International Studies of Birth Defects

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Birth Defects in History

- Records of birth defects in Babylonia
- Ancient Greeks: mothers to be were encouraged to gaze upon statues with ideal human form to avoid birth defects
- Piny said that maternal and paternal thoughts at conception can shape a child
- Norwegian mothers were warned to not look upon rabbits so that their babies would not be born with “harelips”

The proncephalic mummy from Hermopolis. (Drawing by Powers 1978 after Saint-Hilaire 1826.)

Birth Defects in History

- Some European cultures believed that the mother of a child with a birth defect had had intercourse with the devil

- The ‘Theory of Divine retribution’ viewed a birth defect as God’s punishment for the parents past sins

- Later, birth defects were attributed to a narrow cervix, poor posture, or a fall/blow during pregnancy.

Fetal Deaths in New Zealand

	2002		2003	
	#	%	#	%
Total	390		393	
Birth Defects	88	23	103	26
Neural tube defects	24	6	28	7
Heart defects	8	2	23	6
Musculoskeletal	13	3	12	3
Chromosomal anomalies	32	8	26	7

Infant Mortality in New Zealand 2003

	<7 days	7-28 days	28+ days	Total
Total	185	36	116	337
Birth Defects	47	9	26	82
	25%	25%	22%	24%

Mortality in New Zealand 2005

Age (years)	Birth Defects (%)
0	21
1	24
2	18
3	13
4	36
5-9	3
10-14	11

Hospitalisations in New Zealand 2006

	Age group (years)		
	0-4	5-9	10-14
Birth defects	4%	3%	2%
Injury & poisoning	4	19	25
Infectious and parasitic disease	6	5	3
Respiratory	14	14	10

NZ Burden of Disease
Birth Defects, 0-14 years, 1996

Birth Defect	% of total burden from birth defects
Nonchromosomal defects	41.0
Congenital heart defects	20.5
Spina bifida	15.0
Down syndrome	10.2
Urogenital defects	3.0
Defects of the digestive system	1.8
Facial clefts	0.4
Defects of the abdominal wall	0.7
Other defects	7.4
Total	100.0

NZD equivalents* of lifetime cost of selected birth defects, NZD1,000s

New Zealand equivalent (1NZD=0.52USD)

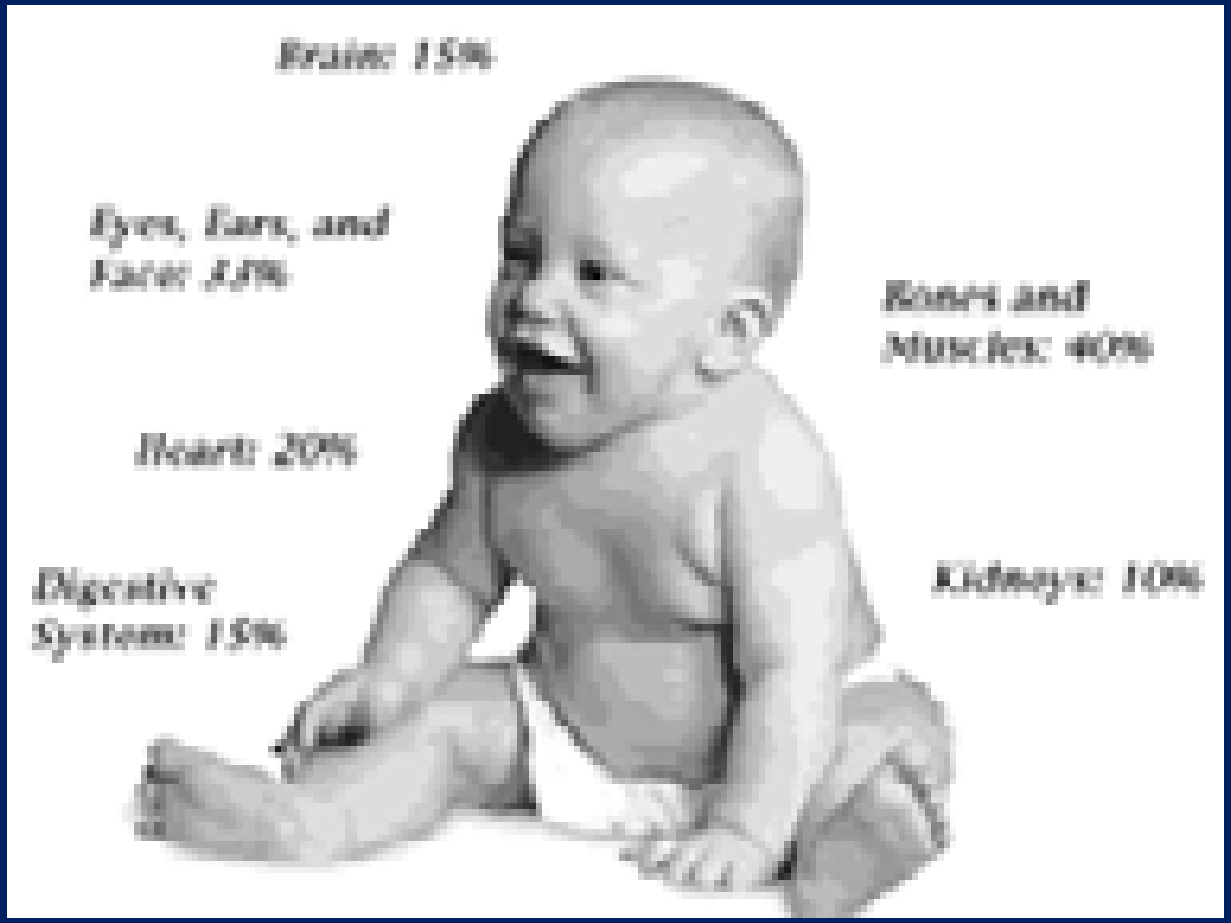
Birth defect	Medical	Direct Costs Special education	Development services	Indirect costs	Total costs
Spina bifida	393,292	80,138	3,425	464,085	940,940
Transposition/DORV	319,873	8,465	-	661,142	989,481
Tetralogy of fallot	356,004	7,642	-	329,596	693,242
Cleft lip or palate	186,781	33,752	5,648	1,113,246	1,339,427
Colorectal atresia	110,025	-	-	311,633	421,658
Renal agenesis	47,525	-	-	768,204	815,729
Lower limb reduction	31,846	22,790	-	266,646	321,283
Diagraphmatic hernia	120,715	-	-	579,954	700,669
Down syndrome	535,954	565,308	182,748	2,269,362	3,553,371
Cerebral palsy	1,638,094	435,996	419,037	2,171,837	4,664,963

Cost of NTDs

- **Singh and Elliot (1996)**
  - NZD355,060 = 20yr cost of treating, managing, caring for one spina bifida
  - excludes: loss of parental income, special schooling needs, family stress, wheelchair, crutches, occupational therapy, GP visits

- **Waitzman et al (1994)**
  - NZD565,000 = lifetime cost of each spina bifida case
  - greater than for:
    - teratology of fallot
    - transposition of the great vessels
    - abdominal wall defects
    - cleft lip and palate

Sites of Birth Defects



Causes of Birth Defects

Incidence

- Incidence – new cases – the preferred measure in aetiological research
- No accurate way of determining numerator or denominator for a rate
- Need to know the number of conceptuses at risk of developing a defect and the fate of these pregnancies

Incidence

- Unlikely any system be available to examine all conceptuses, including the products of abortion and stillbirths
- Fetuses may be so macerated that autopsies may not reveal the true extent of any defects present
- Often reported as ‘birth defects’ rather than the specific defect(s)

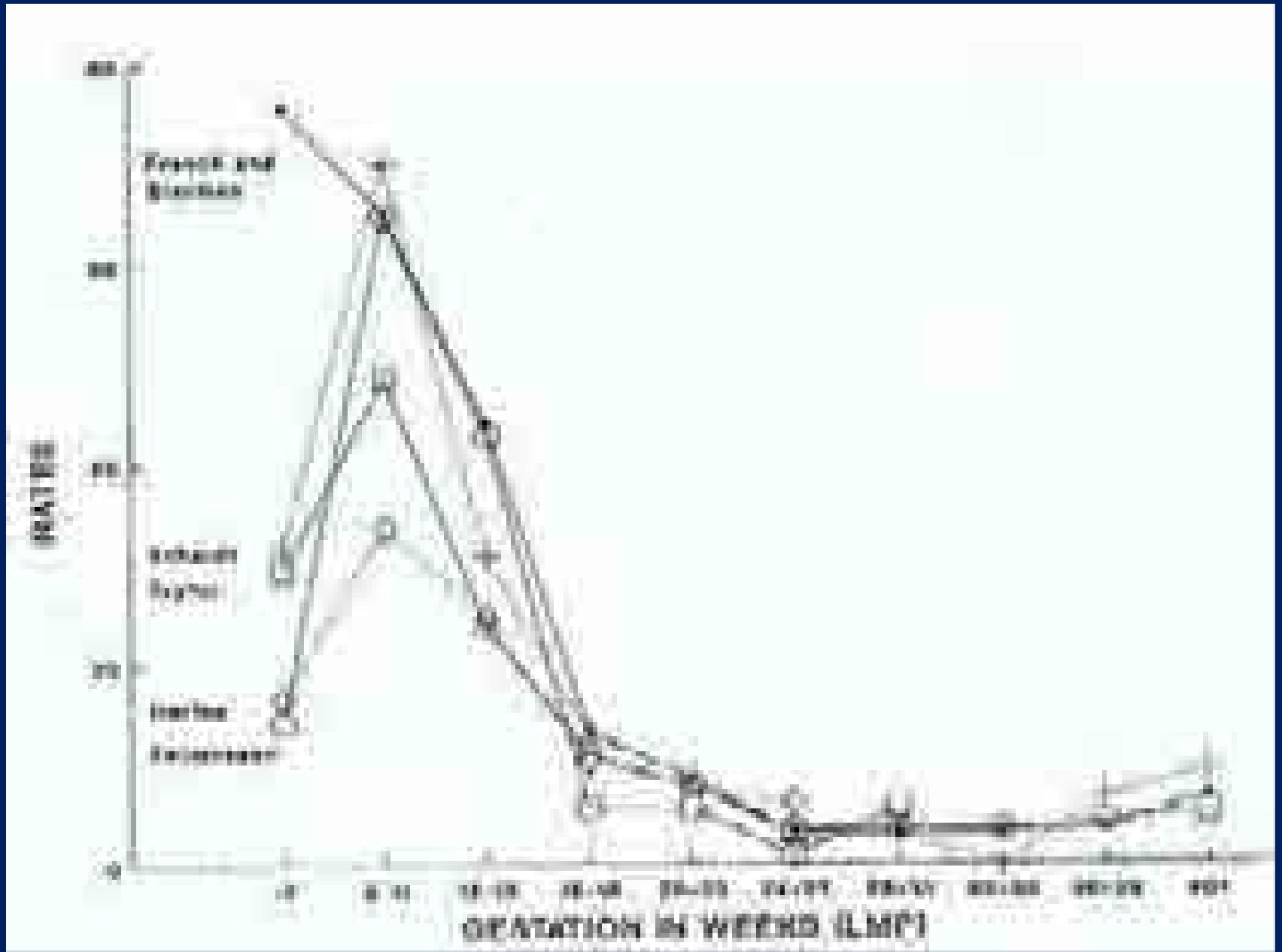
Prevalence at Birth

- Existing cases – those that survived to birth (live or still)
- The result of the incidence rate and the rate of spontaneous or induced abortion among the affected pregnancies
- How close does the prevalence rate reflect the incidence rate?

Prevalence at birth

- A high prevalence rate may reflect either:
  - A high incidence or
  - A uterine environment that is favourable for survival through to birth of a high proportion of fetuses with defects
- Sex ratio at birth?

Pregnancy Loss



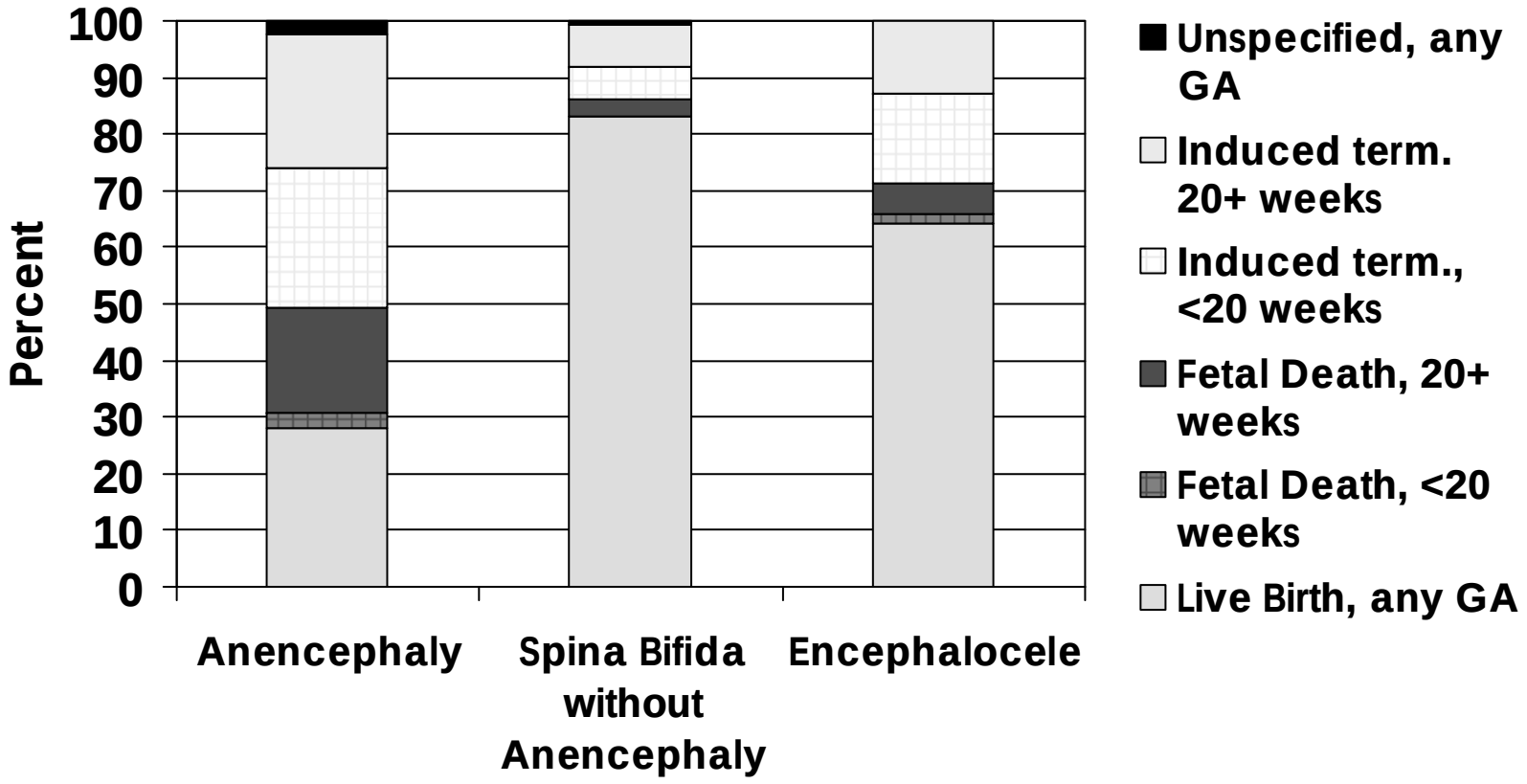
Birth Defects

Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks

Birth status	Defect rate (%)	% of all defects
Livebirths	2.4	73.6
Stillbirths	7.2	2.5
Therapeutic abortions	8.7	16.5
Spontaneous abortions	12.2	7.4

Bieber et al 1988,

Pregnancy Outcomes for Selected Neural Tube Defects Texas, 1999-2000



Stillbirths

Italy	180 days (25 wks + 5 days)
England & Wales	24 wks
Hungary	24 wks or 500 gms
Spain	24 wks or 500gms
Sweden	22 wks
Japan	22 wks
France	22 wks
Canada	20 wks or 500gms
New Zealand	20 wks or 400gms
Australia	20 wks or 400gms
USA	20 wks
Norway	16 wks
South America	500gms
Germany	>/= 500 gms

Terminology

A variety of terms used:

- Birth defects, congenital defects, congential disorders, congenital faults, congenital malformations, congenital anomalies, congenital deformities, birth abnormalities, congenital abnormalities
- Not always include the same defects
- Birth defects preferred term, but synonymous with congenital malformations

One or Many

- Many infants are born with more than one defect
  - Eg, in Texas 58%
- Focus on individual birth defects or individuals with birth defects
- Anencephaly and spina bifida = anencephalus
- Spina bifida + hydrocephalus = spina bifida

Single or Multiple

- An infant or fetus can have single or multiple malformations sometimes form a sequence, an association, or a syndrome, but often multiple malformations are not associated with each other in any way.

Heterogeneity of Birth Defects

- Anencephaly, spina bifida are often referred to as neural tube defects and considered as a group (NTD).
  - There is evidence to show that the epidemiological patterns for one are not the same as for the other – aetiological heterogeneity
- Heart defects encompass a wide range of defects
- Cleft lip can appear with/without cleft palate

Classification of Birth Defects

- Anencephaly and spina bifida =
  - Central nervous system malformations
  - Neural tube defects

- The group may/not include other defects, eg, hydrocephalus, exencephaly, iniencephaly

Major and Minor Defects

- Major defects: incompatible with survival, is life-threatening, or seriously compromises an individual´s capacity to function normally in society
  - about 2-3% newborns have single major defects

- Minor defects: 14% newborns single minor defects
  - Single umblicial artery, colobama, ear tag. Haemangiona, minor hypospadias
- Can suggest the presence of known aetiology
- The greater the number of minor defects, the greater the likelihood of a major defects

Ascertainment

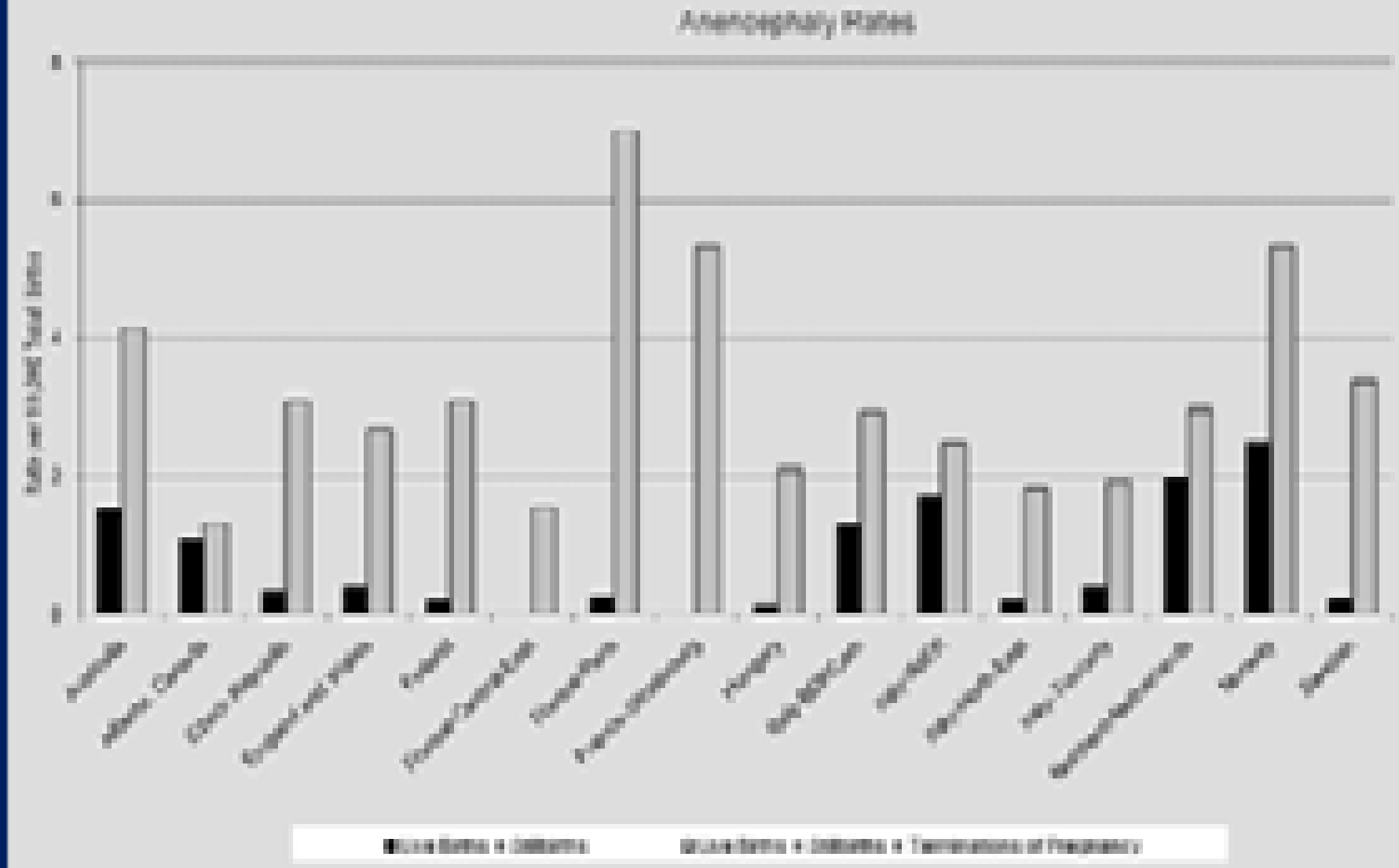
- Hospital studies
  - May not be representative of all births
- Birth certificates
- Mortality
  - Livebirths, stillbirths, general ‘birth defect’ category
- Postmortem
  - Not always evident – macerated fetus
- Multiple sources

- Followup period
  - Additional anomalies are detected during postnatal live – about 6% at 2 year-olds, 8% in 5year-olds, other 2% later

Rates of Major Birth Defects Determined by Various Data Sources

Method and Source	Rate
Birth Certificates*	1.5%
Newborn hospital discharge§	4.3 - 7.1%
Mandatory hospital reporting¶	3.4%
Linked data sources * *	4.7%
Active hospital surveillance § §	3.2%
Physical exam of infants ¶ ¶	8.3%

* Birth Certificates - 1996
§ Florida 1996
¶ New York - 1994-96
* * North Carolina - 1995-96
§ § MACDP 1995-99
¶ ¶ Collaborative Perinatal Project - 1959


Anencephaly Rates

Rates of Neural Tube Defects in NZ

	Anencephaly	Spina Bifida
Hospital Studies		
Auckland	2.7	2.06
Auckland	2.48	1.12
Dunedin	1.49	1.69
Christchurch	1.16	3.25
Regional (hospital)		
Northland	1.04	1.46
National		
Multiple sources	0.78	0.94

Types of Birth Defects

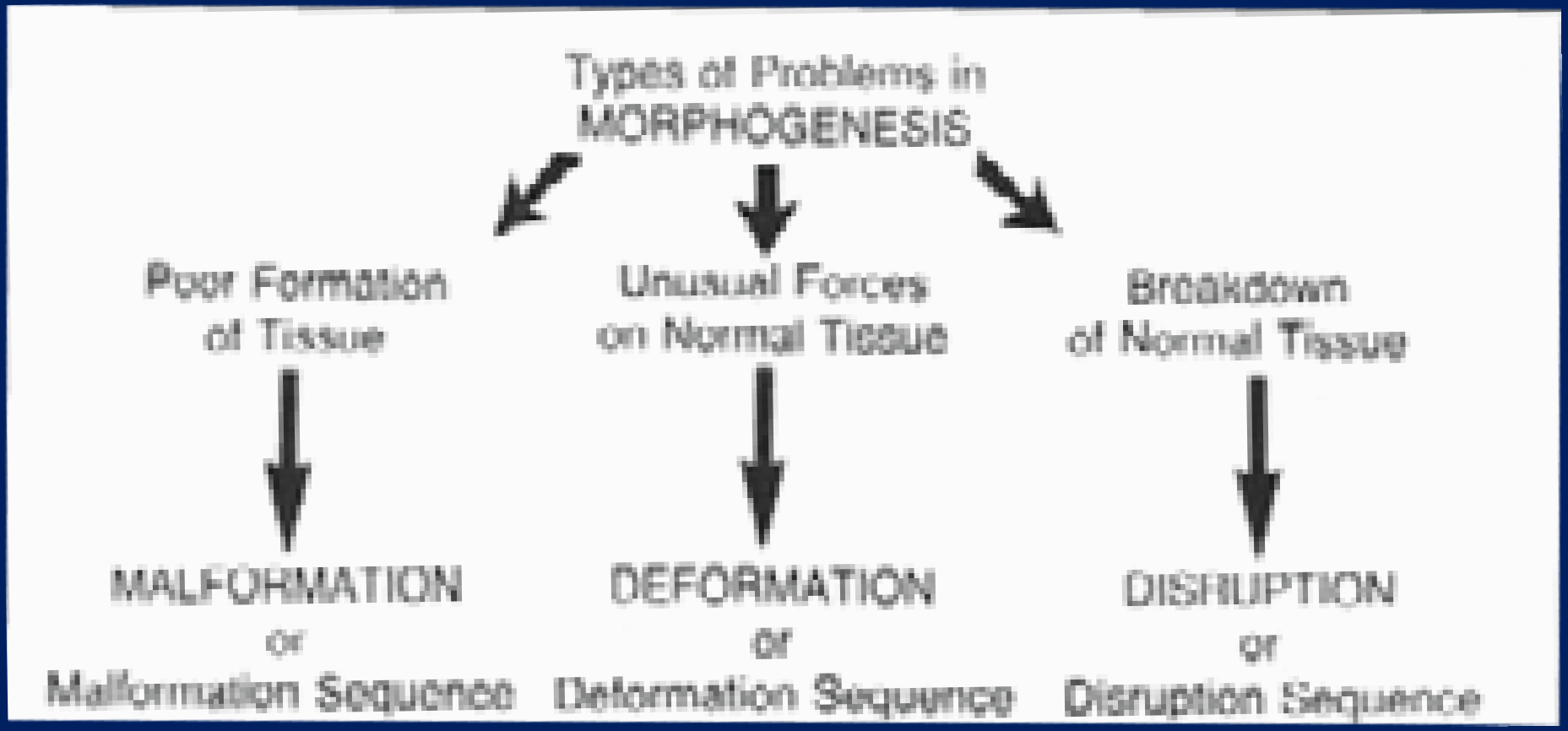
- **Malformation** is a primary structural defect resulting from a localized error of morphogenesis

- **Disruption**- results from disruption of normal developmental processes by either extrinsic or intrinsic factors-amniotic bands, vascular insult, drugs - depends on time not on agent

- **Deformation**- an alteration in shape / structure of previously normally formed part by mechanical forces-uterine constraint – eg talipes (clubfoot)

- **Syndrome** is a recognized pattern of malformations with a given etiology.

Types of Birth defects



Malformation Syndromes

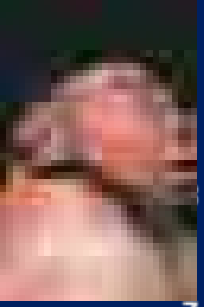
- A group of congenital malformations that is recognizable as a specific genetic condition
- Consist of two or more developmental field defects
- May be chromosomal or nonchromosomal

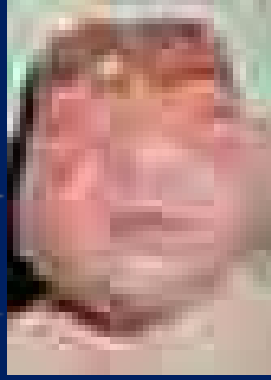
New Zealand 2006

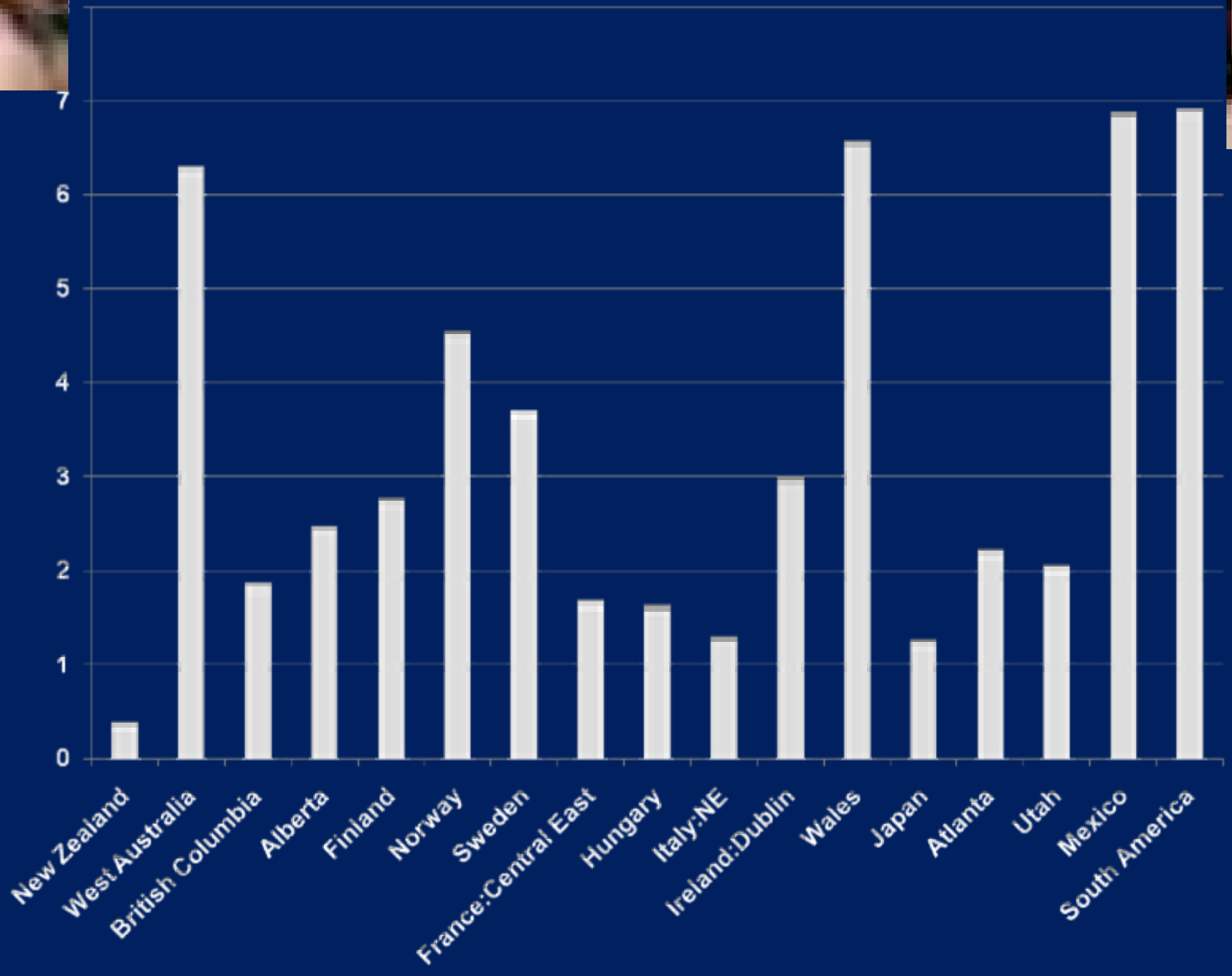
	#	Rate/1000LB
Anencephaly	6	0.10
Spina bifida	13	0.22
Microcephaly	18	0.30
Hydrocephaly	19	0.32
Anophthalmos / Microphthalmos	3	0.05
Transposition of great vessels	27	0.46
Tetralogy of Fallot	26	0.44
Hypoplastic left heart syndrome	6	0.10
Coarctation of aorta	15	0.25
Cleft palate without cleft lip	63	1.06
Cleft lip with or without cleft palate	37	0.63
Oesophageal atresia / stenosis	12	0.20
Small intestine atresia / stenosis	13	0.22
Anorectal atresia / stenosis	15	0.25
Hypospadias + epispadias	186	3.14
Renal agenesis	17	0.29
Cystic kidney	20	0.34
Polydactyly, preaxial	73	1.23
Limb reduction defects	12	0.20
Abdominal wall defects	27	0.46
Trisomy 13	7	0.12
Trisomy 18	11	0.19
Down syndrome	63	1.06

Rates in New Zealand

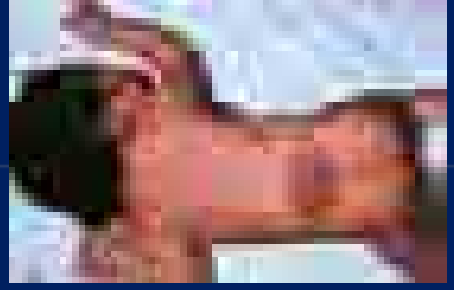
Anencephaly

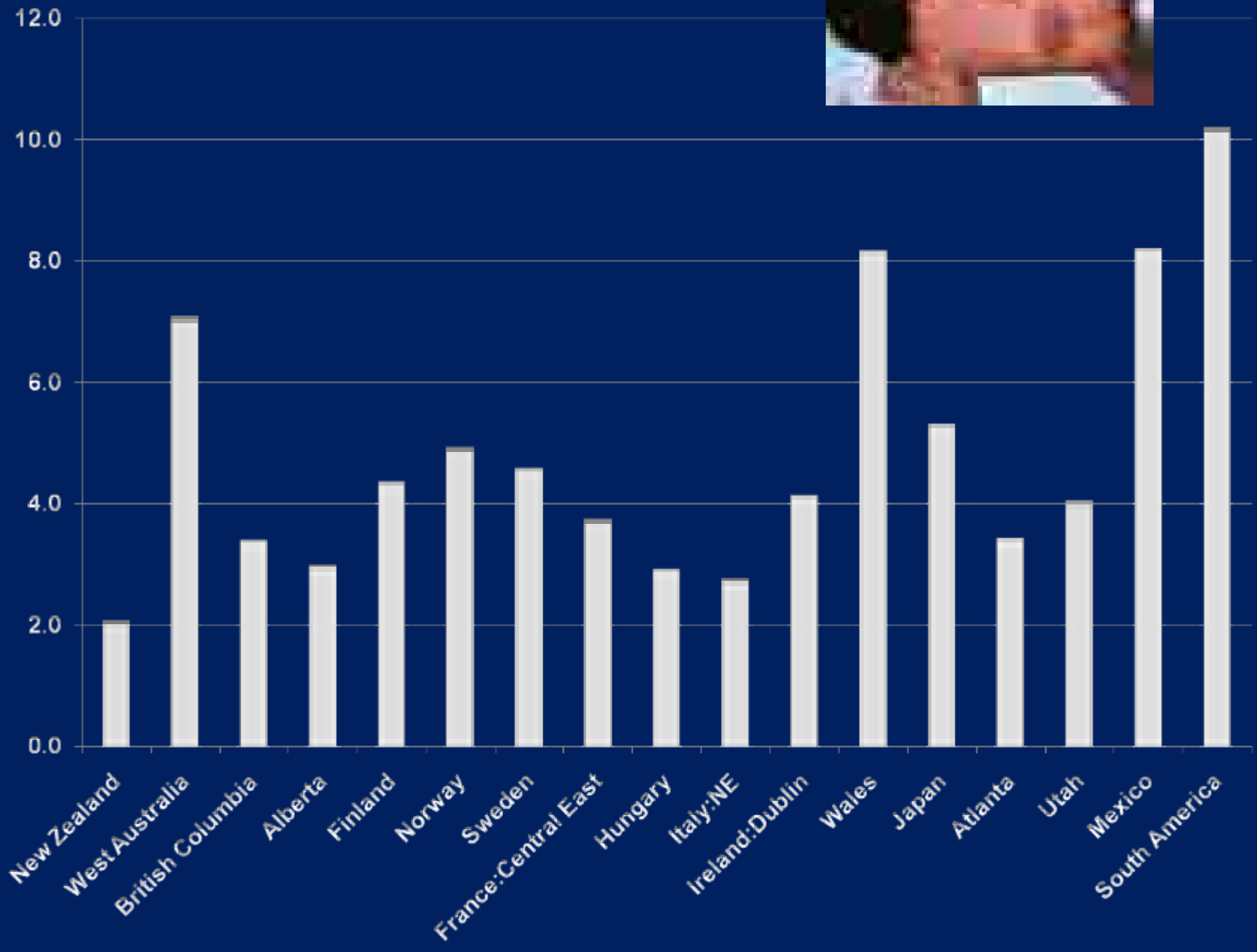




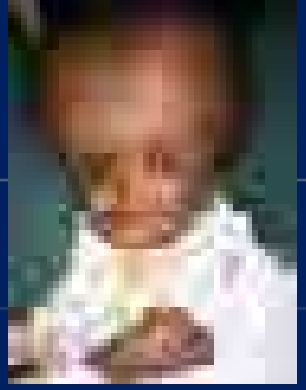


Spina Bifida

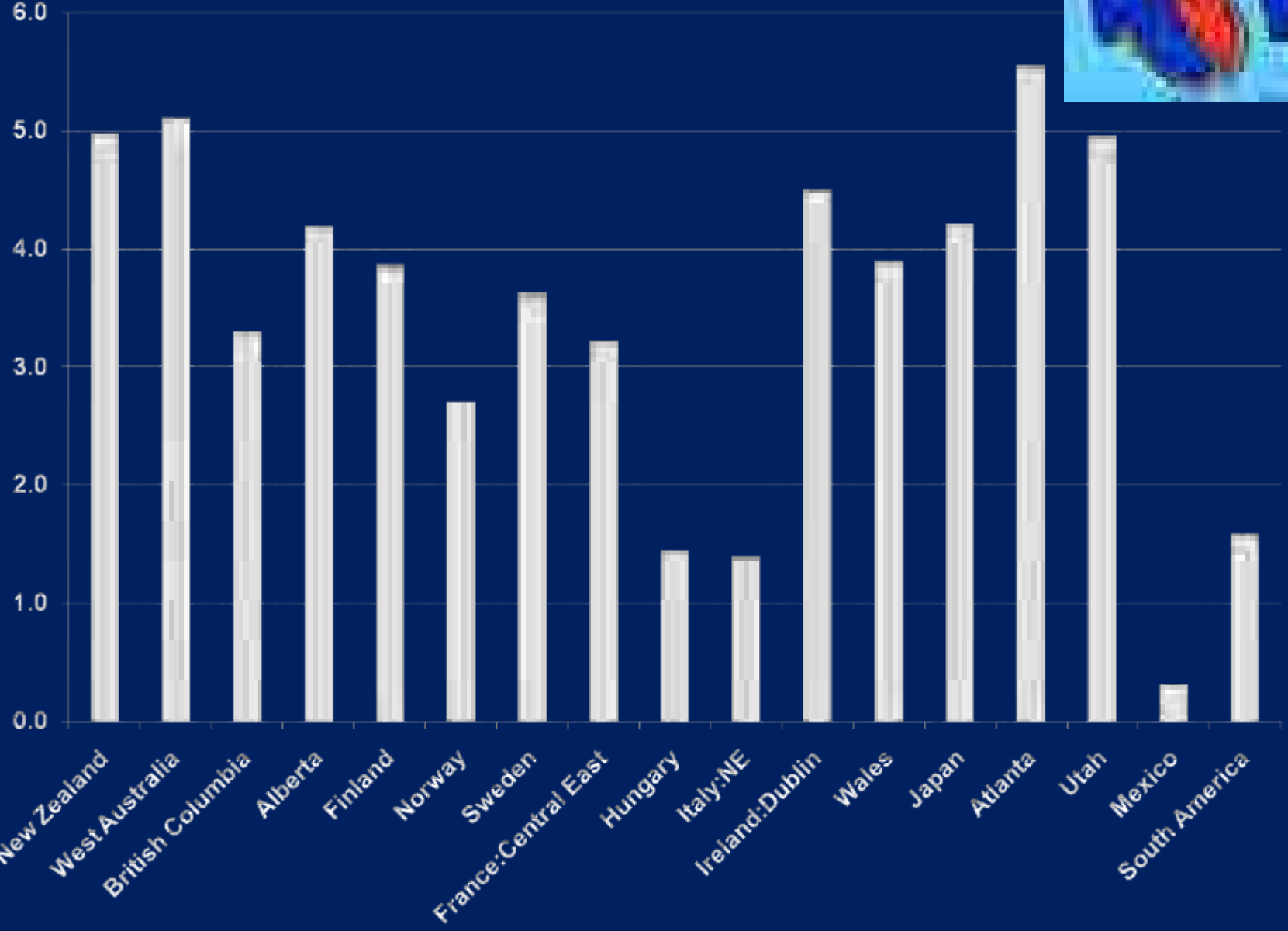




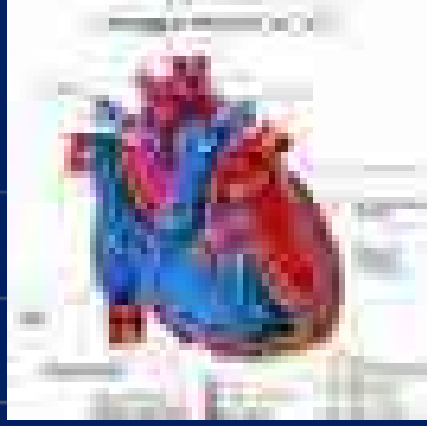
Hydrocephaly

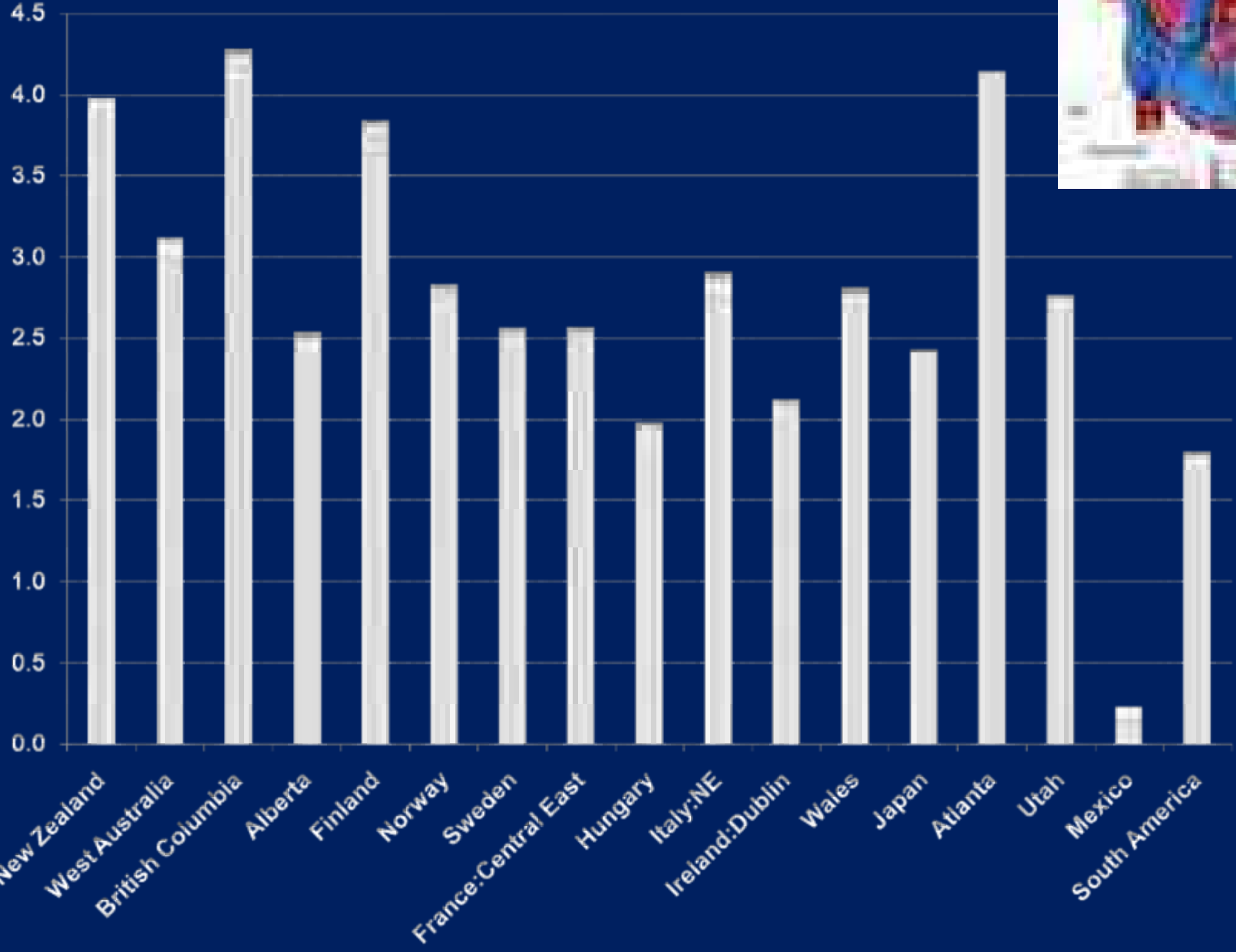


Transposition of Great Vessels



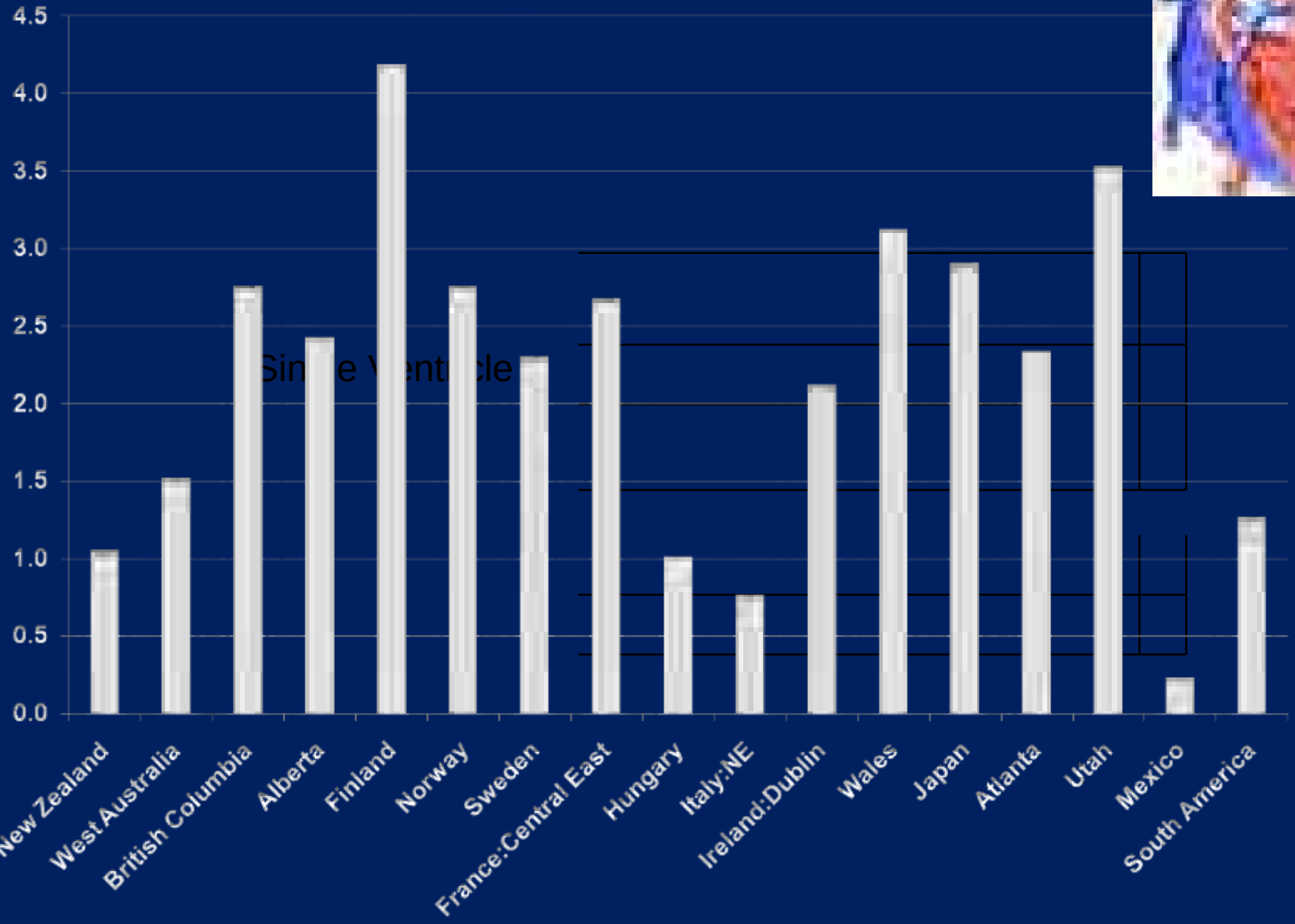
Tetralogy of Fallot



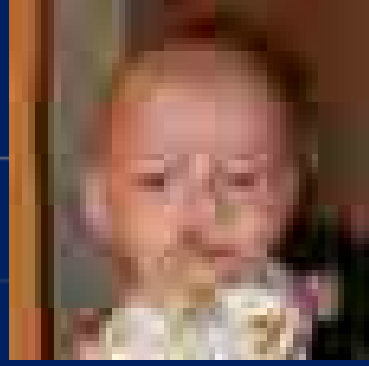


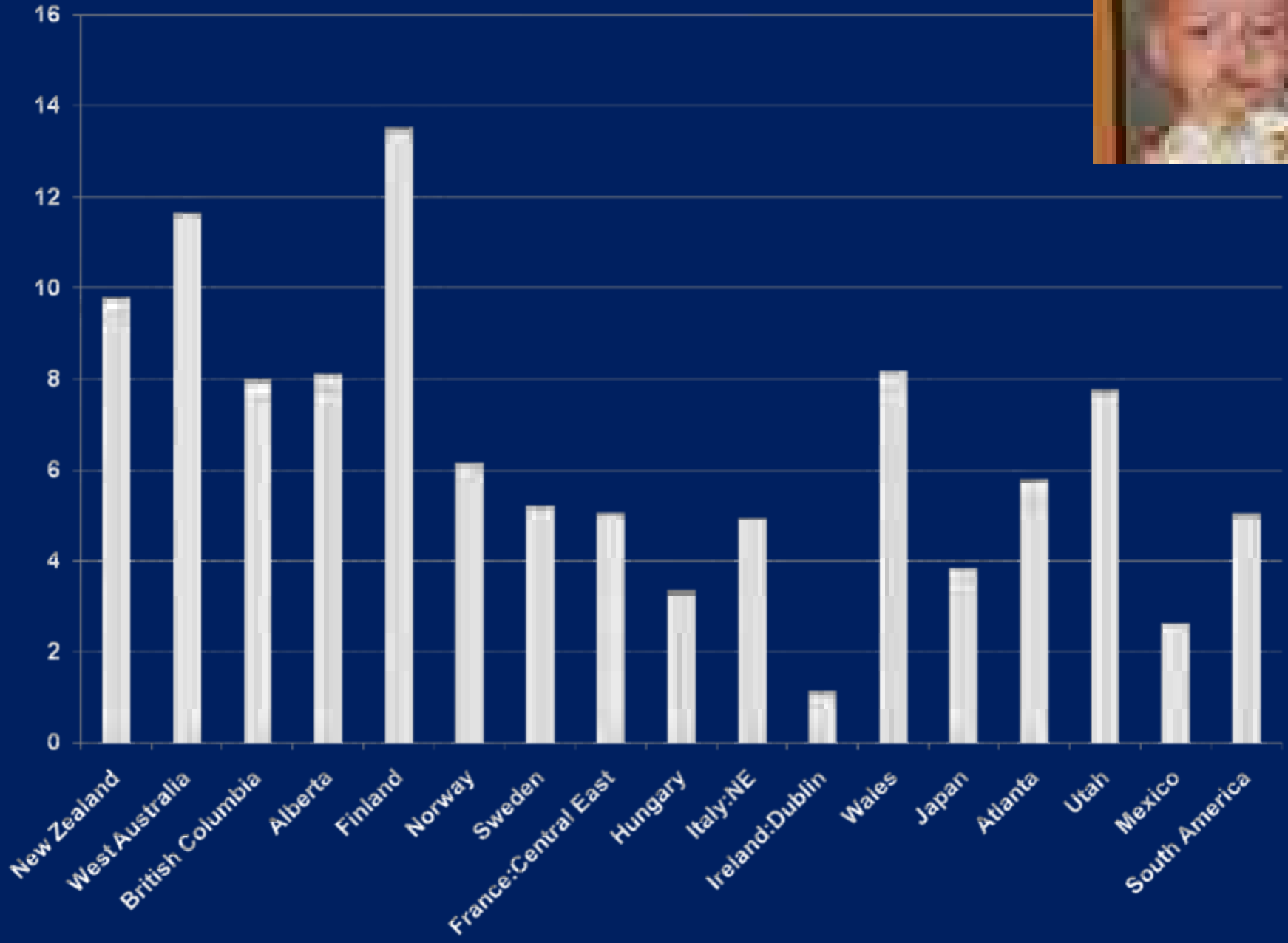
Coarctation of Aorta

Hypoplastic Left Heart Syndrome

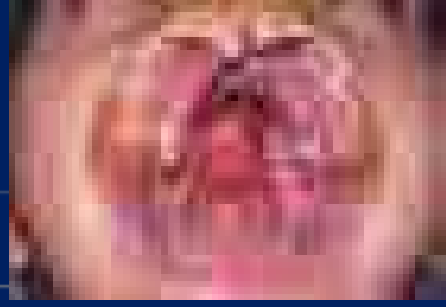


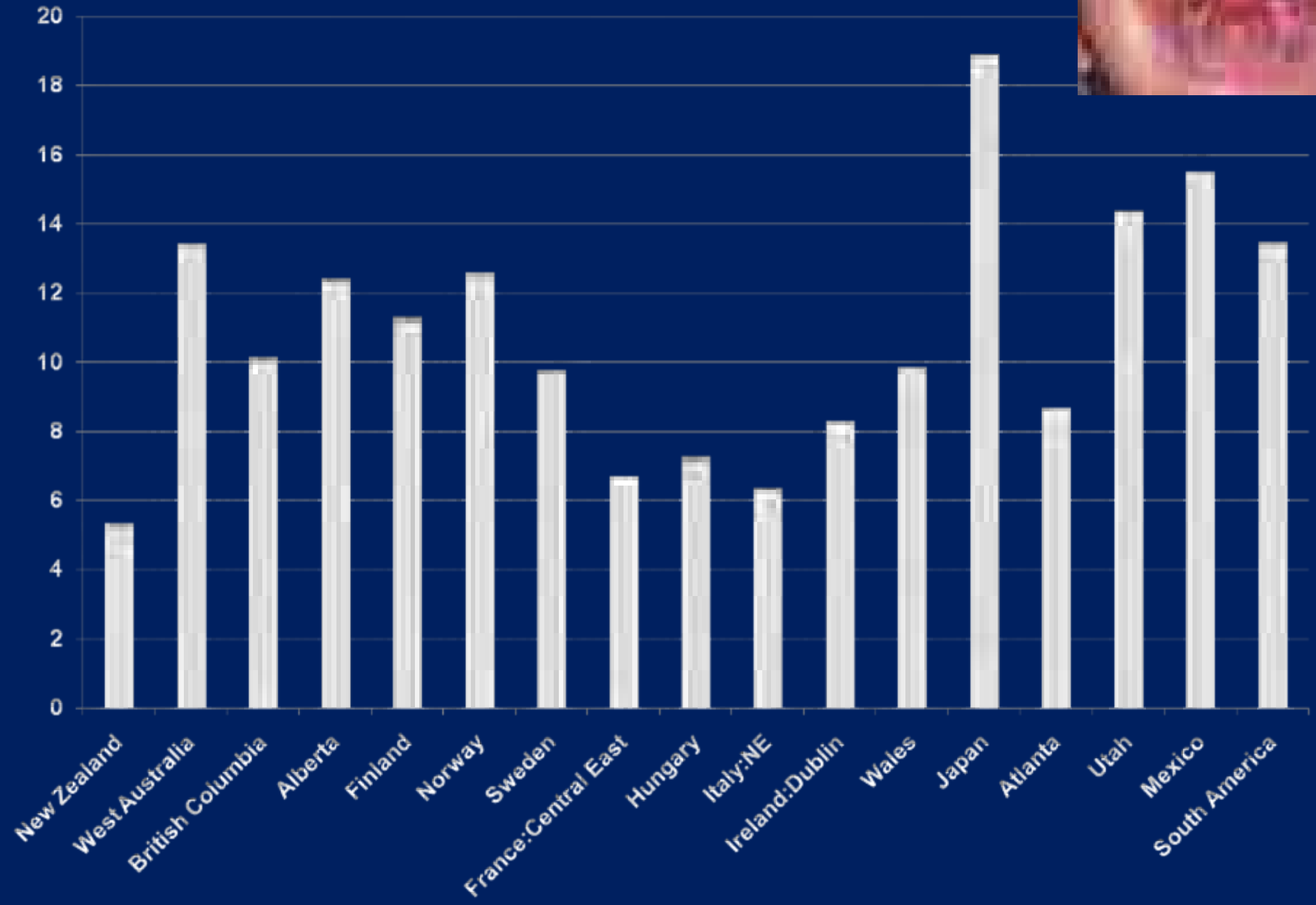
Cleft lip without Cleft Palate



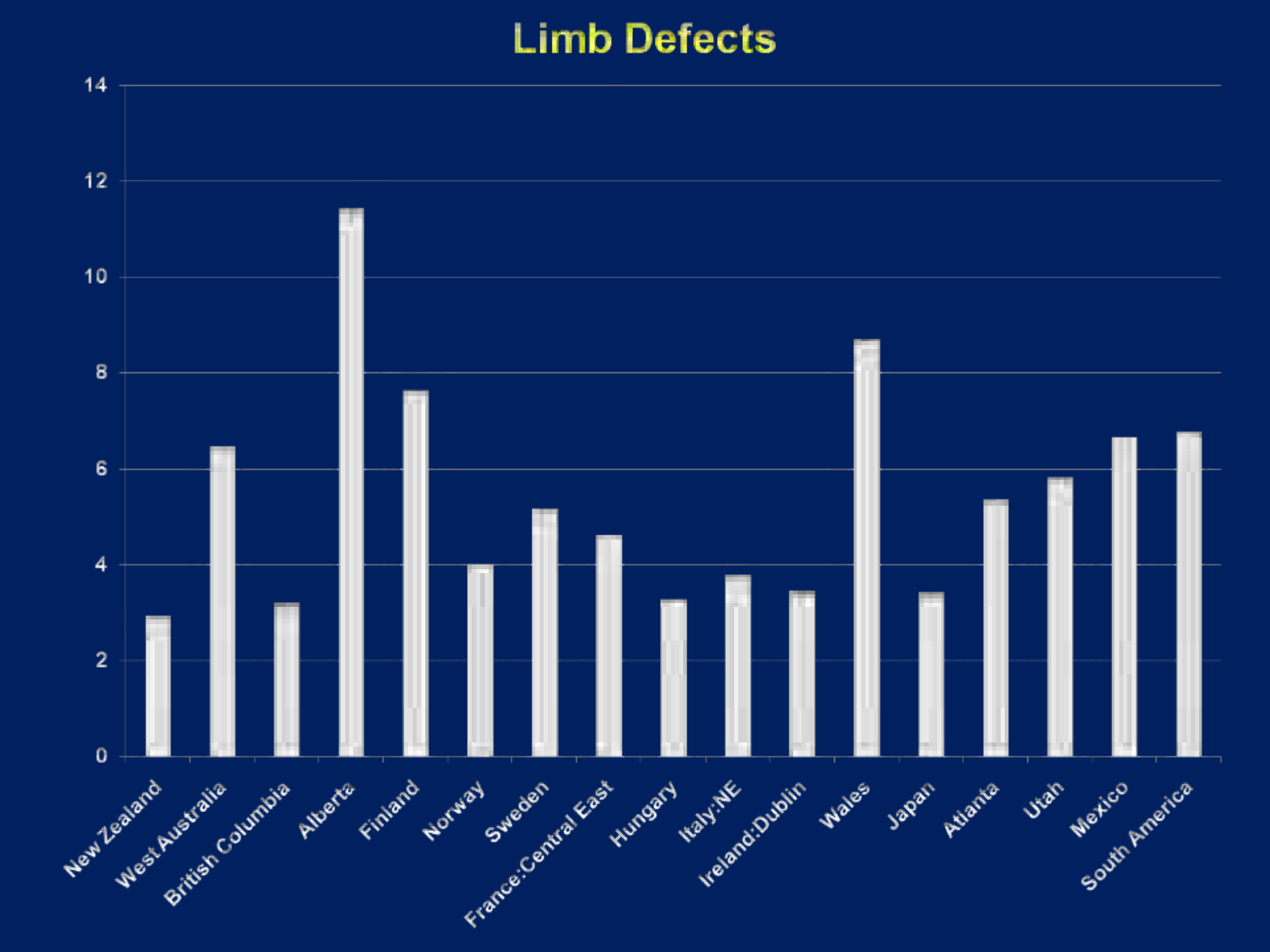


Cleft Lip with or without Cleft Palate

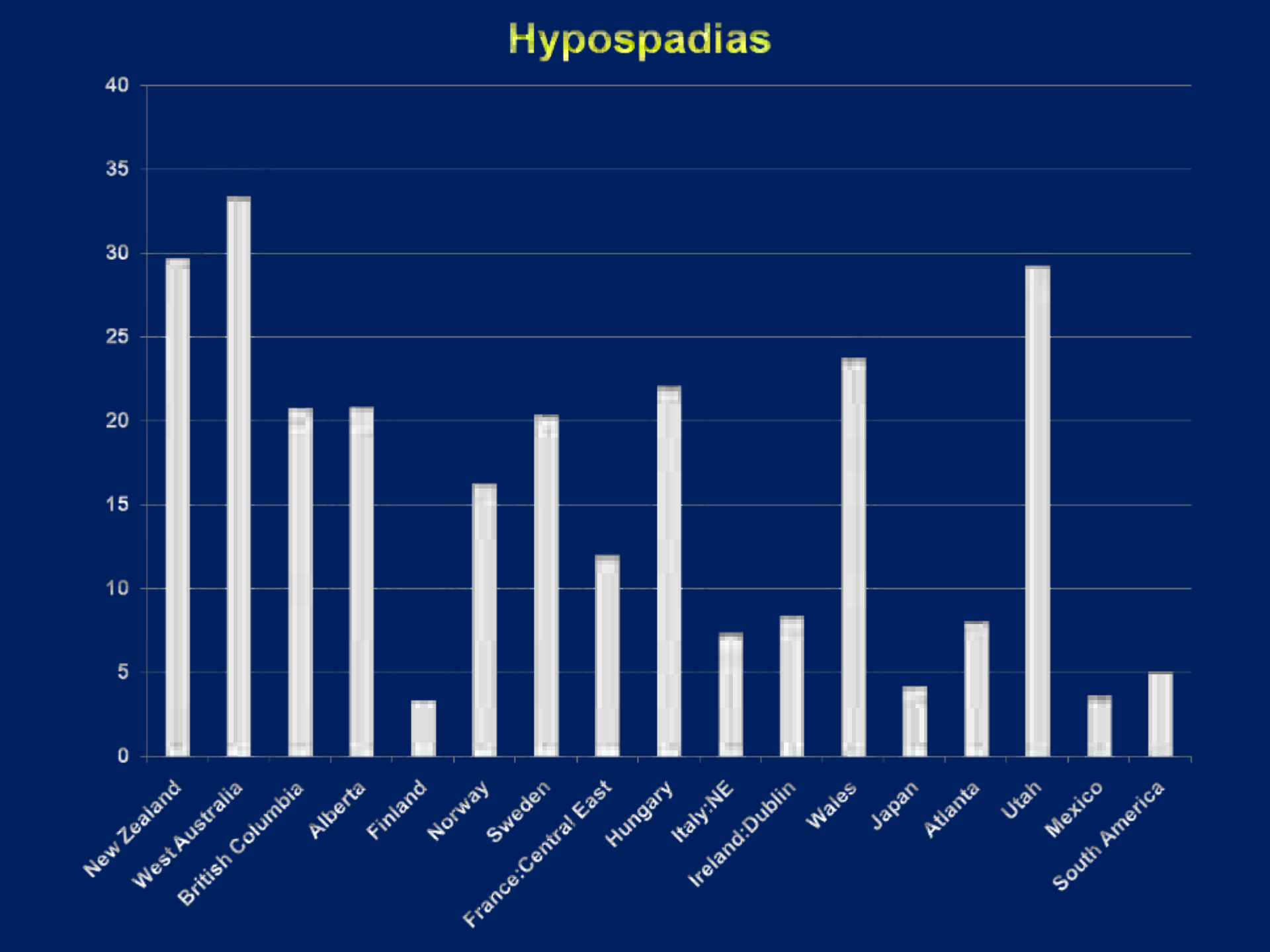




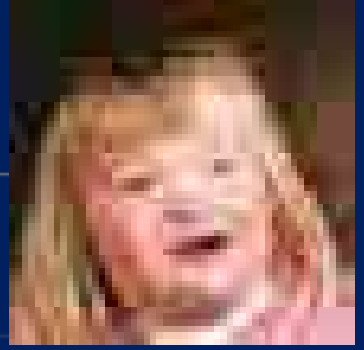
Limb Defects

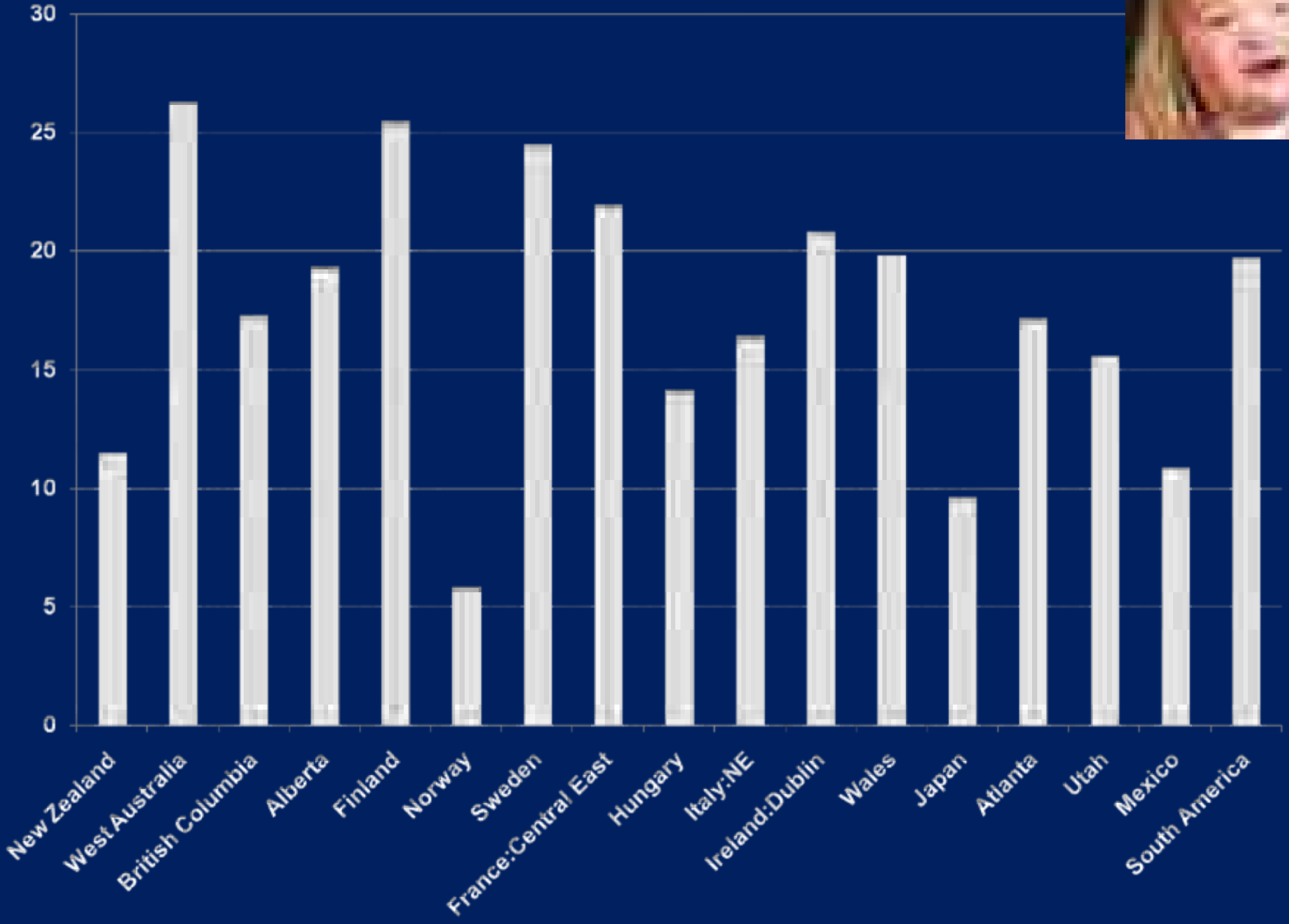


Hypospadias



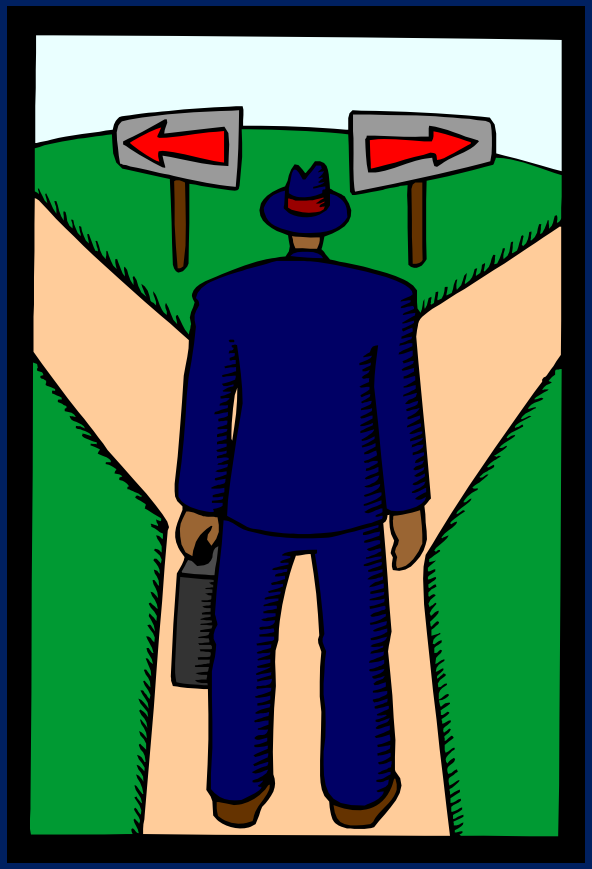
Down syndrome





Causes of Clusters of Birth Defects

Exposures Looking for Outcomes



Outcomes Looking for Exposures

Teratogen

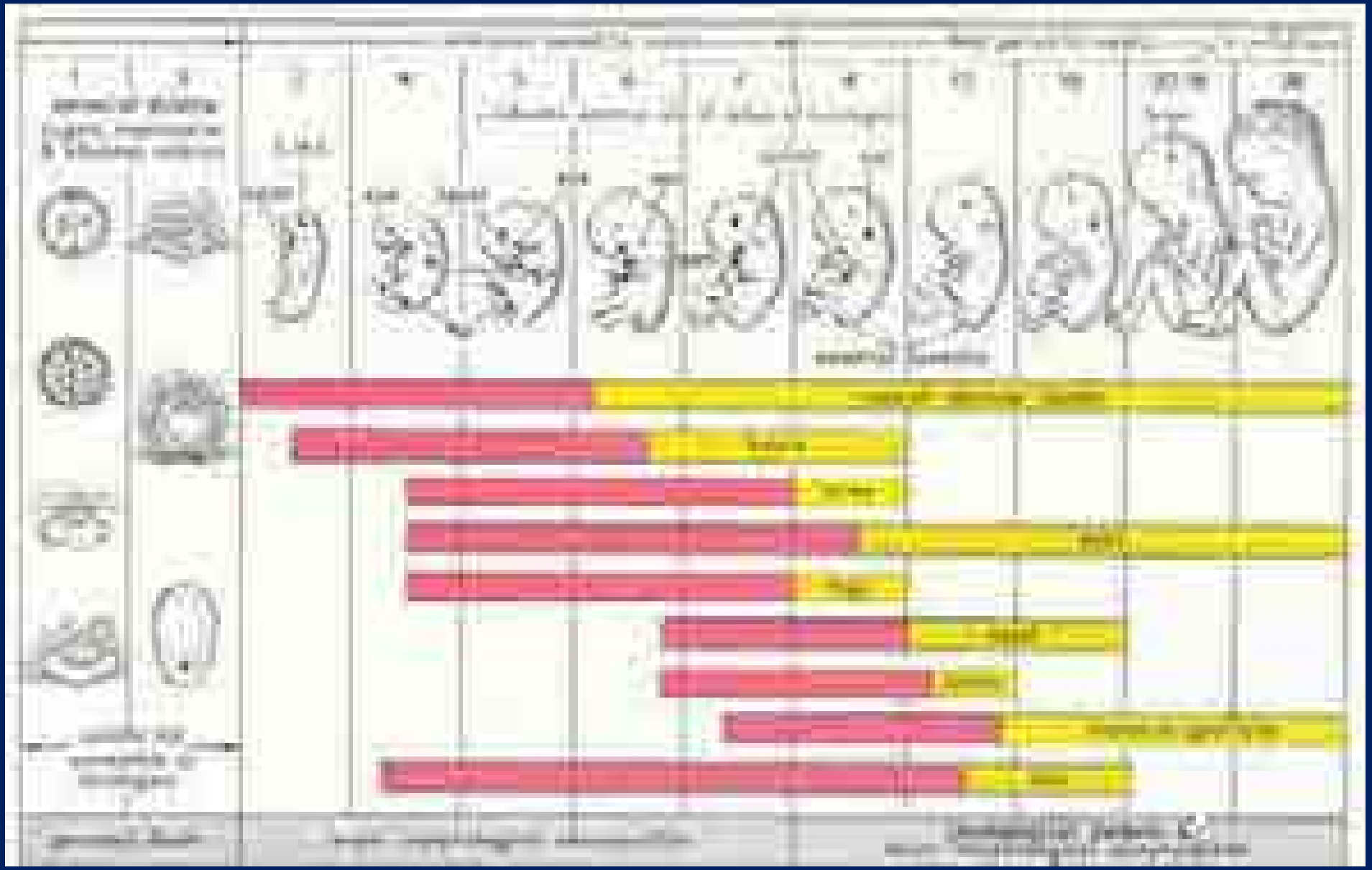
- Teratogen is an agent or factor that causes the production of physical defects in the developing embryo

- Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development
  - "The Study of Monstrosities" (Monsters) –
  - "Teras" Greek word for monster

Basic principles in teratogenesis

- Critical periods of development
- Dosage of the drug or chemical
- Genotype (genetic constitution) of the embryo and mother

Critical “Sensitive” Periods



Clusters in NZ

- 2,4,5-T and spina bifida in Taranaki, Northland, and Waikato
  - No excess
- Congenital cataracts in Wellington region
  - No common association
- Birth defects among Christchurch council workers
  - No association

Causes of Birth Defects Clusters

California, since 1983

- 150+ reported clusters
- 5% with an excess investigated
  - No clue to a teratogen

Texas, 2000-05

  - 21 clusters investigated
  - No aetiological evidence found

Brownsville, Texas, 1991

- Nurse reported 3 babies born with anencephaly in one 36-hour period
  - All died soon after birth
- US rate of anencephaly = <1/1000 births
- Investigation of ‘cluster’
  - No cause identified

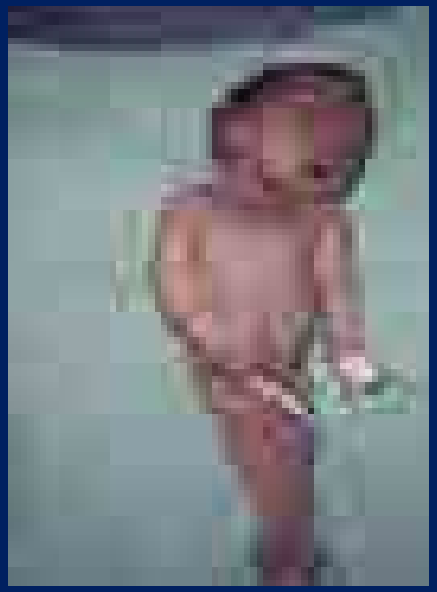
Brownsville, Texas

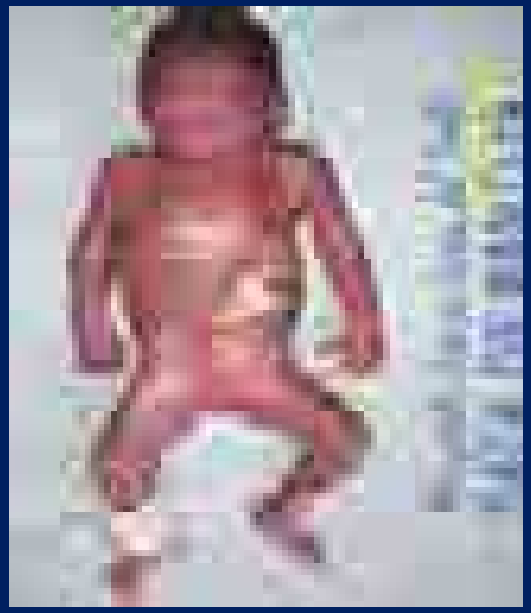
	Anencephaly		Other NTDs (mainly spina bifida)	
	No	Rate	No	Rate
1986-89	23	9.6	12	5.0
1990-91	24	19.7*	12	7.4

* = <0.01

Source: Texas Department of Health, 1992

4 cases of sirenomelia and 4 of cyclops in Cali, Columbia in a short period between 2004-2005





	Cali (rate/1000 births)	Latin America
Sirenomelia	2.24	0.23
Cyclop	2.99	0.32
Gastroschisis	8.96	1.62

Thalidomide

- Thalidomide was first synthesized in West Germany in 1953 by Chemie Grünenthal.
- It was hailed as a “wonder drug” that provided a “safe, sound sleep”
- Introduced in 1956

Thalidomide

Also found to cure morning sickness, nausea, vomitting in pregnant women

A 1961 Swedish advertisement for a liquid form of thalidomide touting it as a completely safe sedative, even for children

Thalidomide

- “Distaval can be given with complete safety to pregnant women and nursing mothers, without adverse effect on mother or child...”

- One of the factors that lead to the drug being marketed in Britain was the belief that it might become an alternative to whisky

Letters to the Editor

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—*Congenital abnormalities are present in approximately* 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. McBride.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED. L.

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Dr. McBride (Dec. 16) describes congenital abnormalities in babies delivered of women who have taken thalidomide. I have [illegible] malformed infants whose mothers had taken 'Contergan' in early pregnancy, and I understand that contergan is a [illegible] under [illegible] trade names, others being 'Distaval', 'Softenon', 'Neurosedyn', 'Isomin', 'Kevadon', 'Talimol', and 'Sedalis'.

Since I discussed the possible [illegible] role of contergan in human malformations [illegible] on Nov. 18, 1961, I have received letters [illegible] in the German Federal Republic, as well as [illegible], England, and Sweden, reporting [illegible] additional cases in which this drug was thought [illegible].

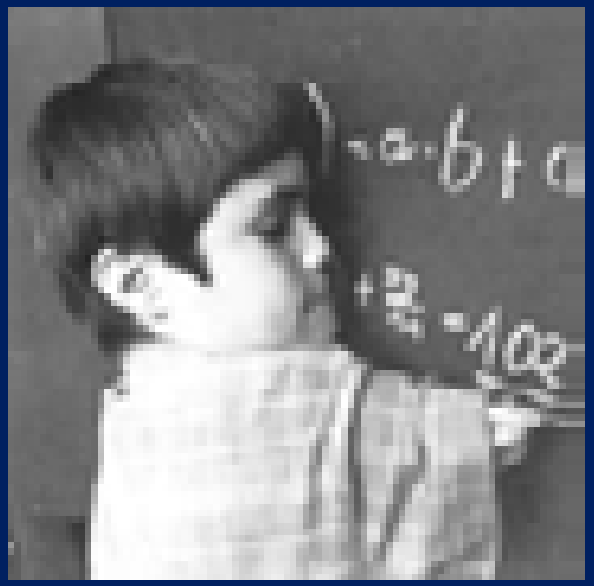
Though these malformations [illegible] are of a rather specific nature. It is usually possible to [illegible] from the type of the abnormalities alone whether contergan has been taken. Typical of a contergan [illegible] defects of the arms (amelia, atypical phocomelia with absence [illegible] thumbs and sometimes of other fingers as well as [illegible] the radius, defects of the long bones of the legs, especially the femora and tibiae, absence of the auricles, haemangiomata of the nose and the upper lip (naevus flammeus), atresia of the oesophagus, the duodenum, or [illegible], cardiac anomalies, and aplasia of the gallbladder and of the appendix).

Judging from [illegible] that 300 women who have borne normal [illegible] of whom [illegible] had taken contergan between the [illegible] conception, the risk to a [illegible] during this period may be [illegible]. I estimate that [illegible] than 2000 "contergan" babies have been born in Western Germany since 1959.

[illegible] W. LENZ

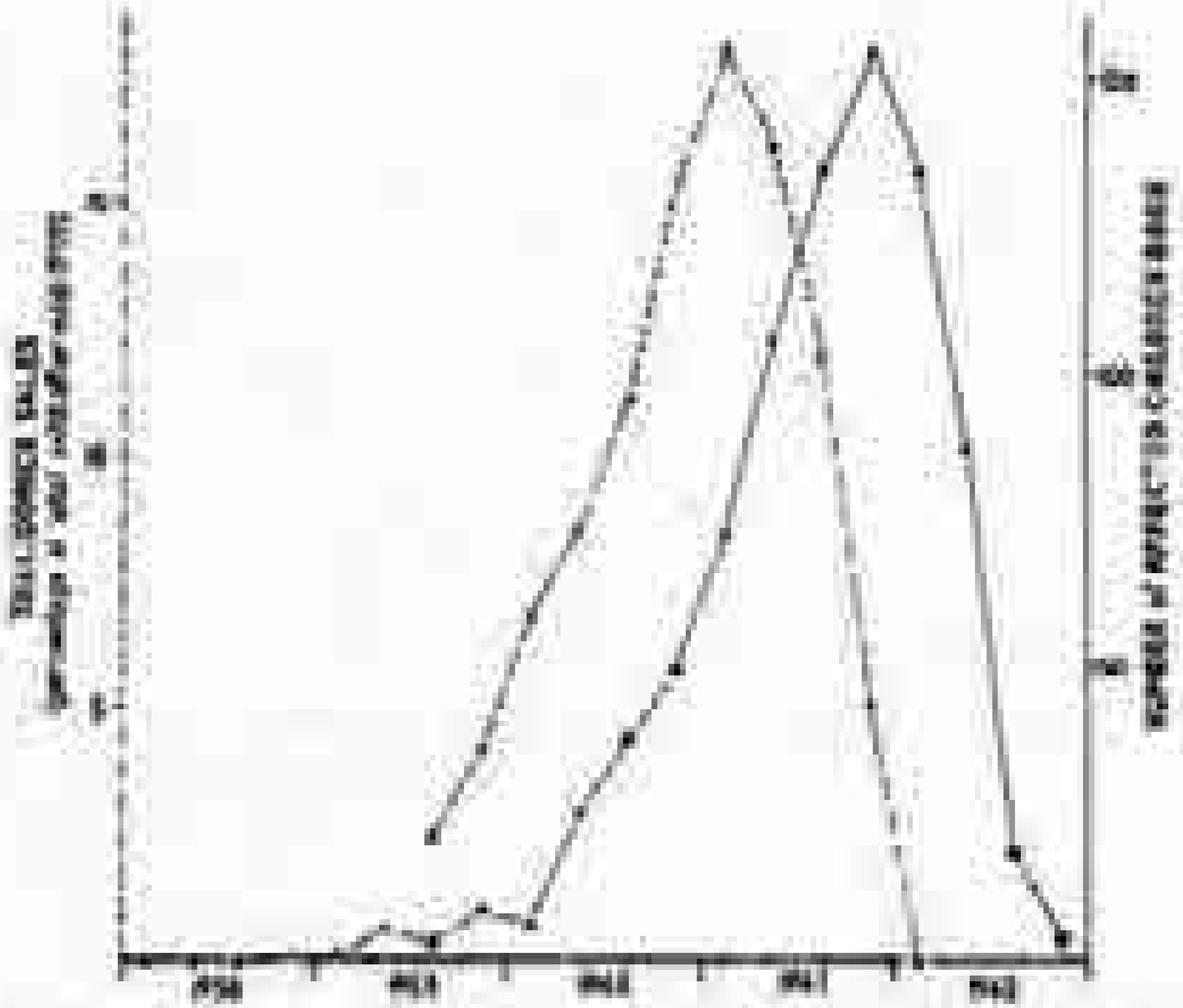
Table I. Dates of birth of children with the new type of malformation.

Born		History of maternal thalidomide intake			
Year	Half	Positive[1]	Positive[2] (by letter)	Negative[3]	In-complete[4]
1959	1.	0	0	0	0
	2.	1	1	1	1
1960	1.	3	7	1	1
	2.	15	24	3	7
1961	1.	28	49	6	5
	2.	28	106	10	3
1962	1.	15	14	1	0
Totals		90	201	22	17



Thalidomide

- 27 November 1961 = drug withdrawn;
- by August 1962 :
  - “there was a dramatic disappearance of this type of deformity within a year of the drug’s withdrawal” (Smithells)
- 10,000 infants were affected



Thalidomide

- 1964 –
  - teratogenicity of active drug substance thalidomide in animal experiments in NZ white rabbits
  - Israeli physician discovers the efficacy in treating leprosy
- 1990s -
  - Shown to have antiflamatory effects on immune system, inhibits formation of new blood vessels; used to treat AIDS, multiple myeloma
- 2003 –
  - Grunenthal stopped supplying it

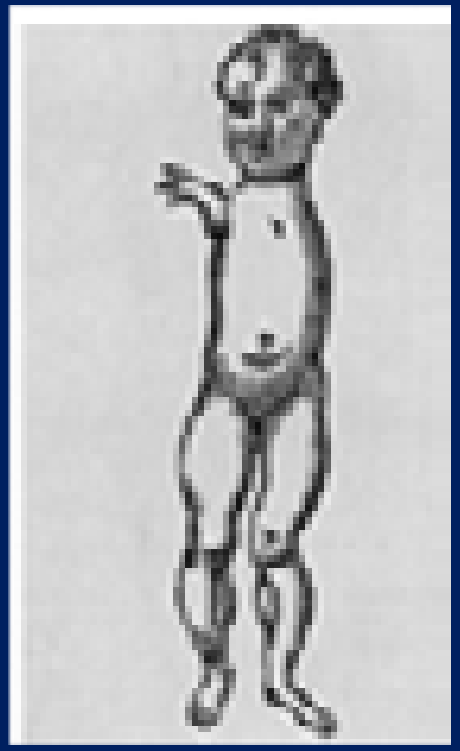
Thalidomide

- Caused a wide variety of defects, not one of which was unique to that drug
- Mothers gave birth to babies with defects unrelated to thalidomide
- Possible for babies exposed to thalidomide during the sensitive period to be born with a variety of defects, of which some, but not all, were drug induced
- Majority of UK mothers denied any knowledge of drug consumption during pregnancy

Smithells & Newman, 1992

Conditions Mistaken for Thalidomide Defects

- Phocomelia has existed throughout history and continues to appear
- These genetic conditions are often mistakenly diagnosed as thalidomide defects:
  - Holt-Oram syndrome, Tar syndrome, Cornelia De Lange syndrome, Ladd syndrome, Poland Anomaly, Goldenhar syndrome, Mobius syndrome, Duane syndrome, VATER association, Wildenvanck syndrome



1642

Thalidomide

- Produces no malformations if only taken before 34th day after the LMP and usually none if taken only after the 50th
- Critical Periods:
  - 35-37th day absence of ears, deafness
  - 39-41st absence of arms
  - 43-44th phocomelia with 3 fingers
  - 46-48th tumbs with 3 joints

- If taken throughout sensitive period = severe defects of ears, arms, legs, + internal defects

Nausea vomiting in pregnancy NVP – 1st trimester

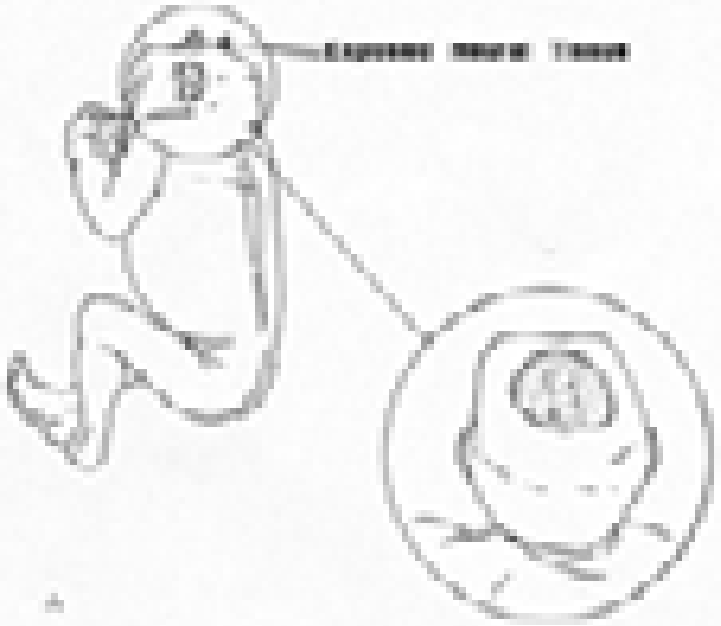
Teratogens

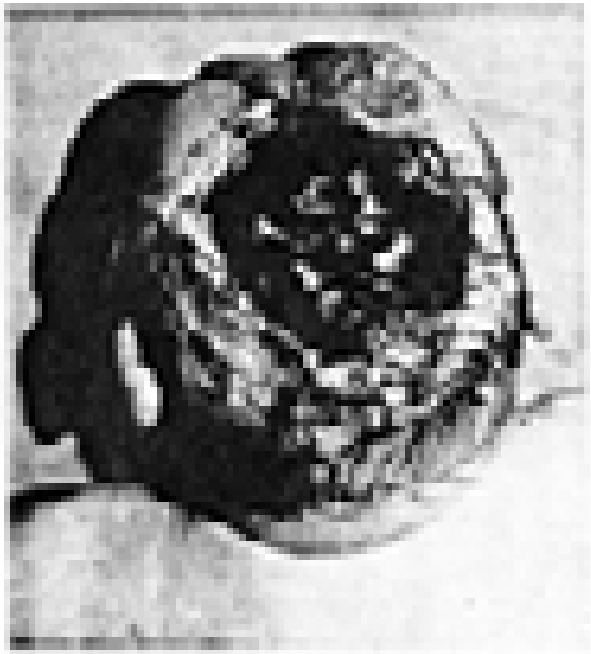
- *Drugs* (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs – cyclophosphamide, lithium carbonate)
- *Chemicals* (PCBs, methylmercury, alcohols)
- *Infections* (rubella, cytomegalovirus, herpes, toxoplasma, syphilis)
- *Ionizing radiation*
- *Maternal factors* (diabetes mellitus, hyperthermia, phenylketonuria, hyper-/hypo-thyreosis)

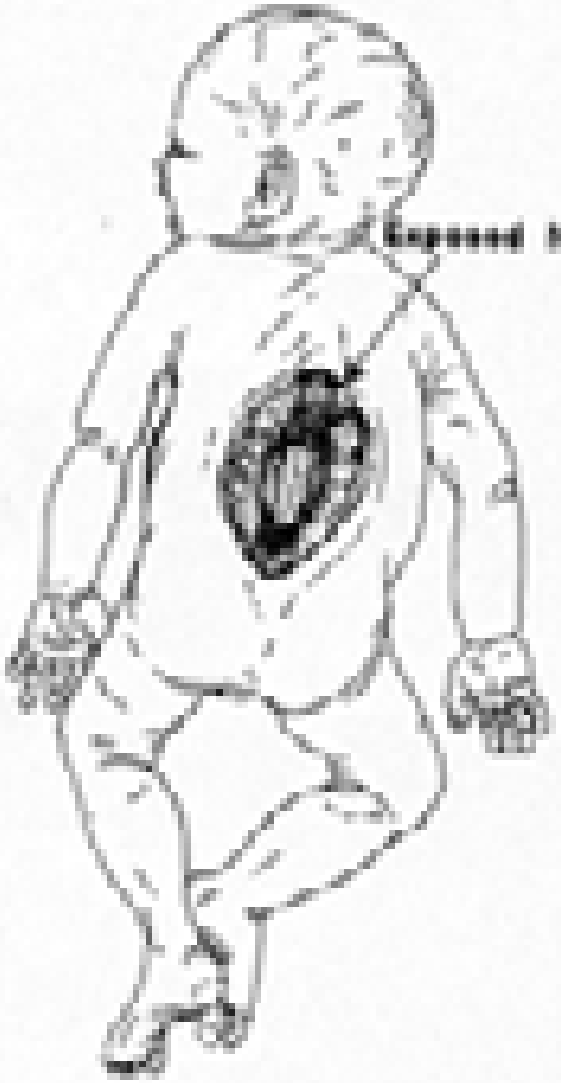
Maternal Occupation Exposure and Birth Defects

- Thulstrup & Bonde (2006) found no "clear evidence for causal associations between maternal occupational exposures and specific birth defects
- epidemiological research has not convincingly demonstrated any workplace exposure as a specific human teratogen
- Limitations of studies:
  - Ascertainment of birth defects
  - Limited study size = small numbers of cases
  - Insufficient exposure data
  - Difficult or impossible to establish exposure–response relationships
- Several concerns implying possible teratogenic effects of volatile organic solvents, glycol ethers, some pesticides and some heavy metals

- Concluded "Research in the field is overwhelmed with methodological problems"







A

B

THE LANCET

detect rare or slight adverse effects was [illegible]. Public
acid supplementation starting before pregnancy can
now be [illegible] for all women who
have had an affected pregnancy, and public health
measures should be taken to ensure that the diet of all
women who may bear children contains an adequate
amount of folic acid.

PREVENTION OF THE FIRST OCCURRENCE OF NEURAL-TUBE DEFECTS BY PERICONCEPTIONAL VITAMIN SUPPLEMENTATION

Andrew E. Czeizel, M.D., D.Sc., and István Dudás, M.D.

Abstract *Background.* The risk of recurrent neural-tube defects is decreased in women who take folic acid or multivitamins containing folic acid during the periconceptional period. The extent to which such supplementation can reduce the first occurrence of defects is not known.

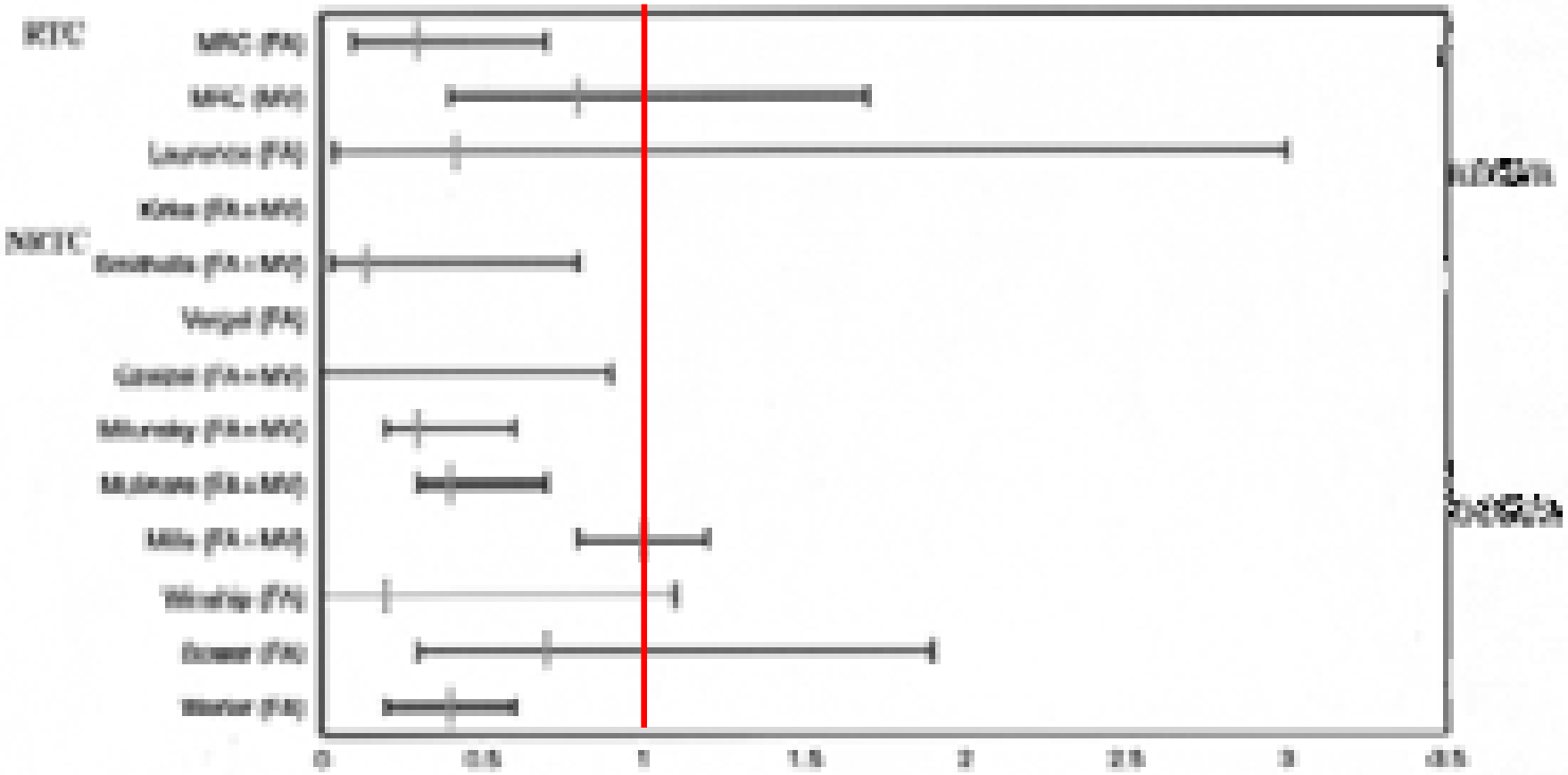
Methods. We conducted a randomized, controlled trial of periconceptional multivitamin supplementation to test the efficacy of this treatment in reducing the incidence of a first occurrence of neural-tube defects. Women planning a pregnancy (in most cases their first) were randomly assigned to receive a single tablet of a vitamin supplement (containing 12 vitamins, including 0.8 mg of folic acid; 4 minerals; and 3 trace elements) or a trace-element supplement (containing copper, manganese, zinc, and a very low dose of vitamin C) daily for at least one month before conception and until the date of the second missed menstrual period or later.

Results. Pregnancy was confirmed in 4753 women. The outcome of the pregnancy (whether the fetus or infant had a neural-tube defect or congenital hydrocephaly) was known in 2104 women who received the vitamin supplements and in 2052 who received the trace-element supplements. Congenital malformations were significantly more prevalent in the group receiving the trace-element supplement than in the vitamin-supplement group (22.9 per 1000 vs. 13.2 per 1000, $P = 0.05$). There were six cases of neural-tube defects in the group receiving the trace element supplement, as compared with none in the vitamin-supplement group ($P = 0.029$). The prevalence of cleft lip with or without cleft palate was not reduced by periconceptional vitamin supplementation.

Conclusions. Periconceptional vitamin use decreases the incidence of a first occurrence of neural-tube defects. (N Engl J Med 1992;327:1832-5.)

Conclusions. Periconceptional vitamin use decreases the incidence of a first occurrence of neural-tube defects. (N Engl J Med 1992;327:1832-5.)

Risk ratios for folic acid use



“One of the most exciting medical findings of the last part of the 20th century is that folic acid, a simple, widely available, water –soluble vitamin, can prevent spina bifida and anencephaly (SBA). Not since the rubella vaccine became available 30 years ago have we had a comparable opportunity for primary prevention of such common and serious birth defects”

Source: Oakley GP. Folic acid-preventable spina bifida and anencephaly. JAMA 1993;269:1292-3

Prevention of congenital abnormalities by periconceptional multivitamin supplementation

Andrew E Czeizel

Abstract

Objective—To study the effect of periconceptional multivitamin supplementation on neural tube defects and other congenital abnormality entities.

Design—Randomised controlled trial of supplementation with multivitamins and trace elements.

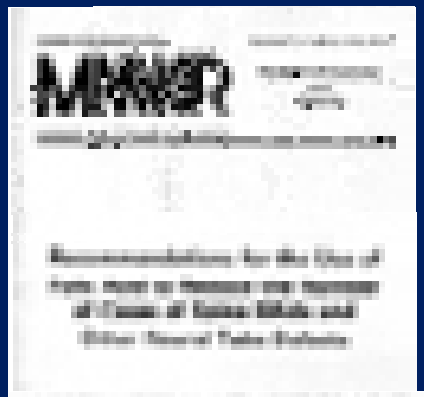
Setting—Hungarian family planning programme.

group of abnormalities were not significant.

Conclusion—Periconceptional multivitamin supplementation can reduce not only the rate of neural tube defects but also the rate of other major non-genetic syndromatic congenital abnormalities. Further studies are needed to differentiate the chance effect and vitamin dependent effect.

Multivitamin Use and Oral Clefts

Multivitamin Use and Heart and Limb Defects



11 September 1992

RECOMMENDATIONS

Available evidence indicates that 0.4 mg (400 µg) per day of folic acid, one of the B vitamins, will reduce the number of cases of NTDs. In order to reduce the frequency of NTDs and their resulting disability, the United States Public Health Service recommends that:

All women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day for the purpose of reducing their risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin B_{12} deficiency, care should be taken to keep total folate consumption at <1 mg per day, except under the supervision of a physician. Women who have had a prior NTD affected pregnancy are at high risk of having a subsequent affected pregnancy. When these women are planning to become pregnant, they should consult their physicians for advice.

March 1996

The US Food and Drug Administration

Regulated that from 1 January 1998, enriched cereal grain products (eg, flour, bread, pasta, rice etc) would be fortified with 140mcg of folic acid per 100g flour

Impact of Folic Acid Fortification of the US Food Supply on the Occurrence of Neural Tube Defects

Inertia on folic acid fortification: public health malpractice

GP Oakley

Teratology. 2002 Jul;66(1):44-54

The unnecessary epidemic of folic acid-preventable spina bifida and anencephaly.

Brent RL, Oakley GP, Mattison DR

Pediatrics. 2000 Oct;106(4):825-7.


DO NOT GET PREGNANT


THERE! SATISFIED?! NOW DO YOU BELIEVE I'M PIGEON-TOED?!


"Rudolph, your nose!"