tr>
<td>in endemic countries</td>
<td>170</td>
<td>217</td>
<td>341</td>
</tr>
<tr>
<td>in non-endemic</td>
<td>5</td>
<td>272</td>
<td>309</td>
</tr>
<tr>
<td>countries</td>
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</table>

**Congenital Rubella Syndrome**

- Gone from the USA, almost gone in Americas
- 100,000 annual cases globally
- We know how to make it go away, globally
- Immunize all the children in the world
- Likely to happen because foundations understand the role of vaccines in preventing disease in developing countries
Lancaster HO, BMJ; December 15, 1951 p 1429-1432.
Valproic Acid and Spina Bifida

• Data: Birth defects surveillance system at the Institut Europeen des Genomutations in Lyon, France during 1976 and from 1978 through September 1982
• Among 146 cases of spina bifida aperta, 9(6.2%) of the mothers had epilepsy and had taken valproic acid during the first trimester
  – Dose of VA: 400 mg to 2,000 mg per day
  – 5/9 were exposed to valproic acid alone
  – 4 were exposed to additional anticonvulsants

Table 1. Spina bifida and treatment with valproic acid of mothers who have delivered infants with birth defects – Lyon, France

<table>
<thead>
<tr>
<th></th>
<th>Spina Bifida</th>
<th>Other Birth Defects</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Valproic acid treatment</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>No valproic acid treatment</td>
<td>137</td>
<td>6,595</td>
<td>6,732</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>6,616</td>
<td>6,762</td>
</tr>
</tbody>
</table>

Odds Ratio: 20.6 (8.2, 47.9); p-value 0.000001

MMWR 1982; 31 (42): 565-6
Valproic Acid and Spina Bifida

- To isolate the effect of valproic acid from the possible effects of seizure disorders and other drug therapy, analysis confined to the 71 epileptic mothers.

Table 2. Spina bifida and treatment with valproic acid of mothers who have seizure disorders and who delivered infants with birth defects – Lyon, France

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</tr>
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<tbody>
<tr>
<td>Valproic acid treatment</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>No valproic acid treatment</td>
<td>1</td>
<td>40*</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>61</td>
<td>71</td>
</tr>
</tbody>
</table>

* 5 not treated with anticonvulsants; 5 with unknown therapy

Odds Ratio: 17.1 (2.1, 769.5); p-value = 0.00068

VPA Causes Spina Bifida

- VPA has been shown consistently to be a potent cause of spina bifida in almost all studies

- Since we knew in 1982 that VPA was a potent cause of a severe, disabling birth defect, it is surprising that exposure has continued.
VPA and Other Risks

- Birth Defects
  - Spina Bifida
  - Atrial Septal Defect
  - Cleft Palate
  - Hypospadias
  - Polydactyly
  - Craniosynostosis
- Cognitive reductions
- Autism

VPA in Women without a Diagnosis of Epilepsy/Seizure

Figure 2. Valproate prescriptions made to all U.S. women aged 15 – 44 years by Epilepsy/Seizure category

Analysis conducted using National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) from 1996-2007. (n = 10,648,000 prescriptions over a 12 year period)
We Need to Talk About Our Eggs

I recently mentioned to a pregnant acquaintance that I was...
A SURVEY OF MONGOLOID BIRTHS IN
VICTORIA, AUSTRALIA, 1942-1957

R. D. Collmann, B.A., B.Sc., M.Ed., Ph.D., and Alan Stoller, M.R.C.S., L.R.C.P., D.P.M.

Figure 3—Variation of Incidence with Maternal Age, 1942-1957

Percentage of Births to Women 35 and Older by Year USA

- 1960 - 10.7%
- 1970 - 6.9%
- 1980 - 4.6%
- 1990 - 8.9%
- 2003 - 14.0%
- 2011 - 14.7%

321% Increase 1980-2011
Down Syndrome **Epidemic**: Estimated Number and Prevalence per 1000 Births by Year USA

- 1980 0.99 3579
- 1990 1.20 4973
- 2003 1.50 6134

71% increase in numbers
51% increase in prevalence

Number of Down Syndrome cases per 10,000 births and percentage of mothers > 35 years, 1993-2004

Figure 1: Number of livebirths in 1989 and 2003 by maternal age (source: ONS)

Crane & Morris (2006). Down Syndrome Research and Practice 10(1);41-43

Maternal Type I Diabetes

- Increases birth defects by **300%**
- Observational studies suggest glucose control prevents birth defects
- Proportion of birth defects among off-spring of women with diabetes has not changed
- Effective programs just not being implemented

• Any **non-cardiac birth defect**:
  
  – With folic acid supplement – RR: 3.17
  
  – Without folic acid supplement – RR: 9.77


• Any **congenital heart defect**:
  
  – With folic acid supplement – RR: 5.51
  
  – Without folic acid supplement – RR: 13.35

**Excess Risk of Diabetes-Associated Birth Defect: 1997-2004**

- **Truncus Arteriosus:**
  - With folic acid supplement – RR: 25.93
  - Without folic acid supplement – RR: 54.04


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**Bell et al**

- “Peri-natal hyperglycaemia is the most important MODIFIABLE risk factor for congenital anomaly in women with diabetes.”
- 400,000 pregnancies
- 1996-2008 North of England
- Birth defects not being prevented.
Bell et al major findings

• 3.7 RR for major non chromosomal birth defects.
• Hgb A1c strong dose related predictor
• Pre-existing nephropathy, but not neuropathy or retinopathy, doubles risk

• DOI 10.1007/s00125-012-2455-y
Fetal Alcohol Spectrum Disorders

- It is a leading preventable cause of birth defects and developmental disabilities

- Fetal Alcohol Syndrome affects from 1,200-6,100 births each year in the U.S (0.3-1.5 cases/1,000 live births)

- Fetal Alcohol Spectrum Disorder (FASD) may affect as many as 1 in 100 babies born in the U.S.

- Average lifetime cost associated with FAS is $2 million

Percentage of Pregnant Women Aged 18 to 44 Years Who Reported Alcohol Consumption: BRFSS, United States 1991–2005

Alcohol Consumption Patterns Non-pregnant Women 18 to 44 Years of Age


Preventing Alcohol-Exposed Pregnancies

- Reduce risk drinking
- Prevent pregnancy
Spina Bifida F and Anencephaly F

- 1991 causality proven—MRC study
- 1991 USA recurrence recommendations
- 1992 USA population recommendation
- 1996 USA regulations permitted and then required by Jan 1, 1998, mandatory folic acid fortification of “enriched cereal grain products”
- Globally prevention only 20% done
Percentage decline in incidence Hib following vaccine introduction

- Finland
- Netherlands
- UK
- Ireland
- Israel

Year relative to introduction

China Folic Acid Community Intervention (Good Compliance)

Intervention = 400 mcg folic acid supplement daily

North South

NTD Rate/1000

No Pills
Pills
Selected worldwide NTD prevalence rates before and after folic acid fortification, per 10,000,000 compared to China Community Intervention Trial of 400 mcg folic acid daily

Percent of Folic Acid-Preventable Spina Bifida and Anencephaly Prevented by Country
Model 2

Percent Prevented
- Increased fortification needed
- 100% Prevented

Urgently Needed
Why Prevention Not Done?

• “…scientific feuds…not only by the purest of intellectual disagreements, but also by intransigence, ambition, jealousy, politics, faith, and the irresistible human urge to be right.”

• Flyleaf for book cover of Great Feuds in Science by Hal Hellman
Why Does No Country in Europe Require Folic Acid Fortification?

By MARIAN BURROS

THE Food and Drug Administration is trying to come to grips with one of the most difficult public health issues: how to balance the interests of the unborn with the interests of the elderly.

The agency must decide whether to fortify the American food supply with folic acid, which helps to prevent birth defects but, at the same time, can mask pernicious anemia, a problem prevalent among the elderly.

Opinions on how to proceed cover the spectrum.

Dr. Irwin H. Rosenberg, director of the United States Department of Agriculture's Human Nutrition Center on Aging, at Tufts University, is opposed to fortification with folic acid until more is known about the risks. The Centers for Disease Control and Prevention does not think the Food and Drug Administration's plan to fortify the food supply goes far enough.

“"The amount recommended can easily be obtained by eating a healthy diet," she said. "There are too many uncertainties about the database on which these decisions are being made. We are not so sure how much people are eating, and the incidence of neural tube defects is dropping. I'm not opposed at all to women of child-bearing age taking folic acid supplements."

Marion Nestle, chairwoman of the Department of Nutrition at New York University, is opposed to fortification on principle.

January 5, 1994

Professor Irvin Rosenberg

“...folic acid fortification may be the most important science-driven intervention in nutrition and public health in decades.”


Dr. Marion Nestle

• Member of FDA Food Advisory Committee at time folic acid fortification discussed
• “I saw this particular situation as a missed opportunity for developing a nationwide education campaign to encourage everyone to eat more fruits and vegetables—the primary dietary source of folate....”
• Food Politics p. 304
Dr. Marion Nestle

• “To skeptics, myself among them, folic acid fortification was almost certain to lead to calls for the addition of larger numbers of essential nutrients—whether needed or not—to the general food supply.”
• Food Politics p. 304

Lifelong disabilities of spina bifida

- Loss of sensation
- Paralysis of muscle groups
- Loss of bladder, and bowel control
- Learning and developmental issues
- Orthopedic problems
How To Stop Folic Acid Fortification

- Suggest it may not be safe, with no data, in policy discussions

- Whatever the real motive to be against fortification, invoking a remote, improbable chance of harm leads to children unnecessarily spending their lives in wheelchairs.
If New Zealand Requires Folic Acid Fortification

- 20,000 elderly at risk for cognitive harm and anemia
- 1000 cases of cancer
Professor David Smith
July 8, 2012  TV interview

• Discussion about requiring folic acid to be put in bread

• Question: “Is there a risk of cancer..”

• Smith: “I believe there is.”

Folic acid is safe!

• RJ Berry and his colleagues have shown MANDATORY folic acid fortification is SAFE!

• Now is time for all governments to require mandatory folic acid fortification.

• There is no need for additional surveys or scientific reports to delay implementation in any country.
Mandatory Folic Acid Fortification is SAFE!

- Mandatory folic acid fortification adds to the daily diet of almost all adults a uniform 150 micrograms of folic acid.
- 150 micrograms is about one-third of RDA and is perfectly safe.
- If there is a problem with folic acid it is at higher doses than occur from mandatory folic acid fortification and happens ONLY when people voluntarily take folic acid supplements.

Sources and Amounts of Folic Acid

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<thead>
<tr>
<th>Source</th>
<th>Amount</th>
<th>Mandatory/Voluntary</th>
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<tbody>
<tr>
<td>Folic Acid Enriched Cereal Grain Products (ECGP)</td>
<td>100-150 µg / day</td>
<td>MANDATORY</td>
</tr>
<tr>
<td>Folic Acid Fortified “Ready-to Eat” Breakfast Cereals (RTE)</td>
<td>Up to 400 µg / serving</td>
<td>VOLUNTARY</td>
</tr>
<tr>
<td>Folic Acid-Containing Supplements</td>
<td>~400 µg / supplement</td>
<td>VOLUNTARY</td>
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Estimated Daily Intake of Folic Acid by Serum Folate Quintile

Data were obtained from the National Health and Nutrition Examination Survey (NHANES) 2001-2004 for 8695 nonpregnant adults aged 19 years and older. For ready-to-eat cereals, \( P < 0.001 \); for enriched cereal grain products, \( P < 0.01 \); and for supplements, \( P < 0.001 \) (Satterthwaite adjusted \( F \) statistic). All analyses were adjusted for age, sex, and race/ethnicity. Error bars indicate 95% confidence intervals. Refer to Table for quintile ranges.

Non-Hispanic white seniors aged \( \geq 60 \) yrs
NHANES, 2001–2002

Proportion who used FA supplements

Serum folate quintiles and their geometric means (nmol/L)

Using FA supplements

Berry, RJ et al. *AJCN* 2007;85:265-7
Birth Defects in the News

• New Zealand Food Safety Minister prohibits implementation of food regulations that would required folic acid fortification

• Company apologizes for birth defects caused by thalidomide

September 3, 2012
“consumer choice was really the one that made the most difference in terms of the decision (mandatory folic acid fortification). When you’ve got two thirds of the submitters actually wanting that choice, rather than debating the science, then that’s what we listened to.”

Kate Wilkinson
Food Safety Minister - New Zealand

**Improving Regulations for Food**

- Must have a culture that is willing to require and does require mandatory fortification on an emergency basis
- It currently is a culture that moves rapidly only then there something in the food thought to be harmful.
Apology from Gruenenthal
Thalidomide Tragedy

"On behalf of Gruenenthal with its shareholders and all employees, I would like to take the opportunity at this moment of remembrance today to express our sincere regrets about the consequences of Thalidomide and our deep sympathy for all those affected, their mothers and their families. We see both the physical hardship and the emotional stress that the affected, their families and particularly their mothers, had to suffer because of Thalidomide and still have to endure day by day."

-CEO, Gruenenthal.

September 1, 2012

Frances Kelsey Gets Presidential Medal of Honor

Spina Bifida F and Anencephaly F affect more than thalidomide did

**Thalidomide Embryopathy**
Total Cases (1950s-60s): 10,000

**Spina Bifida F and Anencephaly F**
Annual Cases: 200,000
Total cases since 1992: 4,200,000
(4.2 million)

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**Thalidomide vs. Spina bifida**

![Graph showing comparison between Thalidomide and Spina bifida cases](chart.png)

- Total cases during years 1950’s – 60’s

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Godfrey P. Oakley
Thalidomide vs. Spina bifida

Global Annual Preventable Cases of Spina Bifida F and Anencephaly F

Total Cases

Thalidomide

Global Annual Preventable Cases of Spina Bifida F and Anencephaly F

Total Cases
Thalidomide vs. Spina bifida

Global Annual Preventable Cases of Spina Bifida F and Anencephaly F

Total Cases

110,000 120,000 130,000 140,000 150,000

Thalidomide vs. Spina bifida

Global Annual Preventable Cases of Spina Bifida F and Anencephaly F

Total Cases

160,000 170,000 180,000 190,000 200,000
Preventable cases of spina bifida

Total Global Preventable Cases of Spina Bifida F and Anencephaly F - Year 1992

Total Cases

10,000 20,000 30,000 40,000 50,000

Preventable cases of spina bifida

Total Global Preventable Cases of Spina Bifida F and Anencephaly F - Year 1992

Total Cases

60,000 70,000 80,000 90,000 100,000
Preventable cases of spina bifida

Total Global Preventable Cases of Spina Bifida F and Anencephaly F - Year 1992

Preventable cases of spina bifida

Total Global Preventable Cases of Spina Bifida F and Anencephaly F - Year 1992
Preventable cases of spina bifida since 1991

Total Global Preventable Cases of Spina Bifida F and Anencephaly F

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<tbody>
<tr>
<td>Cases</td>
<td>400,000</td>
<td>600,000</td>
<td>800,000</td>
<td>1 M</td>
<td>1.2 M</td>
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Preventable cases of spina bifida since 1991

Total Global Preventable Cases of Spina Bifida F and Anencephaly F

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<th>Year</th>
<th>1998</th>
<th>1999</th>
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<th>2001</th>
<th>2002</th>
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<tbody>
<tr>
<td>Cases</td>
<td>1.4 M</td>
<td>1.6 M</td>
<td>1.8 M</td>
<td>2 M</td>
<td>2.2 M</td>
</tr>
</tbody>
</table>
Preventable cases of spina bifida since 1991

Total Global Preventable Cases of Spina Bifida and Anencephaly

Year: 2003 2004 2005 2006 2007

Total Cases

Year: 2008 2009 2010 2011 2012

Total Cases
One wonders when will Kate Wilkinson and other food and health ministers apologize for food policy decisions responsible each year for 20 times as many children having spina bifida and anencephaly as there were children ever affected by thalidomide.

One wonders when will academic advisors to governments apologize for advice that has and continues to delay mandatory fortification.

Bill Foege
May 24, 2012

• “But here is the magic.
•
• You only need to prevent spina bifida once and it lasts for a life time.”
Take Home Messages

- Birth defects are preventable.
- Lack of mandatory folic acid fortification in Europe is a tragic failure in public policy that should be reversed immediately as mandatory fortification is completely safe.
- We can substantially improve the health of children by creating the political will for birth defects prevention.