

# 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

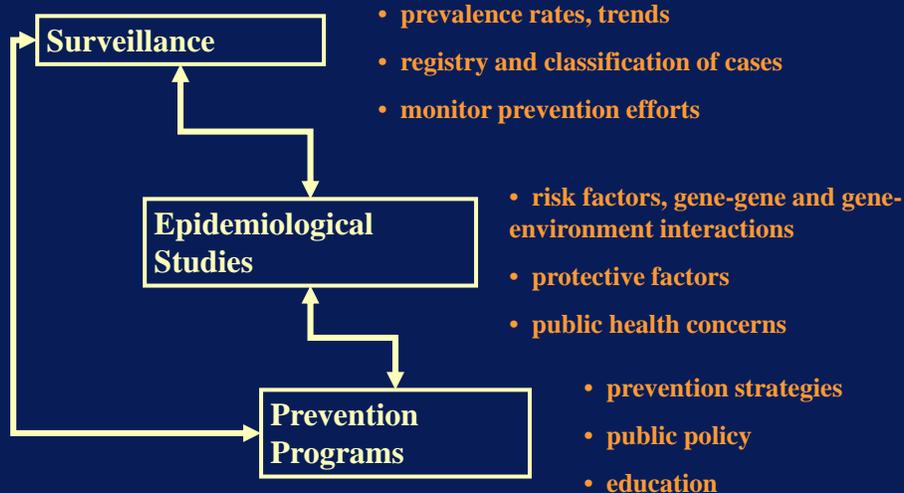
MPH - University of Minnesota

PhD - University of Washington

## Important people I met in Seattle



## CDC Disease Prevention Framework



## 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\*

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

Births and cases from Illinois cities of maternal residence with 100-100,000 populations, 1950-1957  
 \*Rapaport, Bull Acad Nat'l de Medecine (Paris) 1959  
 (data obtained from CDC, June 2012)

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

	Fluoridated Areas		Nonfluoridated Areas	
	166,186 Births		101,639 Births	
	DS	Rate per	DS	Rate per
Age	Births	1000 Births	Births	1000 Births
≤19	19	0.77	7	0.38
20-24	41	0.69	15	0.40
25-29	34	0.68	11	0.42
30-34	25	1.13	13	1.10
35-39	15	18.5	25	45.8

## 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					
	Veteran Fathers N (%)	NonVeteran Fathers N (%)	Total	O.R.	C.I.
Case	1659 (38)	2727 (62)	4386	0.94	0.85 – 1.04
Control	1047 (39)	1652 (61)	2699		

## Risks for Spina Bifida Vietnam Veterans

Vietnam Veterans Risks, Spina Bifida						
	VietnamVet Fathers N (%)	All Other Fathers N (%)	Total	O.R.	C.I.	
<b>A.O. Exposure Opportunity Index Regression Beta 0.20 (p&lt;.05) implies:</b>						
Index	0	1	2	3	4	5
O.R.	1	1.2	1.5	1.8	2.2	2.7

# Veterans and Agent Orange

Update 1996

Committee to Review the Health Effects in  
Vietnam Veterans of Exposure to Herbicides

Division of Health Promotion and  
Disease Prevention

INSTITUTE OF MEDICINE



NATIONAL ACADEMY PRESS  
Washington, D.C. 1996

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.)

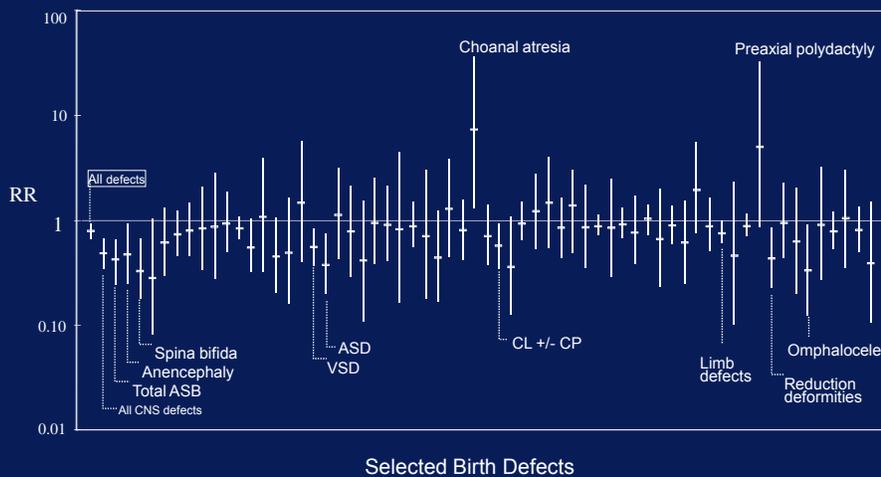
As a result, Congress authorized the Veterans Administration to provide benefits to Viet Vets’ children with spina bifida, including lifetime health care for the defect and related disabilities.

In 2008 the law was amended to provide ALL health care for the children for life.



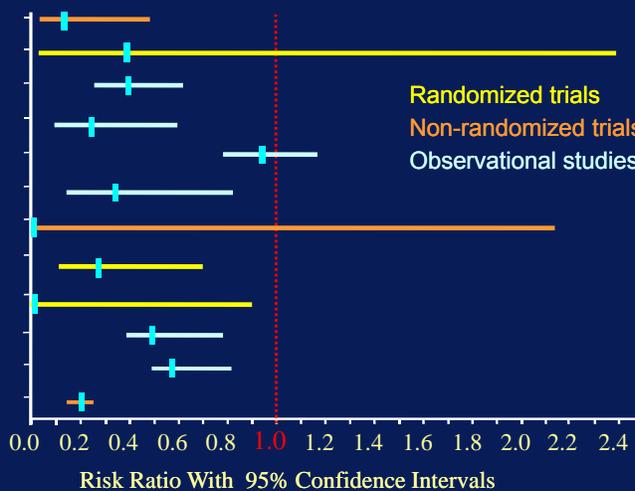
## Periconceptional Multivitamin use and the Risk of selected birth defects

Vietnam Veterans Study 1968-1980



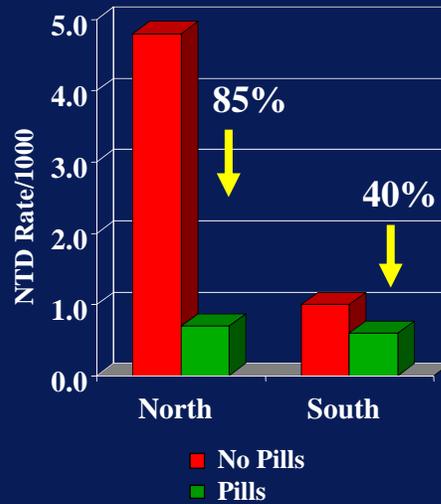
## Folic Acid (multivitamins) and the risk for neural tube defects, 1980-1999

- '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

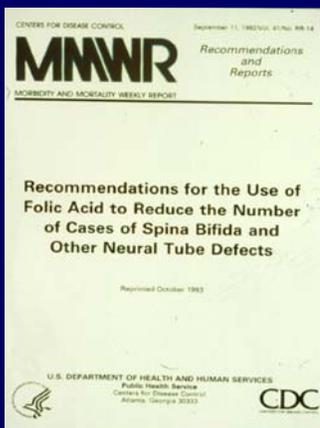


## China Folic Acid Community Intervention (Good Compliance)

Intervention = 400 mcg  
folic acid supplement daily



2012 is the 20<sup>th</sup> 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)

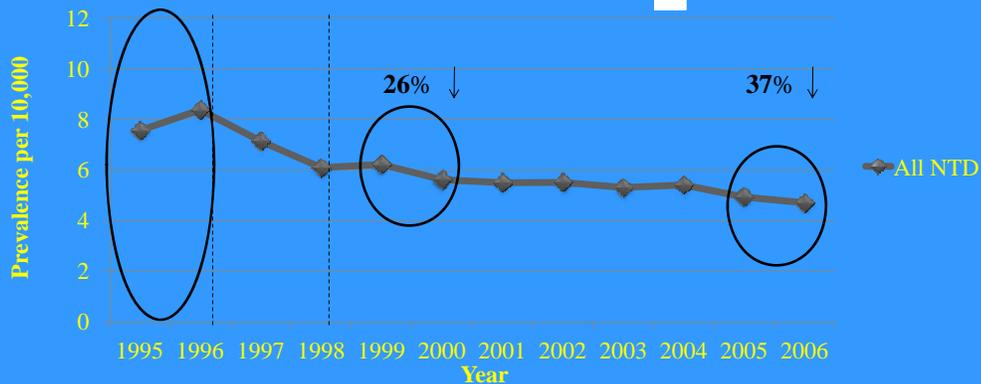
- Network of surveillance programs (members)
- Executive Committee, program coordinator, and work Committees
- Funded mainly through Annual Dues
- Annual and Quarterly Surveillance
- Special Projects and studies
- Since 1974



#### 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

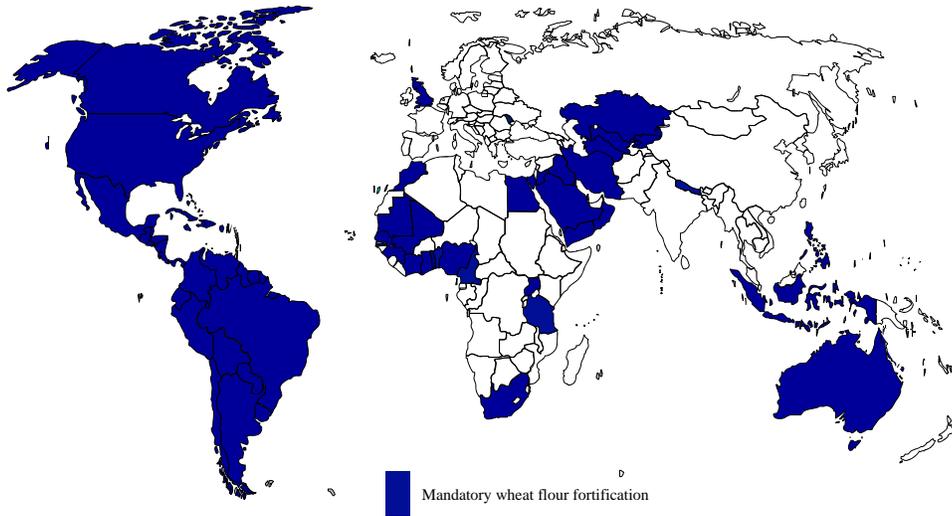
### NTD Prevalence by Fortification Status 25 States, National Birth Defects Prevention Network 1995-2006



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*

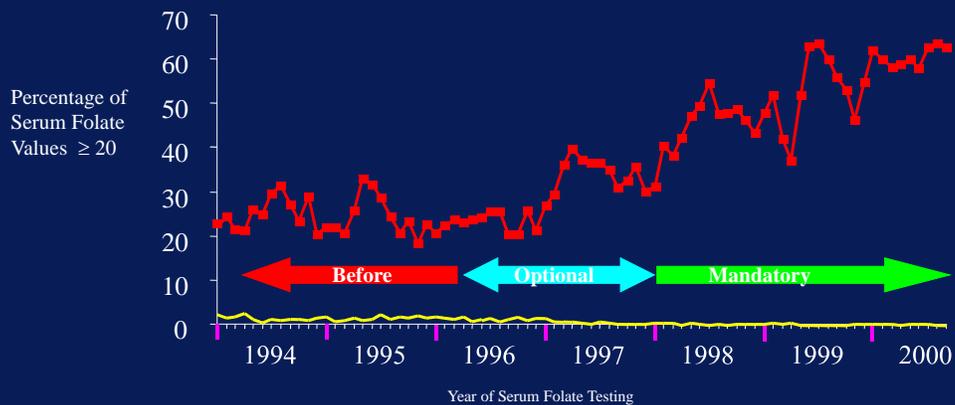
**A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis**

Joel B. Mason,<sup>1,2</sup> Aaron Dickstein,<sup>2</sup> Paul F. Jacques,<sup>1</sup> Paul Haggarty,<sup>3</sup> Jacob Selhub,<sup>1</sup> Gerard Dallal,<sup>1</sup> and Irwin H. Rosenberg<sup>1,2</sup>

<sup>1</sup>Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University; <sup>2</sup>Tufts University School of Medicine, Boston, Massachusetts; and <sup>3</sup>Rowett Research Institute, University of Aberdeen, Aberdeen, United Kingdom

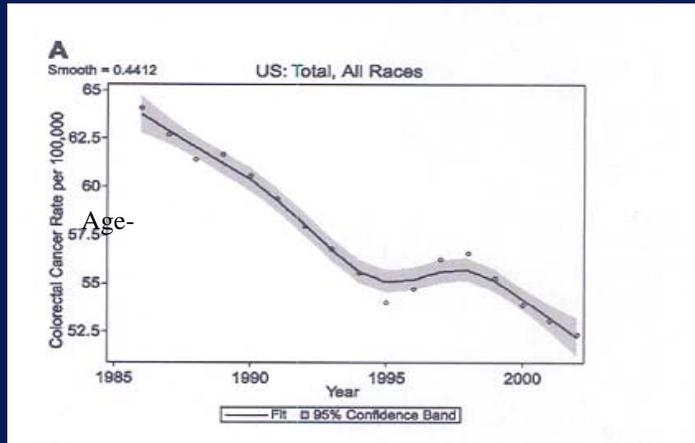
Mason et al. *Cancer Epidemiol. Biomarkers Prev.* 2007;16(7):1325-1329

Percentage of Serum Folate Values  $\geq 20$  ng/mL, by Fortification, and by Year, 1994-2000.  
Kaiser Permanente Southern California Patients



Lawrence JM, Peititi DB, Watkins M, Umekubo MA. Trends in serum folate after food fortification. *Lancet* 1999;354:915-6.  
Lawrence JM, Chiu V, Peititi DB. Fortification of Foods with Folic Acid [Letter]. *NEJM* 2000; 343: 970.  
Data for 2000 added since publication. Data for 2000 is from January through September.

# Age-adjusted Colorectal Cancer, United States 1986-2002



Plot taken from: Mason J et al: Cancer Epidemiol Biom

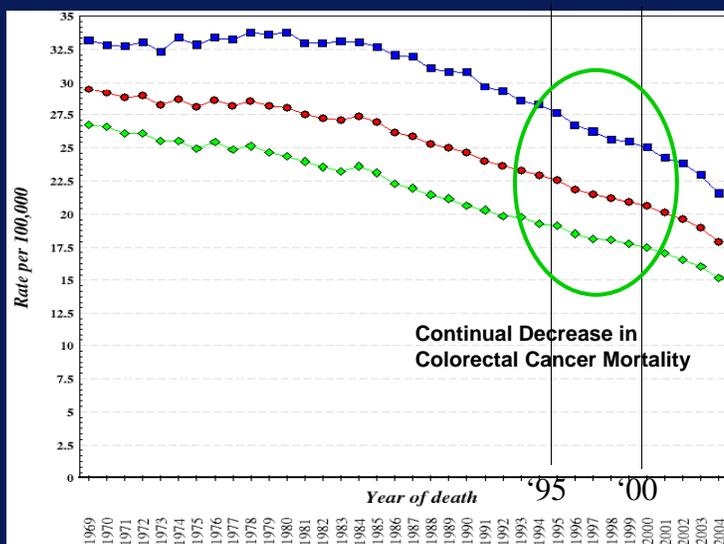
## Kaiser Folate

	Median $\mu\text{g/L}$
1994	12.6
1995	12.7
1996	11.7
1997	14.9
1008	18.7

325-9

## 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/>



- Male
- ◆ Male & Female
- ◆ Female

## 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

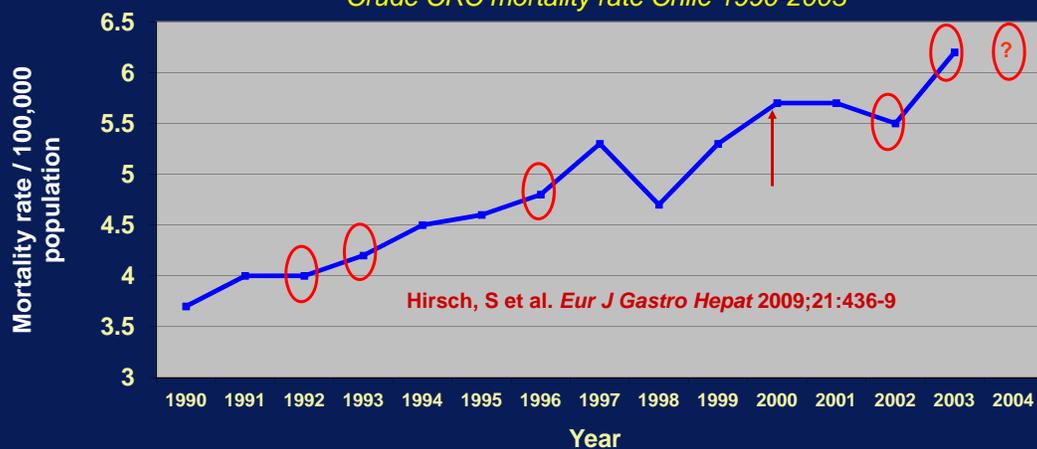
Sandra Hirsch, Hugo Sanchez, Cecilia Albala, María Pía de la Maza, Gladys Barrera, Laura Leiva and Daniel Bunout

Outcome was number of hospital discharge diagnoses

Hirsch, S et al. *Eur J Gastro Hepat* 2009;21:436-9

## Potential Adverse Outcomes: Cancer (cont'd)

Crude CRC mortality rate Chile 1990-2003



Hirsch, S et al. *Eur J Gastro Hepat* 2009;21:436-9

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

## Cognitive Issues

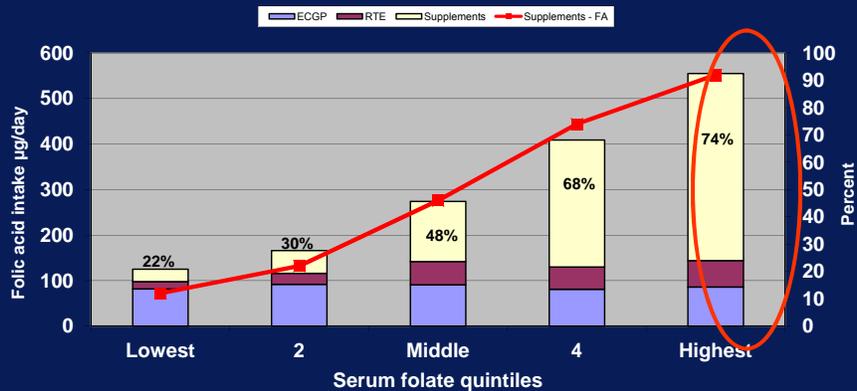
Morris presents data from NHANES showing poorer performance on cognitive tests if one has low serum B12 and high serum folates

Berry shows that the only people with high serum folates are people 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  $\geq 60$  y  
NHANES, 2001–2002



Berry, RJ et al. *AJCN* 2007;85:265-7

## Teratogen Update: Iodine Deficiency

JOSEF WARKANY  
*Children's Hospital Research Foundation, Cincinnati, Ohio 45229*

This deficiency was once one of the most important and widespread teratogens that caused a disease picture of dwarfism, neuromuscular disturbances, deafness, and mental retardation. It occurred, and still occurs, in endemic form; it is called "endemic cretinism" and is associated with endemic goiter. The disorder prevailed in many regions of the world where the soil and water were poor in iodine and isolation prevented importation of foodstuffs from the outside. Owing to isolation of affected populations, valid prevalence figures could not be obtained worldwide, but it was estimated that about 25 years ago there were still 200 million people affected by endemic goiter and there existed hundred thousands of cretins (Kelly and Snedden, '60). There has been a continuous decrease of this condition as iodine in one form or another reached the deficient areas, but it still exists in some parts of the world (Warkany, '71).

were sufficiently refined to achieve credibility.

Much of the work and research was done in Switzerland, where the present concept of the origin, prevention, and treatment was conceived by a number of physicians who helped to eradicate endemic goiter and cretinism in their homeland. Based on the knowledge that the thyroid gland contained much iodine and that iodine is excreted and lost daily in small amounts, it was concluded that the human body needs replenishment from the outside to keep its thyroid gland supplied for formation of its hormones (Hunziker, '24). A similar theory was developed by Marine and Kimball ('17) in the United States; like their Swiss colleagues, they recommended goiter prophylaxis by "minimal doses" of iodine, since in the absence of iodine supplementation, the thyroid gland responds by enlargement and goiter formation.

A regional association of goiter and cretin-

“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!)

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## 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!**

# National food-fortification program with folic acid in Chile

Eva Hertrampf and Fanny Cortes

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.

*Food and Nutrition Bulletin, vol. 29, no. 2  
(supplement) © 2008, The United Nations University.*

## Fortification of wheat flour in Chile

	(mg/kg)
<b>Since 1955</b>	
Iron (ferrous sulfate)	30.0
Thiamine	6.3
Riboflavine	1.3
Niacine	13.0
<b>Since Jan. 2000</b>	
FOLIC ACID	2.2 (220ug/100g)

= consumption of  $\approx 400 \mu\text{g/day}$

## Folic Acid consumption.

98% of women consume bread on daily basis

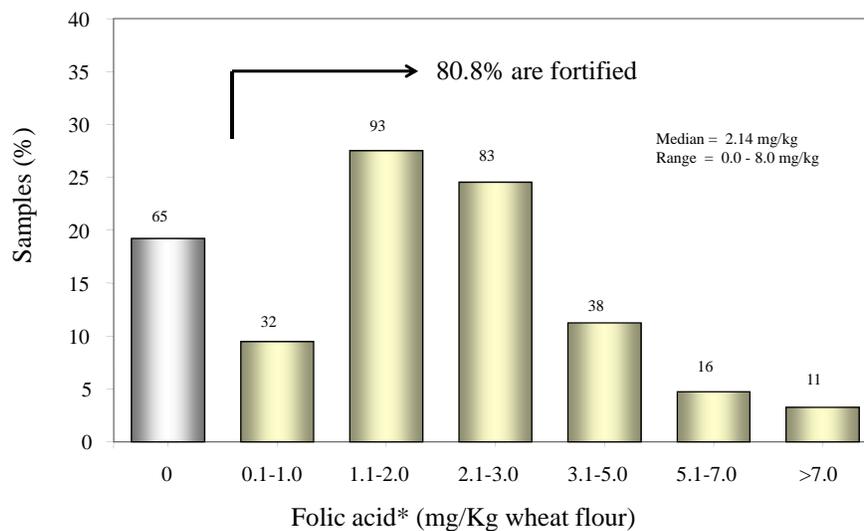
89% consume more than 180 g of bread/daily  
(2 units, ~370 ug of FA)

No consumption of other folic acid fortified foods

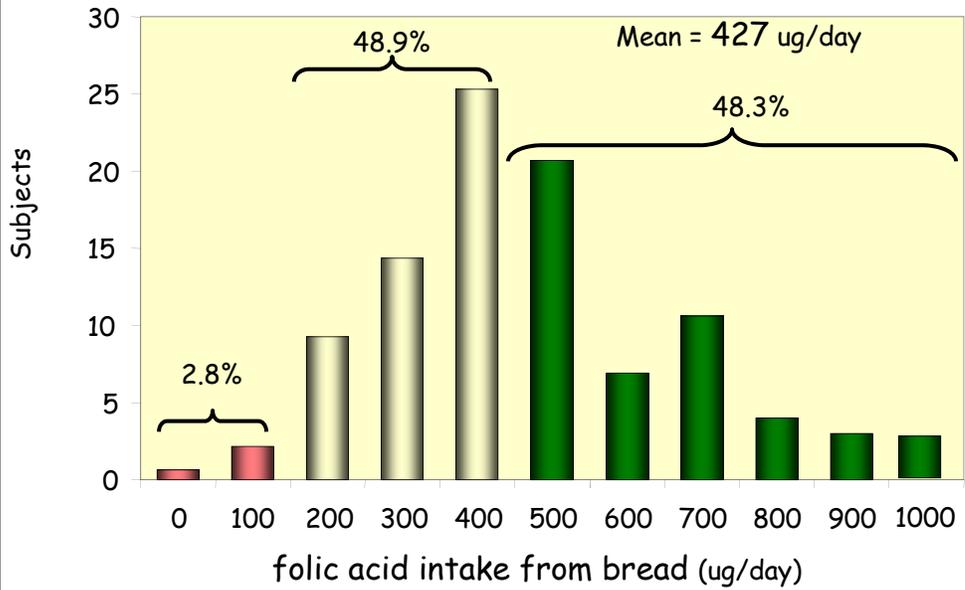
No consumption of folic acid supplements

## Folic acid contents of wheat flour in Chile-2005

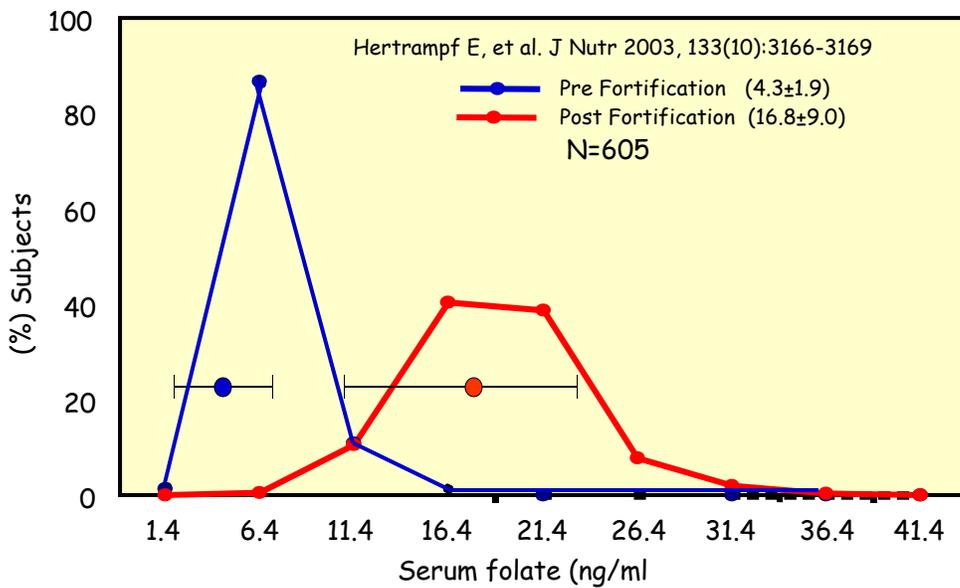
n samples=338

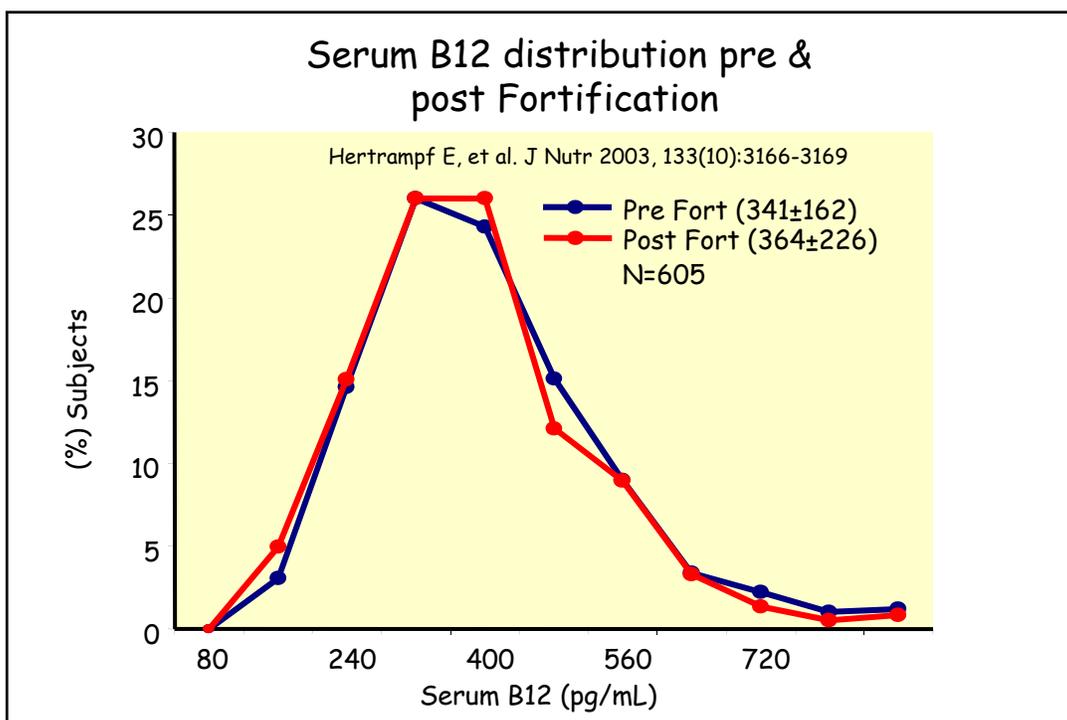
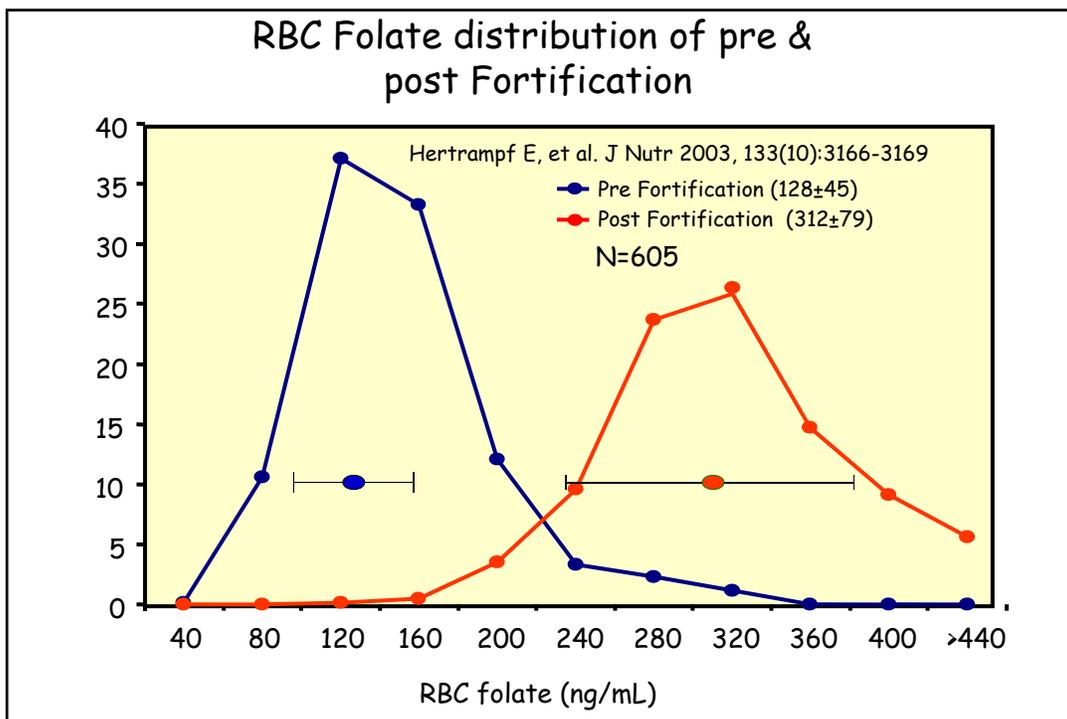


### Estimated folic acid intake from bread

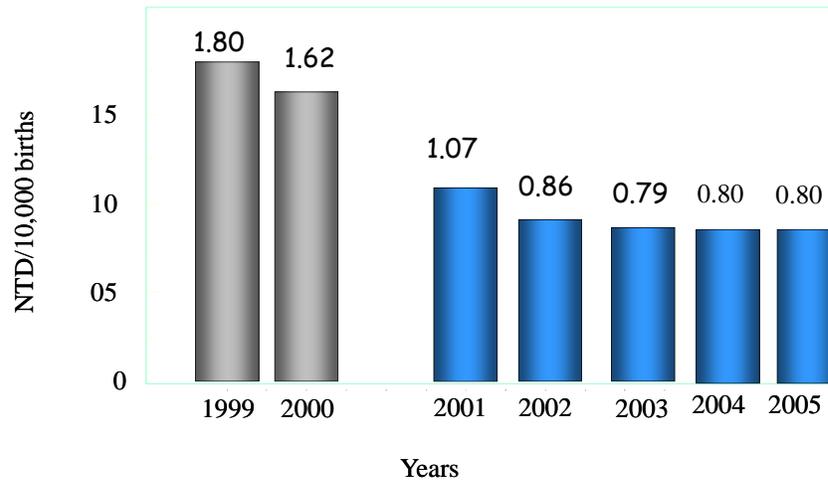


### Serum Folate pre & post Fortification





## 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.

## Changes in stillbirth and multiple births prevalence\*

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

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

	Before Fort*	After Fort*	RR (95% IC)	% reduction
Stillbirth	76.4	61.8	0.81 (0.73-0.89)	19.6
Multiple births	83.6	88.2	1.06 (0.96-1.15)	-5.5

\* Prevalence per 10,000 total births

## Folic Acid and NTD, ECLAMC Data Chile, Argentina & Brazil, thru 2007\*

	Chile	Argentina	Brazil
Year 1st Fortified Births	2001	2005	2005
Monitored Births (After FA)	243624	147853	92843
FA In Flour, mg/kg	2.2	2.2	1.5
Est. Daily FA intake, µg	499	486	264

\* Lopez-Camelo et al. Am J Med Gen 2010

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

	Chile	Argentina	Brazil
Anencephaly	0.54	0.59	0.57
Spina Bifida - Total	0.43	0.59	0.99
Spina Bifida - Cephalic	0.17	0.27	0.49
Spina Bifida - Caudal	0.55	0.75	1.12

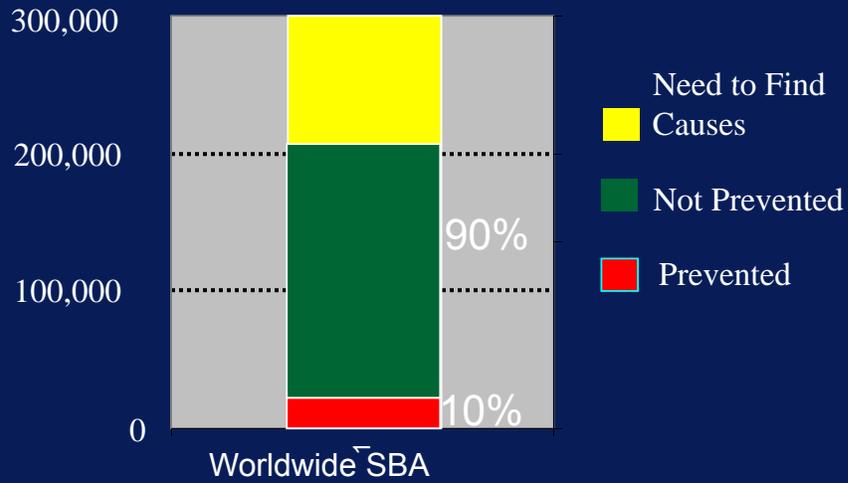
\* Lopez-Camelo et al. Am J Med Genet 2010

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

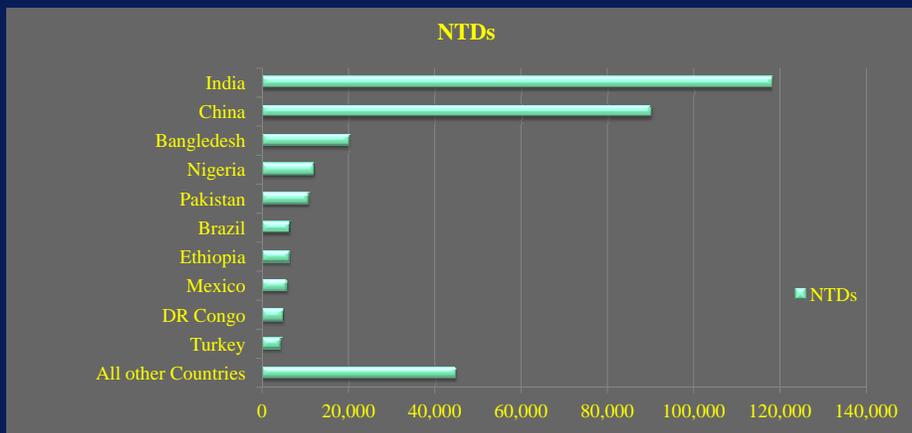
	Chile	Argentina	Brazil
Anencephaly	0.63, 0.37	0.86, 0.37	1.12, 0.69
Spina Bifida - Total	1.02, 0.46	1.27, 0.66	1.45, 1.42
Spina Bifida - Cephalic	0.26, 0.05	0.37, 0.05	0.33, 0.14
Spina Bifida - Caudal	0.72, 0.38	0.88, 0.60	1.04, 1.23

\* Lopez-Camelo et al. Am J Med Genet 2010

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

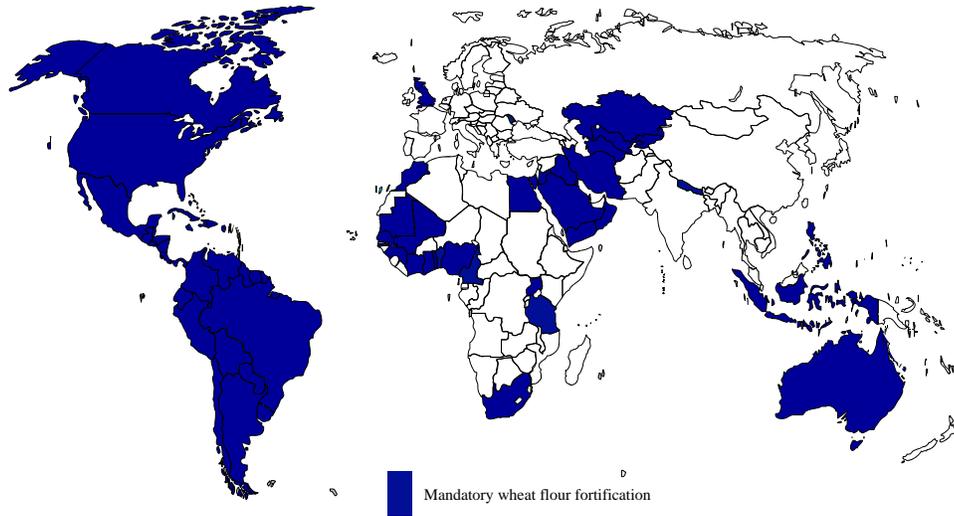


## Neural Tube Defect Surveillance Worldwide 2006



## 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

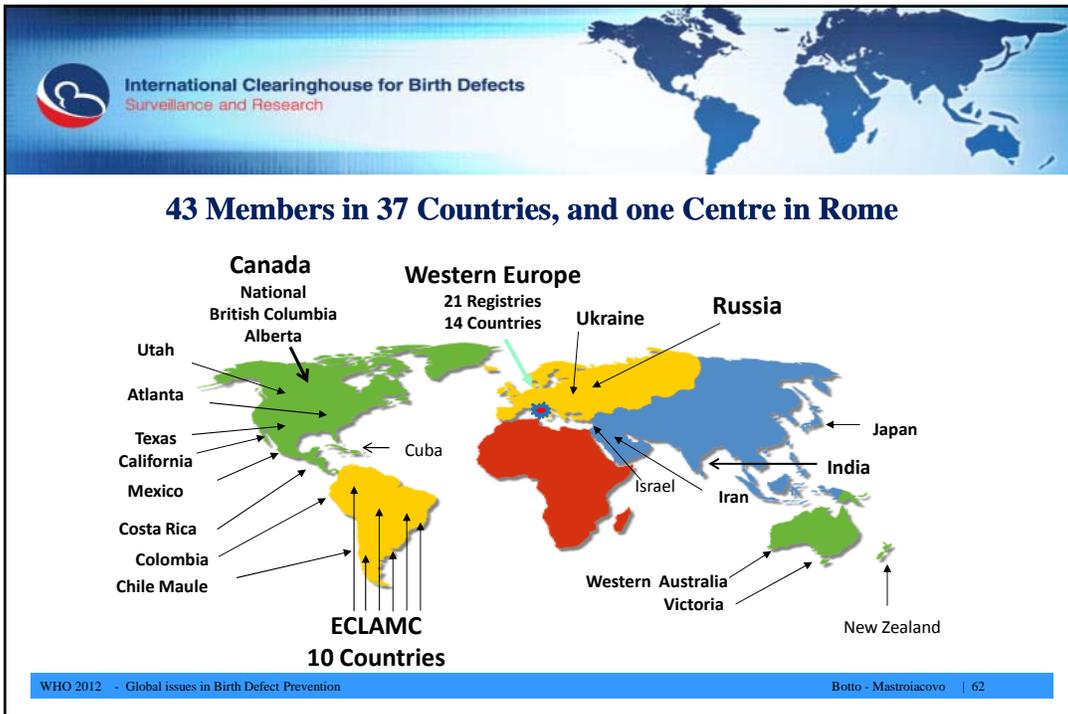
### People who have helped me with this presentation

RJ Berry, CDC Atlanta  
Joe Mulinare, CDC Atlanta  
Godfrey Oakley, Emory Atlanta  
Pierpaolo Mastroiacovo, ICBDR Rome  
Sonja Rasmussen, CDC Atlanta

PRESIDENTIAL ADDRESS  
 First Annual Meeting, the Teratology Society  
 MAY 26, 1961  
 JOSEF WARKANY  
 Children's Hospital Research Foundation  
 Cincinnati, Ohio

*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.*

Warkany J, *Teratology* 9:1-4, 1974



## 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)

