Society for Birth Defects Research & Prevention

EST. 1960 AS THE TERATOLOGY SOCIETY

Identifying New Human Teratogens: Revisiting Shepard's Criteria

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Society for Birth Defects Research and Prevention's **2021 Virtual 61st Annual Meeting**

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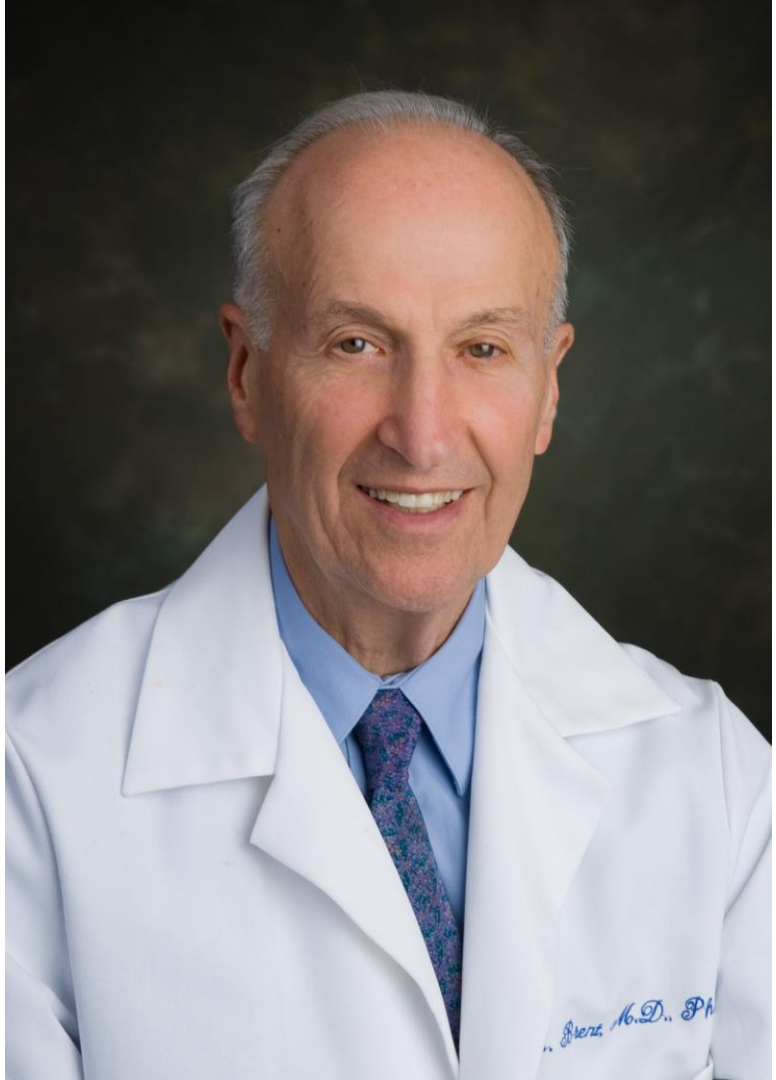


Robert L Brent, MD, PhD
1927-2021

The NEW ENGLAND JOURNAL of MEDICINE

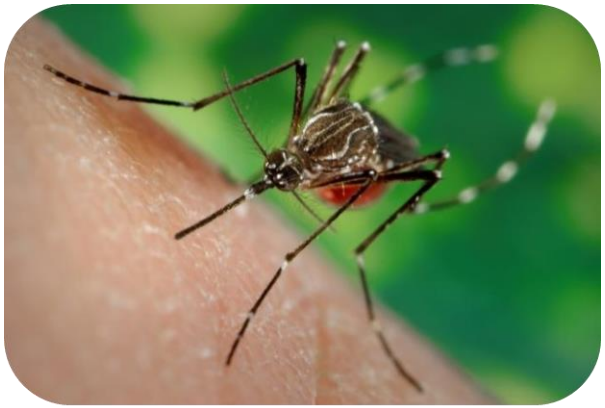
SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

Challenges to Determining if Zika Virus Causes Birth Defects (early 2016)

- Large proportion of persons infected with Zika infection asymptomatic
- Laboratory testing initially not widely available (most early cases not laboratory-confirmed) and IgM testing challenging (cross-reactivity with other flaviviruses, length of IgM persistence unknown, etc.)
- Consistent and standardized case definitions of microcephaly not being used and baseline rate of microcephaly not well defined
- Mosquito-borne viruses not previously recognized as teratogenic in humans
- Rumors circulating about other possible causes (e.g., insecticides, genetically modified mosquitoes, vaccines)



Aedes aegypti mosquito

Shepard's Criteria for Teratogenicity

Shepard T, Teratology 50:97-98, 1994

TERATOLOGY 50:97–98 (1994)

Letters

"Proof" of Human Teratogenicity

To the Editor:

TABLE 1. Amalgamation of criteria for proof of human teratogenicity[1]

1. Proven exposure to agent at critical time(s) in prenatal development (prescriptions, physicians' records, dates).
2. Consistent findings by two or more epidemiologic studies of high quality
   a. control of confounding factors,
   b. sufficient numbers,
   c. exclusion of positive and negative bias factors,
   d. prospective studies, if possible, and
   e. relative risk of six or more (?).
3. Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.
4. Rare environmental exposure associated with rare defect. Probably three or more cases (e.g., oral anticoagulants and nasal hypoplasia, methimazole and scalp defects(?), and heart block and maternal rheumatism).
5. Teratogenicity in experimental animals important but not essential.
6. The association should make biologic sense.
7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.

[1]Note: Items 1–3 or 1, 3, and 4 are essential criteria. Items 5–7 are helpful but not essential. From Brent ('78), Stein et al. ('84), Hemminki and Vineis ('85), Wilson ('77), and Shepard ('86a,b,'89,'92).

Rare Exposure-Rare Defect

1 – Proven exposure to agent at critical time

3 – Careful delineation of the clinical cases – a specific defect or syndrome, if present, is helpful

4 – Rare environmental exposure associated with rare defect – probably 3 or more cases

Examples from Shepard (1994) – congenital rubella, diethylstilbestrol, rheumatic disease (and congenital heart block), cyclophosphamide, and retinoic acid

Mycophenolate Mofetil

Birth Defects Research (Part A) 85:63–68 (2009)

Review Article

Determination of Human Teratogenicity by the Astute Clinician Method: Review of Illustrative Agents and a Proposal of Guidelines

John C. Carey,[1,2*] Lynn Martinez,[2] Elizabeth Balken,[2] Marsha Leen-Mitchell,[2] and Julia Robertson[2]
[1]Department of Pediatrics, Division of Medical Genetics, University of Utah Health Sciences Center, Salt Lake City, Utah
[2]Pregnancy Risk Line, Utah Department of Health, Salt Lake City, Utah

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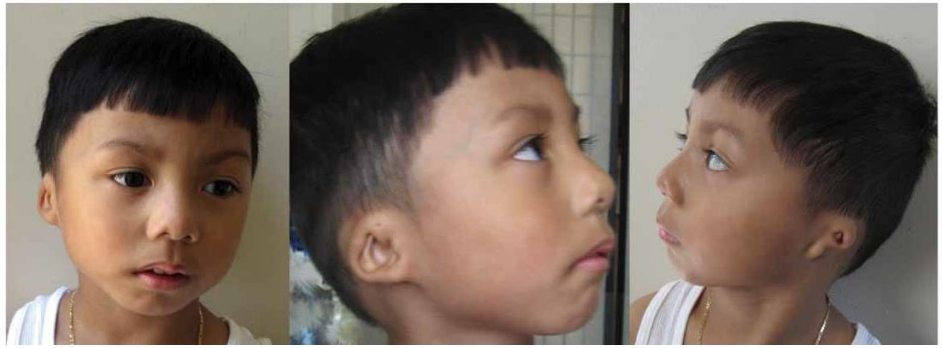

Anderka et al., Am J Med Genet A 149A:1241-8, 2009

Table 1
Summary of Clinical Data on the Reported Cases of the Mycophenolate Mofetil Embryopathy

Case No.	Reference	Indication for MMF	Time of exposure (weeks)	Other related exposures	Key defects
1	Le Ray et al.	Kidney transplant	0–13	Tacrolimus, prednisone, azathioprine	CL/P, microtia
2	Sifontis et al	Kidney transplant	0–24	Prednisone, tacrolimus	CL/P, microtia
3	Sifontis et al.	Kidney transplant	0–35	Prednisone, tacrolimus	CL/P, microtia, CDH, CHD
4	Sifontis et al.	Kidney transplant	0–15	Prednisone, tacrolimus	Microtia
5	Tjeertes et al.	Kidney transplant	0–12	Tacrolimus	Microtia, hydrops
6	Perez-Aytes et al.	Kidney transplant	0–10	Tacrolimus	Microtia, CL/P, coloboma
7	Schoner et al.	Lupus	0–8	cyclophosphamide, azathioprine	CL/P, microtia, coloboma, CHD, TEF
8	El Sebally et al.	Lupus	0–25	Prednisone, hydroxychloroquine	Anotia, polydactyly, CHD
9	Velino and Zellers	Lupus	0–8	Adalimumab	Microtia, cleft palate
10	Jackson et al.	Liver transplant	0–40	Prednisone, tacrolimus	CL/P, microtia, CHD, microphthalmia

CL/P, cleft lip or palate; CDH, congenital diaphragmatic hernia; CHD, congenital heart defect; TEF, tracheo-esophageal fistula.

Birth Defects Research (Part A) 85:63–68 (2009)

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 157:188–194 (2011)

ARTICLE

The Importance of Dysmorphology in the Identification of New Human Teratogens

KENNETH LYONS JONES* AND JOHN C. CAREY

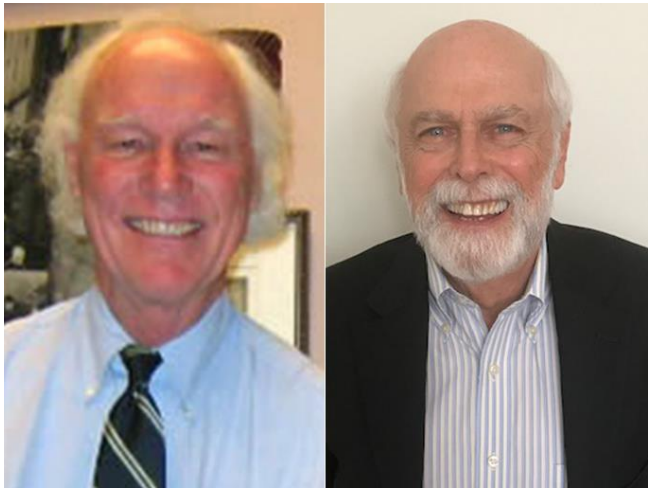

TABLE I. Selected Teratogens Categorized by Types of Evidence
Established human teratogens recognized by astute observer and confirmed by epidemiological methods/animal models
Alcohol
Valproic acid
Isotretinoin
Warfarin
Human teratogens based on clinical evidence
Aminopterin/methotrexate
D-Penicillamine
Fluconazole
Mycophenolate mofetil

Briggs et al. [2011], Carey et al. [2009], and Jorde et al. [2010].

As is well recognized in the clinical teratology community, most of the well-established human teratogens were initially identified by astute clinicians making observations during the course of clinical practice. The basic premise of this approach is that the occurrence of the unique pattern of malformation associated with the rare gestational exposure suggests causation in and of itself because of the rarity of the events occurring together by chance alone.

Epidemiologic Evidence

1 – Proven exposure to agent at critical time

2 – Consistent findings by 2 or more epidemiologic studies of high quality

3 – Careful delineation of the clinical cases – a specific defect or syndrome, if present, is helpful

How do Shepard's Criteria Define "Epidemiologic Studies of High Quality"?

- Control of confounding factors
- Sufficient numbers
- Exclusion of positive and negative bias factors
- Prospective studies, if possible
- Relative risk of 6 or more

Valproic Acid

CDC Home | Search | Health Topics A-Z

MMWR Weekly

October 29, 1982 / 31(42);565-566

International Notes Valproic Acid and Spina Bifida: A Preliminary Report -- France

Valproic acid use during the first trimester of pregnancy has been reported among an unusually high proportion of mothers of infants with spina bifida. During 1976 and from 1978 through September 1982, the birth defects surveillance system at the Institut Europeen des Genomutations in Lyon, France, ascertained 146 cases of spina bifida aperta. Among these cases, nine (6.2%) of the mothers had epilepsy and had taken valproic acid during the first trimester at dosages between 400 mg and 2,000 mg per day. Five of the nine patients with spina bifida were exposed to valproic acid alone, and four were exposed to additional anticonvulsants. Twenty-one (0.32%) of the mothers of the 6,616 infants in the surveillance system with other malformations had taken the drug (Table 1). These data show a highly statistically significant odds ratio of 20.6.* To isolate the effect of valproic acid from the possible effects of seizure disorders and other drug therapy, the analysis was then confined to the 71 epileptic mothers. Nine (90%) of the 10 such mothers of spina bifida infants had taken valproic acid, compared with 21 (34.4%) of the 61 mothers of infants with other defects (Table 2). The odds ratio of 17.1 is statistically significant. Reported by E Robert, MD, Institut Europeen des Genomutations, Lyon, France; Epidemiology Development Br, Div of Drug Experience, Food and Drug Administration; Birth Defects Br, Chronic Diseases Div, Center for Environmental Health, CDC. *The odds ratio is an estimation of relative risk in case-control studies.

Robert et al., MMWR Morb Mortal Wkly Rep 31(42):565-6, 1982

Use of Epidemiologic Studies in Assessment of Teratogenicity

- "Well-powered epidemiology studies of teratogenic birth defects usually require many hundreds or thousands of babies to be born with birth defects before causality can be established."

Editorial

In Bed with The Devil: Recognizing Human Teratogenic Exposures

Jan M. Friedman[1]

[1]Department of Medical Genetics and Genomics, University of British Columbia, Vancouver, Canada

BIRTH DEFECTS RESEARCH 109:1407–1413 (2017)

Factoring in Magnitude of Risk

- Smoking and birth defects

Conclusions

1. The evidence is sufficient to infer a causal relationship between maternal smoking in early pregnancy and orofacial clefts.

Table 9.2 **Summary of a systematic review of maternal smoking during pregnancy and its relationship with specific congenital malformations**

Outcome	Number of studies published, 1959–2010	Findings (95% CI)
Orofacial clefts	38	OR = 1.28 (1.20–1.36)
Clubfoot	12	OR = 1.28 (1.10–1.47)
Gastroschisis	12	OR = 1.50 (1.28–1.76)
Congenital heart defects	25	OR = 1.09 (1.02–1.17)
Craniosynostosis	5	OR = 1.33 (1.03–1.73)
Anorectal atresia	7	OR = 1.20 (1.06—1.36)

Source: Hackshaw et al. 2011.
Notes: **CI** = confidence interval; **OR** = odds ratio.

https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm

Brief Report
Prevention of Orofacial Clefts Caused by Smoking: Implications of the Surgeon General's Report

Margaret A. Honein*, Owen Devine, Scott D. Grosse, and Jennita Reefhuis

TABLE 2. *Estimates of the Attributable Fraction and Preventable Number for Orofacial Clefts Caused by Smoking in Early Pregnancy, and the Estimated Resulting Childhood Healthcare Costs in the United States per Year*

Parameter estimated	Estimates (mean of the simulations) and uncertainty intervals
Attributable fraction for orofacial clefts caused by smoking in early pregnancy	6.1% (4.4% – 7.7%)
Annual preventable number of orofacial clefts[a]	430 (310 – 550)
Estimate of potential cost savings (through age 10) with prevention of orofacial clefts caused by smoking[b]	$40.4 million ($29.3 million – $51.3 million)

[a]Preventable number is rounded to the nearest 10.
[b]Cost estimate is rounded to the nearest $100,000.

What about Shepard's Criteria that are Listed as "Helpful but not Essential"?

- Teratogenicity in experimental animals important but not essential
- The association should make biologic sense
- Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention

“Proof”

- Do we need proof or are we aiming for sufficient data for clinical and public health action?
- In paper by Shepard (1994), ‘. . . “proof” (or better stated strong association)’
- In paper by Friedman (2017), “The only way we can ever know with certainty that an exposure is teratogenic in humans is to recognize that it has caused birth defects in children. Our challenge is to do this as quickly and efficiently as possible, when the fewest babies have been harmed.”

There is need for a multiauthored scholarly discussion of the weight of evidence that leads us to the assignment of human teratogenicity. Perhaps this could be undertaken by the Teratology Society's Public Affairs Committee. If this is done we should acknowledge our historic dependence on Koch's postulates and writing of Bradford Hill ('65).

T.H. Shepard, 1994

What about Other Criteria?

Birth Defects Research (Part A) 73:421–423 (2005)

Teratology Society Public Affairs Committee Position Paper

Causation in Teratology-Related Litigation

The Public Affairs Committee of the Teratology Society

Received 14 February 2005; Accepted 17 February 2005

Correspondence: Anthony R. Scialli, M.D., Sciences International, Inc., 1800 Diagonal Road, Suite 500, Alexandria VA 22314. E-mail: ascialli@sciences.com
Published online 6 May 2005 in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/bdra.20139

Table 2
Two Criteria Sets for Causation in Teratology*

Brent (1995)	Shepard (2001)[a]
1. Epidemiology studies *consistently* demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.	1. Proven exposure to agent at critical time(s) in prenatal development (prescriptions, physician's records, dates)
2. Secular trend analysis reveals that the frequency of congenital malformations is associated with the changes in population exposure, i.e., the introduction or withdrawal of environmental agents for which there has been a high population exposure.	2. Consistent findings by two or more epidemiologic studies of high quality: (a) Control of confounding factors; (b) Sufficient numbers; (c) Exclusion of positive and negative bias factors; (d) Prospective studies, if possible; and (e) Relative risk of six or more (?).
3. An animal model has been developed that is similar to the reports in the human and can be produced with pharmacokinetically equivalent exposures.	3. Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.
4. In the appropriate animal model, the frequency and severity of the teratogenesis and embryopathology increases with a dose or exposure that is within the range of human exposures.	4. Rare environmental exposure associated with rare defect. Probably three or more cases (examples: oral anticoagulants and nasal hypoplasia, methimazole and scalp defects (?), and heart block and maternal rheumatism).
5. The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict basic principles of biologic or common sense.	5. Teratogenicity in experimental animals important but not essential.
	6. The association should make biologic sense.
	7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.
	[a]Items 1, 2, and 3 or 1, 3, and 4 are essential criteria. Items 5, 6, and 7 are helpful but not essential.

*Wording and punctuation as in the originals.

Pergamon

Reproductive Toxicology, Vol. 9, No. 4, pp. 337–349, 1995

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0890-6238(95)00020-8

• *Reproductive Toxicology Review*

BENDECTIN: REVIEW OF THE MEDICAL LITERATURE OF A COMPREHENSIVELY STUDIED HUMAN NONTERATOGEN AND THE MOST PREVALENT TORTOGEN-LITIGEN

ROBERT L. BRENT

Distinguished Professor of Pediatrics, Radiology, Pathology, Anatomy and Developmental Biology, Louis and Bess Stein Professor of Pediatrics, Jefferson Medical College, Alfred I duPont Institute, the Department of Pediatrics and Medical Cell Biology, Wilmington, DE

Table 1. Characteristics of an environmental agent that is teratogenic in humans

1. Epidemiology studies *consistently* demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.
2. Secular trend analysis reveals that the frequency of congenital malformations is associated with changes in population exposure, i.e., the introduction or withdrawal of environmental agents for which there has been a high population exposure.
3. An animal model has been developed that is similar to the reports in the human and can be produced with pharmacokinetically equivalent exposures.
4. In the appropriate animal model, the frequency and severity of the teratogenesis and/or embryopathology increases with a dose or exposure that is within the range of human exposures.
5. The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict biologic principles or biologic common sense.

Brent Criteria (1)

- Epidemiology studies *consistently* demonstrate an increase in the frequency of congenital malformations, and especially a recognizable syndrome in the exposed population.
- Secular trend analysis reveals that the frequency of congenital malformations is associated with changes in population exposure
- An animal model has been developed that is similar to the reports in the human can be produced with pharmacokinetically equivalent exposures

Brent Criteria (2)

- In the appropriate animal model, the frequency and severity of the teratogenesis and/or embryopathology increases with a dose or exposure that is within the range of human exposures
- The teratogenic effect is consistent with the basic principles of embryology and teratology and does not contradict biologic principles or biologic common sense

Bradford Hill Criteria

Meeting January 14 1965

President's Address

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly 'to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury

observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of 'causation'. The 'cause' of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a

Sir Austin Bradford Hill

Bradford Hill, Austin, Proceedings of the Royal Society of Medicine. 58 (5): 295–300, 1965

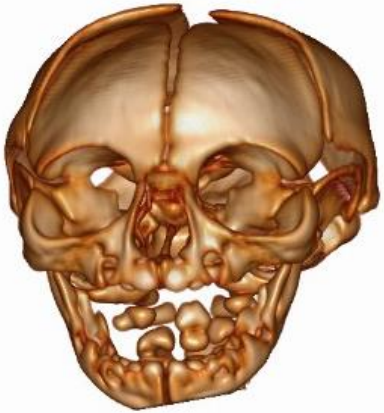
Quotes from Bradford Hill's Paper

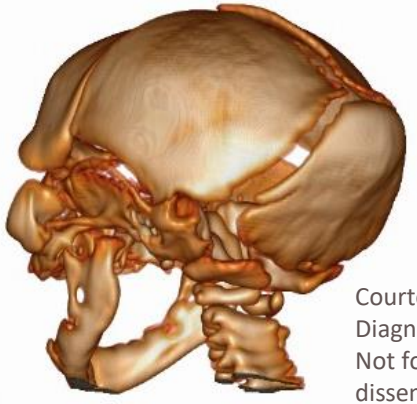
- Here then are nine different *viewpoints* from all of which we should study association before we cry causation.
- What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect.
- None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non.
- What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally or more likely than cause and effect?

Bradford Hill “Criteria” (AKA Viewpoints)

- Strength of association – higher size of risk makes causality more likely
- Consistency – results are replicated in other studies
- Specificity – single putative cause produces a specific effect
- Temporality – exposure always precedes the outcome
- Biologic gradient – an increasing level of exposure increases the risk
- Plausibility – association agrees with currently accepted understanding
- Coherence – association should be compatible with existing theory and knowledge
- Experiment – condition can be produced by an appropriate experimental regimen
- Analogy – findings of analogous associations between similar factors and similar disease

Microcephaly and Zika Virus





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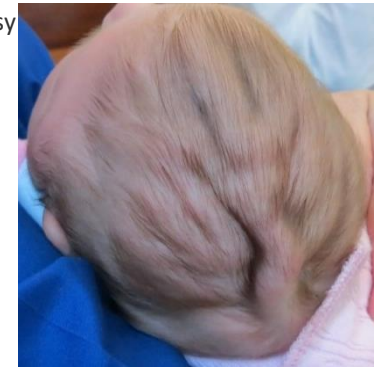
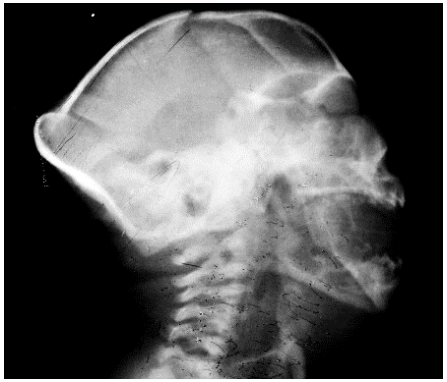
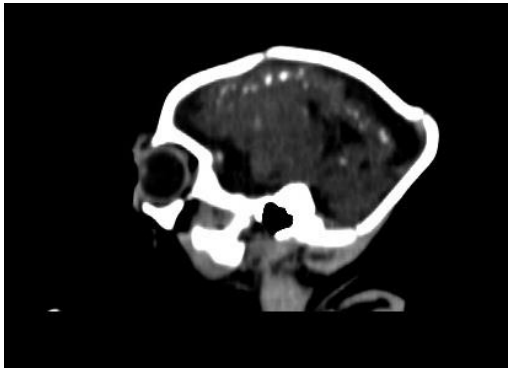






FETAL BRAIN DISRUPTION SEQUENCE: A Brief Case Report

Sonja A. Rasmussen, M.S., and Jaime L. Frias, M.D.

University of Florida College of Medicine, Gainesville, Florida (SAR), and Department of Pediatrics, University of Nebraska College of Medicine, Omaha, Nebraska (JLF)

ABSTRACT

The fetal brain disruption sequence, described by Russell and colleagues in 1984, is a pattern of defects characterized by severe microcephaly, cutis verticis gyrata, overlapping sutures, prominent occipital bone, and marked destruction of the cerebral hemispheres. These patients also have severe neurologic impairment and a shortened life span. We present here another patient with this pattern of anomalies.

KEY WORDS: fetal brain disruption sequence, central nervous system defect, brain abnormality

Dysmorphology and Clinical Genetics 4(2):53–56 (1990)

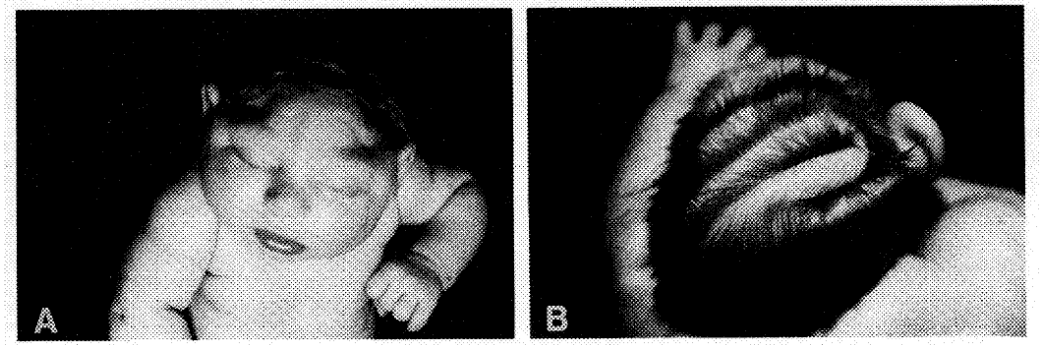
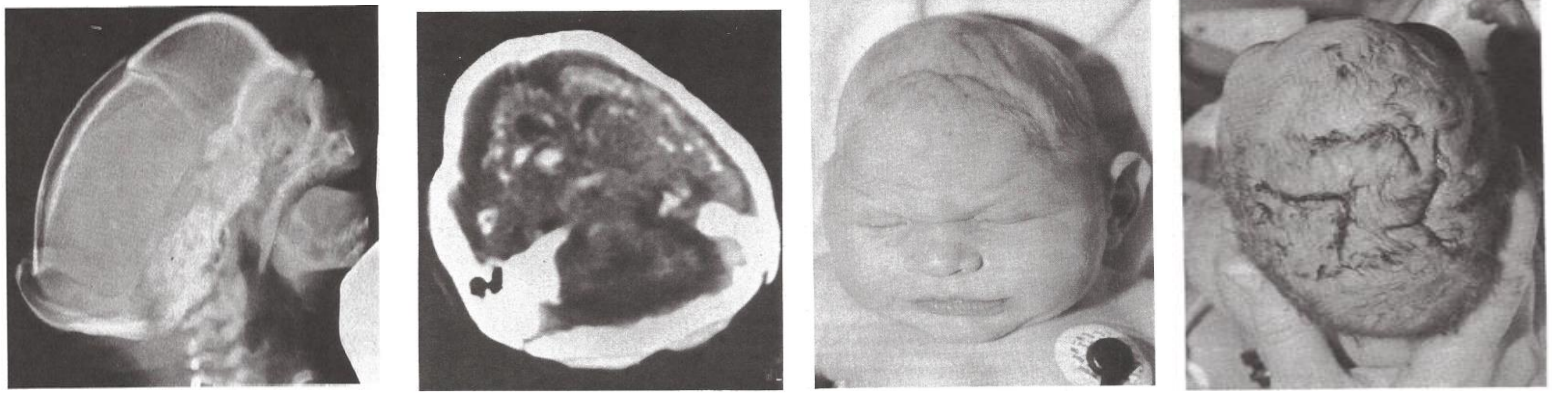


Fig. 2. **A.** Patient's face and **B.** skull at 5 months of age. Note the severe reduction of the bifrontal diameter and the marked redundancy of the scalp.

Fetal Brain Disruption Sequence

- Findings in some cases were consistent with fetal brain disruption sequence
- First described in 1984 but noted in earlier literature
- Fetal brain disruption sequence includes severe microcephaly, overlapping sutures, prominent occipital bone, scalp rugae, and marked neurological impairment



Moore, et al. J Pediatr 1990;116:383-386.

Does Zika Virus Cause Adverse Pregnancy and Birth Outcomes?

Criteria for Proof of Human Teratogenicity

Items 1-3 OR 1, 3, 4 are essential criteria,
5-7 are helpful, but not essential

Criterion	Criterion Met?
1. Proven exposure to agent at critical time(s) during prenatal development	Yes
2. Consistent findings by ≥2 high-quality epidemiologic studies	Partially
3. Careful delineation of clinical cases	Yes
4. Rare environmental exposure associated with rare defect	Yes
5. Teratogenicity in experimental animals important but not essential	No
6. Association should make biologic sense	Yes
7. Proof in an experimental system that the agent acts in an unaltered state	NA

Table 1. Shepard's Criteria for Proof of Teratogenicity in Humans as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies.*

Criterion No.	Criterion	Evidence	Criterion Met?
1	Proven exposure to the agent at one or more critical times during prenatal development	On the basis of case reports, case series, and epidemiologic studies of microcephaly that are associated with laboratory-confirmed or presumed Zika virus infection, the timing of Zika virus infection associated with severe microcephaly and intracranial calcifications appears to be in the late first or early second trimester.[14-20]	Yes
2	Consistent findings by ≥2 high-quality epidemiologic studies, with control of confounding factors, sufficient numbers, exclusion of positive and negative bias factors, prospective studies if possible, and relative risk ≥6	On the basis of data from Brazil, the temporal and geographic association between Zika virus illness and cases of microcephaly is strong.[1] Two epidemiologic studies have been published. In a study in Brazil[14] that used a prospective cohort design, 29% of women with Zika virus infection at any time during pregnancy had abnormalities on prenatal ultrasonography, some of which have not been confirmed postnatally, In a study in French Polynesia,[2] retrospective identification of eight cases of microcephaly and the use of serologic and statistical data and mathematical modeling suggested that 1% of fetuses and infants born to women with Zika virus infection during the first trimester had microcephaly; the risk ratio in this analysis was approximately 50, as compared with the baseline prevalence of microcephaly. No other epidemiologic studies have examined this association to date.	Partially
3	Careful delineation of clinical cases; a specific defect or syndrome, if present, is very helpful	The phenotype has been well characterized in fetuses and infants with presumed congenital Zika virus infection, including microcephaly and other serious brain anomalies, redundant scalp skin, eye findings, arthrogryposis, and clubfoot.[15,20-23] The phenotype in some infants appears to be consistent with the fetal brain disruption sequence,[20,22] which has been observed after infection with other viral teratogens.[24]	Yes
4	Rare environmental exposure that is associated with rare defect	Reports of fetuses and infants with microcephaly who are born to women with brief periods of travel to countries with active Zika virus transmission are consistent with Zika virus being a rare exposure.[16,18,19] The defect, congenital microcephaly, is rare, with a birth prevalence of approximately 6 cases per 10,000 liveborn infants, according to data from birth-defects surveillance systems in the United States.[25]	Yes
5	Teratogenicity in experimental animals important but not essential	No results of an animal model with Zika virus infection during pregnancy and fetal effects have yet been published.	No
6	Association should make biologic sense	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus, rubella virus).[26] Animal models have shown that Zika virus is neurotropic,[27,28] which supports biologic plausibility. Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
7	Proof in an experimental system that the agent acts in an unaltered state	This criterion applies to a medication or chemical exposure, not to infectious agents.	NA

* The criteria listed here were proposed by Shepard.[9] Criteria 1, 2, and 3 or criteria 1, 3, and 4 are considered to be essential, whereas criteria 5, 6, and 7 are helpful but not essential. Partial evidence is insufficient to meet a criterion. NA denotes not applicable.

Table 2. Bradford Hill Criteria for Evidence of Causation as Applied to the Relationship between Zika Virus Infection and Microcephaly and Other Brain Anomalies*

Criterion	Evidence	Criterion Met?
Strength of association	A recent epidemiologic study from French Polynesia suggests a strong association between prenatal Zika virus infection and microcephaly (estimated risk ratio, approximately 50).[2] The substantial increase in the number of cases of microcephaly and other brain anomalies that have been associated with the Zika virus outbreak in Brazil suggests a strong association.[1,2]	Yes
Consistency	Two epidemiologic studies, one from Brazil and one from French Polynesia,[2,14] support the association between prenatal Zika virus infection and microcephaly and other serious brain anomalies. The observed increase in the number of cases of microcephaly after outbreaks of Zika virus infection in Brazil and French Polynesia, as well as preliminary reports of cases in Colombia, support consistency.[1,2,42] Case reports of Zika virus infection in fetuses or infants with microcephaly or other brain anomalies who were born to mothers who traveled to areas of active Zika virus transmission support consistency.[16,18,19]	Yes
Specificity	Other causes of microcephaly exist; however, on the basis of clinical descriptions that are available for a small number of infants with presumed congenital Zika virus infection,[20] the clinical phenotype linked to the Zika virus appears to be an unusual form of microcephaly that is consistent with the fetal brain disruption sequence.	Yes
Temporality	Zika virus infection in mothers during pregnancy precedes the finding of microcephaly or other brain anomalies in fetuses or infants.[14-20] Zika virus outbreaks in Brazil and French Polynesia preceded the increase in the number of cases of microcephaly.[1,2]	Yes
Biologic gradient	Infection is a phenomenon that is either present or absent; there is no dose–response relationship. No data are available regarding whether women with an increased viral load have a higher risk of adverse pregnancy or birth outcomes.	NA
Plausibility	Findings are similar to those seen after prenatal infection with some other viral teratogens (e.g., cytomegalovirus and rubella virus).[26] Evidence that Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] along with evidence of Zika virus in brains of fetuses and infants with microcephaly, on the basis of on immunohistochemical staining and identification of Zika virus RNA and live virus,[16,17,19] provides strong biologic plausibility.	Yes
Coherence	No results in an animal model of effects of Zika virus on pregnancy have yet been published, but animal models have shown that Zika virus is neurotropic,[27,28] a finding that is consistent with prenatal Zika virus infection causing microcephaly and other brain anomalies. Zika virus infects neural progenitor cells and produces cell death and abnormal growth,[29] a finding that is consistent with a causal relationship between Zika virus infection and microcephaly.	Yes
Experiment	No experimental animal model of Zika virus teratogenicity is available.	No
Analogy	No other flavivirus has been shown to definitively cause birth defects in humans,[4] but flaviviruses, Wesselsbron and Japanese encephalitis viruses, have been shown to cause stillbirth and brain anomalies in animals.[43] Findings are similar to those seen after prenatal infection with other viral teratogens (e.g., cytomegalovirus, rubella virus).[26]	Yes

* The criteria listed here were proposed by Hill.[40] We have updated a recent analysis by Frank et al.[41]

Zika Is a Cause of Microcephaly (Released by NEJM on April 13, 2016)

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Zika Virus and Birth Defects — Reviewing the Evidence for Causality

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

HEALTH ZIKA

Zika Definitely Causes Birth Defects, U.S. Officials Announce

CDC confirms Zika virus causes microcephaly

Zika virus definitely causes birth defects, CDC says

By Debra Goldschmidt, CNN
Updated 9:45 PM ET, Wed April 13, 2016

Transcript for CDC Telebriefing: Zika Virus Update - 4-13-2016

MIKE STOBBE: Thank you for taking my question. I had two actually. i wanted to clarify, is the CDC's statement that Zika causes Microcephaly alone or is it that it causes Microcephaly and other severe brain severe related birth defects, and what — exactly which birth defects is it being named a cause of. And my second question was why declare this now? We've seen the evidence a couple months ago about evidence of Zika in spinal fluid, in brain tissue, and there are ongoing epi studies to try to establish more conclusively what happens if you — i was wondering, why exactly now, why not wait.

HELEN BRANSWELL: I have a couple of questions. My first relates to something that mike asked but i kind of look at it from a different point of view. instead of why wait, i kind of — you folks have been saying for a while now that this is — there is really — Dr. Petersen said it a month ago and WHO said it a couple weeks ago, too. So is there — is this just sort of dotting the i's and crosses the ts for the science or is there a public health reason for needing to say this clearly at this point?

CDC: Zika definitely causes severe birth defects

MIKE STOBBE April 13, 2016

Investigators gradually cast those theories aside and found more and more circumstantial evidence implicating Zika. CDC officials relied on a checklist developed by a retired University of Washington professor, Dr. Thomas Shepard, who listed seven criteria for establishing if something can be called a cause of birth defects.

Among other things, researchers found that the spike in microcephaly in Brazil involved women who were infected with Zika during the first or early second trimester of pregnancy. They also discovered more direct evidence in the form of the virus or its genetic traces.

"In the case of Zika, if you get live virus from spinal fluid from microcephalic kids, that's pretty damn good evidence," Shepard said in an interview.

"The purist will say that all the evidence isn't in yet, and they're right," the WHO's Aylward said, "but this is public health and we need to act."

The hope is that the public will start paying closer attention.

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— William Wilberforce

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CDC Bets Farm on Zika Based on Conclusion of Rasmussen, Jamieson, Honein & Petersen Paper

by Marco Cáceres
Published September 10, 2016 | Media, Politics

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CDC's Rasmussen Paper on Zika and Microcephaly: Poor Case for 'Smoking Gun'

by Marco Cáceres
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by Marco Cáceres - 4 Comments

Redpill1 September 11, 2016 at 2:35 pm

Zika Virus and Birth Defects — Reviewing the Evidence for Causality.

I can't believe that reputable researchers would put their name on that piece of mumble jumble. My Incredible Opinion with Forrest Maready put it concisely so people don't have to wade though the CDC medical jargon that can be misleading. This is the paper the CDC is using to claim that ZIKA causes Birth Defects: https://www.youtube.com/watch?v=HfrMHnU6xwM.

Angela Coral Eisenhauer September 19, 2016 at 6:12 am

This is the report CDC where presented with, which was meant for publication (banned by CDC it seems)..... Three weeks later, instead of this repport being published, CDC presented their toilet paper report. And NEJM actually published this CRAP?????? Good God!! Are CDC attempting to be serious, or is it really 1st April here?

https://www.academia.edu/27297345/Areas_of_Research_and_Preliminary_Evidence_on_Microc
Barr%C3%A9_Syndrome_and_Zika_Virus_Infection_in_the_Western_Hemisphere

As for CDCs own page, serious, Frienden has something to do with statistics, well he don't understand maths. A worry! 671 zika babies so far USA

Additional Data after Publication of the NEJM Paper

- Epidemiologic data, including case-control study with overall odds ratio of 55.5 (95% CI, 8.6–infinity) (de Araujo et al., 2016)
- Registry data from US and territories (Honein et al., 2017; Reynolds et al., 2017; Shapiro-Mendoza et al., 2017)
- Animal models, including mice (Cugola et al., 2016; Li et al., 2016; Miner et al., 2016), chick (Goodfellow et al., 2016), macaque (Adams Waldorf et al., 2016) models

Does Zika Virus Cause Adverse Pregnancy and Birth Outcomes?

Criteria for Proof of Human Teratogenicity

Items 1-3 OR 1, 3, 4 are essential criteria,
5-7 are helpful, but not essential

UPDATE

Criterion	Criterion Met?
1. Proven exposure to agent at critical time(s) during prenatal development	Yes
2. Consistent findings by ≥2 high-quality epidemiologic studies	~~Partially~~ **Yes**
3. Careful delineation of clinical cases	Yes
4. Rare environmental exposure associated with rare defect	Yes
5. Teratogenicity in experimental animals important but not essential	~~No~~ **Yes**
6. Association should make biologic sense	Yes
7. Proof in an experimental system that the agent acts in an unaltered state	NA

Conclusions

- Shepard's criteria have stood the test of time and remain useful but might benefit from updating
  - ✓Are the criteria about epidemiologic studies too hard to meet?
  - ✓Should an animal model be required?
  - ✓Should biologic plausibility be required?
- Criteria should serve as a framework – not strict criteria
- Goal of criteria should be to guide decision-making for clinical and public health actions - waiting for proof might mean that many babies are unnecessarily exposed

QUESTIONS

Contact information:

Sonja.Rasmussen@peds.ufl.edu

Polling Question #1

- Did CDC's confirmation of Zika virus as a cause of birth defects come too early, on time, or too late?
  a. Too early
  b. On time
  c. Too late
  d. Not sure

Polling Question #2

- Should the Society for Birth Defects Research and Prevention review Shepard's criteria and update if needed?
  a. Yes
  b. No
  c. Not sure

From: Ramon-Pardo, Dr. Pilar (WDC) [mailto:ramonpap@paho.org]
Sent: Monday, October 26, 2015 1:01 PM
To: 'tshq@teratology.org'
Cc: Almiron, Dra. Maria (WDC)
Subject: request of technical resources: protocols and research tools

Dear Teratology Society colleagues,

From the Pan American Health Organization / World Health Organization, we are concerned about the introduction of new arbovirus in the continent, in particular Chikungunya and Zika virus, and would like to provide tools to the countries to study and identify potential congenital arboviral infections, including their possible teratogenicity.

Any tool or protocol for clinical data collection (mothers and newborns) you may recommend / share with us will be extremely helpful. We are available if you would like to discus or clarify any issue with specific experts in a conference call.

Looking forward to hearing from you.

With best regards,

Pilar

Pilar Ramón-Pardo, MD, PhD – Advisor on clinical management of infectious diseases and antimicrobial resistance – IHR, Epidemic Alert and Response, and Water Borne Diseases - Pan American Health Organization/World Health Organization - 525, 23rd Street, NW. Washington, DC 20037 - Tel:+ 1 202 974 3901 - Fax:+ 1 202 974 3634 - Email: ramonpap@paho.org

“. . .we are concerned about the introduction of new arbovirus in the continent, in particular Chikungunya and Zika viruses, and would like to provide tools to the countries to study and identify potential congenital arboviral infections, including their possible teratogenicity.”

History of Zika Virus and Microcephaly

- 1947 — Zika virus identified in monkey in Uganda (Zika forest)
- 2007 — Large outbreak of Zika virus illness in the State of Yap, Federated States of Micronesia
- 2013-2014 — Large outbreak of Zika in French Polynesia
- Early 2015 — Zika virus first identified in the Americas in Brazil
- Sept 2015 — Increased number of infants born with microcephaly noted in Brazil
- Early 2016 — Increase in microcephaly retrospectively noted in French Polynesia following the 2013-2014 outbreak
- Jan 2016 — CDC issues interim travel guidance for pregnant persons for areas with ongoing Zika virus transmission, CDC activates its Emergency Operations Center

TABLE 1. Amalgamation of criteria for proof of human teratogenicity[1]

1. Proven exposure to agent at critical time(s) in prenatal development (prescriptions, physicians' records, dates).
2. Consistent findings by two or more epidemiologic studies of high quality
   a. control of confounding factors,
   b. sufficient numbers,
   c. exclusion of positive and negative bias factors,
   d. prospective studies, if possible, and
   e. relative risk of six or more (?).
3. Careful delineation of the clinical cases. A specific defect or syndrome, if present, is very helpful.
4. Rare environmental exposure associated with rare defect. Probably three or more cases (e.g., oral anticoagulants and nasal hypoplasia, methimazole and scalp defects(?), and heart block and maternal rheumatism).
5. Teratogenicity in experimental animals important but not essential.
6. The association should make biologic sense.
7. Proof in an experimental system that the agent acts in an unaltered state. Important information for prevention.

[1]Note: Items 1–3 or 1, 3, and 4 are essential criteria. Items 5–7 are helpful but not essential. From Brent ('78), Stein et al. ('84), Hemminki and Vineis ('85), Wilson ('77), and Shepard ('86a,b,'89,'92).

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Either 1-3 OR 1,3, and 4 are essential criteria - these consider the ways that teratogens had previously been recognized

Both require the following:

1 - Proven exposure to agent at critical time
3 - Careful delineation of the clinical cases - a specific defect or syndrome, if present, is helpful

1, 3, and 4 - Incorporates *rare exposure-rare defect* by requiring #4:

> **4 - Rare environmental exposure associated with rare defect - probably 3 or more cases**

1-3 - Incorporates *epidemiologic evidence* by requiring #2:

> **2 - Consistent findings by 2 or more epidemiologic studies of high quality**

Isotretinoin

The New England
Journal of Medicine

Volume 313 OCTOBER 3, 1985 Number 14

RETINOIC ACID EMBRYOPATHY

EDWARD J. LAMMER, M.D., DIANE T. CHEN, M.D., M.P.H., RICHARD M. HOAR, PH.D., NARSINGH D. AGNISH, PH.D., PAUL J. BENKE, M.D., PH.D., JOHN T. BRAUN, M.D., CYNTHIA J. CURRY, M.D., PAUL M. FERNHOFF, M.D., ART W. GRIX, JR., M.D., IRA T. LOTT, M.D., JAMES M. RICHARD, M.D., AND SHYAN C. SUN, M.D.

Retrospective Case Series

There were 23 retrospectively reported isotretinoin-exposed pregnancies. Four pregnancies ended in first-trimester spontaneous abortion. The abortuses were not examined. Of the 19 pregnancies in which the fetuses reached a viable gestational age, 2 resulted in malformed stillborn infants, 14 in malformed live-born infants, and 3 in infants without major malformations.

Prospective Cohort

Of the 36 prospectively identified isotretinoin-exposed pregnancies, 8 (22 per cent) resulted in first-trimester spontaneous abortion, 1 (3 per cent) in a malformed stillborn infant, 4 (11 per cent) in live-born infants with at least one major malformation, and 23 (64 per cent) in infants without major malformations. Neither minor malformations nor the developmental status of the 23 infants without major malformations has been systematically evaluated. The abortuses were not examined for abnormalities.

Relative Risk

Each of the five malformed infants from the prospective cohort had at least one of the selected major malformations listed in Methods. The rate for the selected major malformations among fetuses surviving beyond 19 weeks of gestation in the exposed cohort was 18 per cent (5 of 28). The rate for the selected major malformations among stillborn infants and infants born in Atlanta in 1982 was 7.0 per 1000 total births (194 of 27,866). The relative risk was 25.6 (95 per cent confidence interval, 11.4 to 57.5).

American Journal of Epidemiology

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November 20, 2012

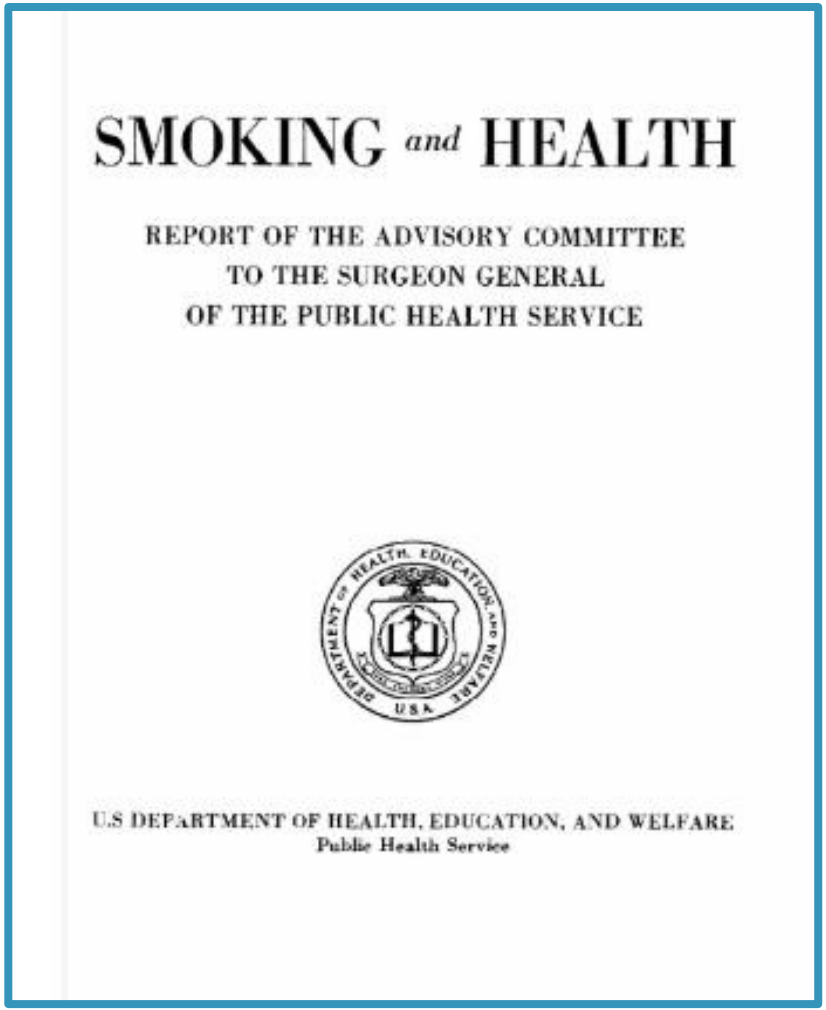
Special Article

Stories From the Evolution of Guidelines for Causal Inference in Epidemiologic Associations: 1953–1965

Henry Blackburn* and Darwin Labarthe

* Correspondence to Dr. Henry Blackburn, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South Second Street, Minneapolis, MN 55454 (e-mail: black002@umn.edu).

Initially submitted May 16, 2012; accepted for publication August 30, 2012.


SMOKING and HEALTH

REPORT OF THE ADVISORY COMMITTEE
TO THE SURGEON GENERAL
OF THE PUBLIC HEALTH SERVICE

U.S DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

On the basis of more than 7,000 articles, the Advisory Committee concluded that cigarette smoking is:

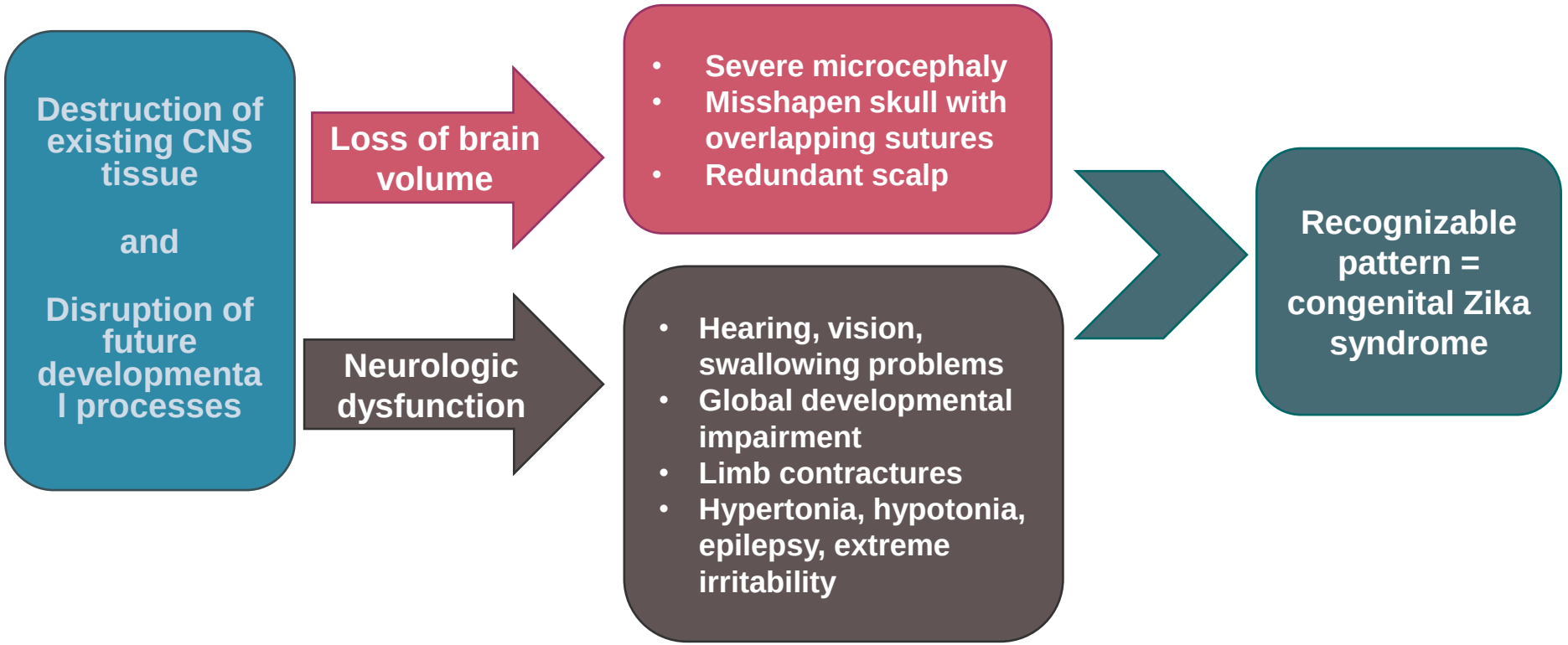
- A cause of lung cancer and laryngeal cancer in men
- A probable cause of lung cancer in women
- The most important cause of chronic bronchitis

January 11, 1964 -- Luther L. Terry, M.D., Surgeon General, released the first report of the Surgeon General's Advisory Committee on Smoking and Health

Appendix Table 1. Guidelines for Causal Inference Proposed by the Advisory Committee to the US Surgeon General on Smoking and Health and Austin Bradford Hill

US Advisory Committee Criteria, 1964 (2)	Bradford Hill's Criteria, 1965 (3)
1. Consistency	1. Strength
2. Strength	2. Consistency
3. Specificity	3. Specificity
4. Temporality	4. Temporality
5. Coherence	5. Biologic gradient
	6. Plausibility
	7. Coherence
	8. Experiment
	9. Analogy

Prenatal Zika Virus Infection – Congenital Zika Syndrome



Moore et al., *JAMA Pediatr* 2017;171(3):288-295.