Leids Universitair
Medisch Centrum

Collection of epidemiological data in haemophilia

EHC Clinical Trials in Haemophilia

Brussels, 7 March 2017

EHC
european haemophilia consortium

F.R.Rosendaal

Department of Clinical Epidemiology

LEIDEN UNIVERSITY MEDICAL CENTER

Conflicts of interests

None

Optimal data collection

- not ‘one size fits all’
  - depends on content (disease)
  - depends on methodology (type of question)

Main distinction

- effect
  - depends on disease
  - requires randomised trials

- side-effect
  - disaster control
  - requires efficient design
    - randomised trials rarely feasible
    - observational studies often valid

Disasters

- thalidomide (Softenon ®)
  - no prior research
- di-ethylstilbestrol (DES)
  - no prior research
- postmenopausal hormones
  - wrong research

Disasters: how were they discovered?

- thalidomide (Softenon ®)

back to form the subject of further discussion. It may not be too much to hope that either the Ministry of Health or the Medical Research Council, or the Ministry through the Medical Research Council, will take the lead.

Department of Surgery,
University of Liverpool. CHARLES WELLS.

SMOKING BY SCHOOLCHILDREN

SIR,—Your issue of Nov. 25 contains, under Public Health, yet another comment on smoking by schoolchildren. This repeated what has often been said before—namely, that there is an urgent need for increased anti-smoking education of schoolchildren and of the general population if the rising incidence of lung cancer is to be halted and reversed. Such anti-smoking education has been the function of local health authorities for the past three or four years, but there is little evidence that it is having any effect.

In my opinion the principal difficulty is that the power of the local health authority is limited, both in money and manpower, and that opposed to its efforts are those of the cigarette manufacturers who promote cigarette smoking with an energy that the local health authority cannot approach. Your issue of Oct. 28 contains the gist of an exchange in Parliament between Mr. Francis papers and on television on the same scale as is put forth by the tobacco manufacturers. Only in this way can we feel locally that our efforts are really worth while.

Public Health Department,
Hadleigh, Essex. ALFRED YARROW
Medical Officer of Health.

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 antiemetic 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).

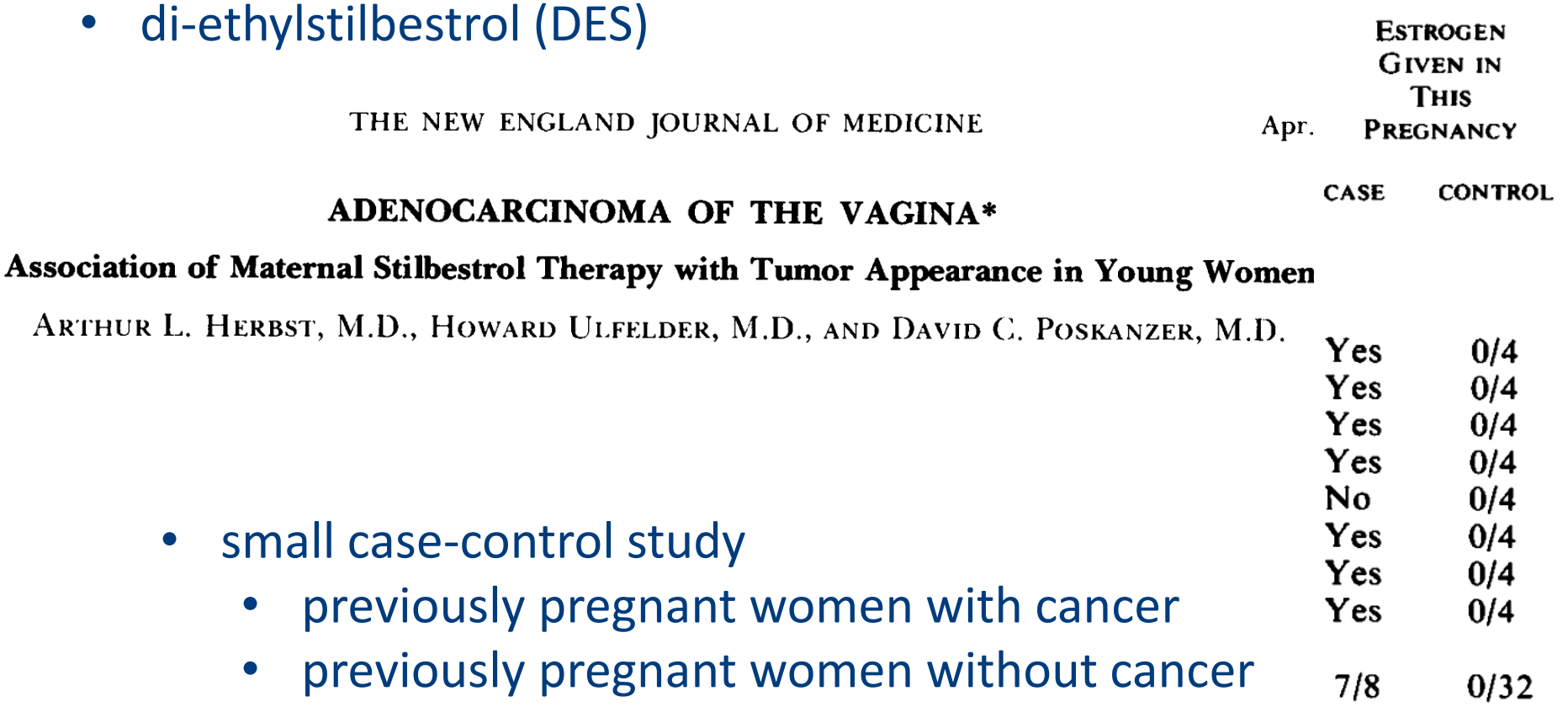
Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

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

- small case series

Disasters: how were they discovered?

- di-ethylstilbestrol (DES)



THE NEW ENGLAND JOURNAL OF MEDICINE

Apr.

ADENOCARCINOMA OF THE VAGINA*

Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women

ARTHUR L. HERBST, M.D., HOWARD ULFELDER, M.D., AND DAVID C. POSKANZER, M.D.

	ESTROGEN GIVEN IN THIS PREGNANCY	
	CASE	CONTROL
	Yes	0/4
	Yes	0/4
	Yes	0/4
	Yes	0/4
	No	0/4
	Yes	0/4
	Yes	0/4
	Yes	0/4
	7/8	0/32

- small case-control study
  - previously pregnant women with cancer
  - previously pregnant women without cancer

Disasters: how were they discovered?

- postmenopausal hormones
  - summary of 35 studies

Condition	Relative Risk*	
	Estrogen Therapy	Estrogen plus Progestin
	%	
Coronary heart disease	0.65	0.65 to 0.80
Stroke	0.96	0.96
Hip fracture	0.75	0.75
Breast cancer	1.25	1.25 to 2.00
Endometrial cancer	8.22	1.00

■ *Conclusions:* Hormone therapy should probably be recommended for women who have had a hysterectomy and for those with coronary heart disease or at high risk for coronary heart disease. For other women, the best course of action is unclear.

Disaster became widespread

country	age	prevalence	number of users
USA	40+	22.4%	30 million women
UK	50+	33.0%	3 million women
Italy	45+	~8%	
Spain	40+	~4%	
Germany	45+	~23%	
Denmark	50+	~30%	
Netherlands	50+	~15%	
Greece	50+	~2%	

data 1999-2002

Spragye, Obstet Gynecol 2012; IARC 2007 (Monograph 91)

Disaster: early warnings not heeded

Variable	% of PME Users	% of PME Nonusers
Upper social class†	91	88
Current cigarette smoker‡	25.6	22.9
Family history of heart attack§	43.3	43.4
Family history of diabetes§	18.9	18.1
Obesity‖	13.3	24.9

	Cholesterol, mg/dL		Triglyceride, mg/dL		Fasting Blood Glucose, mg/dL	
Age, yr	Users	Nonusers	Users	Nonusers	Users	Nonusers
55-59	219.6±33.2	240.0±38.7†	143.2±60.1	131.3±96.3	104.3±15.2	109.8±16.4‡
60-64	223.0±39.5	232.4±39.3§	129.2±54.8	116.7±59.0§	103.2±16.4	106.3±27.9
65-69	221.5±31.2	233.0±39.0†	131.2±68.5	117.7±50.5§	107.4±41.0	106.2±18.0
70-74	215.8±30.3	230.4±38.3‡	123.0±50.8	120.4±58.6	105.5±18.5	104.9±15.0

	Systolic Blood Pressure, mm Hg		Diastolic Blood Pressure, mm Hg	
Age, yr	Users	Nonusers	Users	Nonusers
55-59	130.8±18.8	135.0±25.1	79.4±9.6	81.3±12.0
60-64	134.1±18.9	136.5±19.2	79.4±9.4	81.6±9.8†
65-69	139.3±20.3	140.4±21.4	81.9±10.8	82.6±12.2
70-74	147.9±25.9	147.8±20.9	82.0±10.3	83.8±22.7

Disasters: how were they discovered?

- postmenopausal hormones
  - randomised trial

JAMA. 2002 Jul 17;288(3):321-33.

Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial.

- trial of 16 000 women
- increased risk of
  - coronary disease
  - ischaemic stroke
  - breast cancer

How to investigate effects and side-effects

- randomised controlled trial (RCT)
- cohort study
- case-control study
- case series

How to investigate effects and side-effects

- randomised controlled trial (RCT)

- cohort study
- case-control study
- case series

Observational studies

- may suffer from chance findings
  - as do all studies
- may suffer from confounding by indication
  - as is typical for observational studies
- try to reduce likelihood of spurious finding
  - replication, preferably in different population
  - adjustment
- If confounding cannot be adjusted for: randomise

Why is randomisation so powerful?

- it removes confounding
- confounding: two groups that are compared differ in the presence of another cause of disease
- example: grey hair and mortality
- other example: doctor who chooses treatment
  - give new drug to younger patients
  - give lower dose to people with renal disease
  - decide on treatment based on many factors

Confounding by indication

- non-smokers
- low blood pressure
- low cholesterol
- .....

Confounding by indication

- non-smokers
- low blood pressure
- low cholesterol
- .....

Experimental versus observational

studies on treatment effects (‘intended effects’)

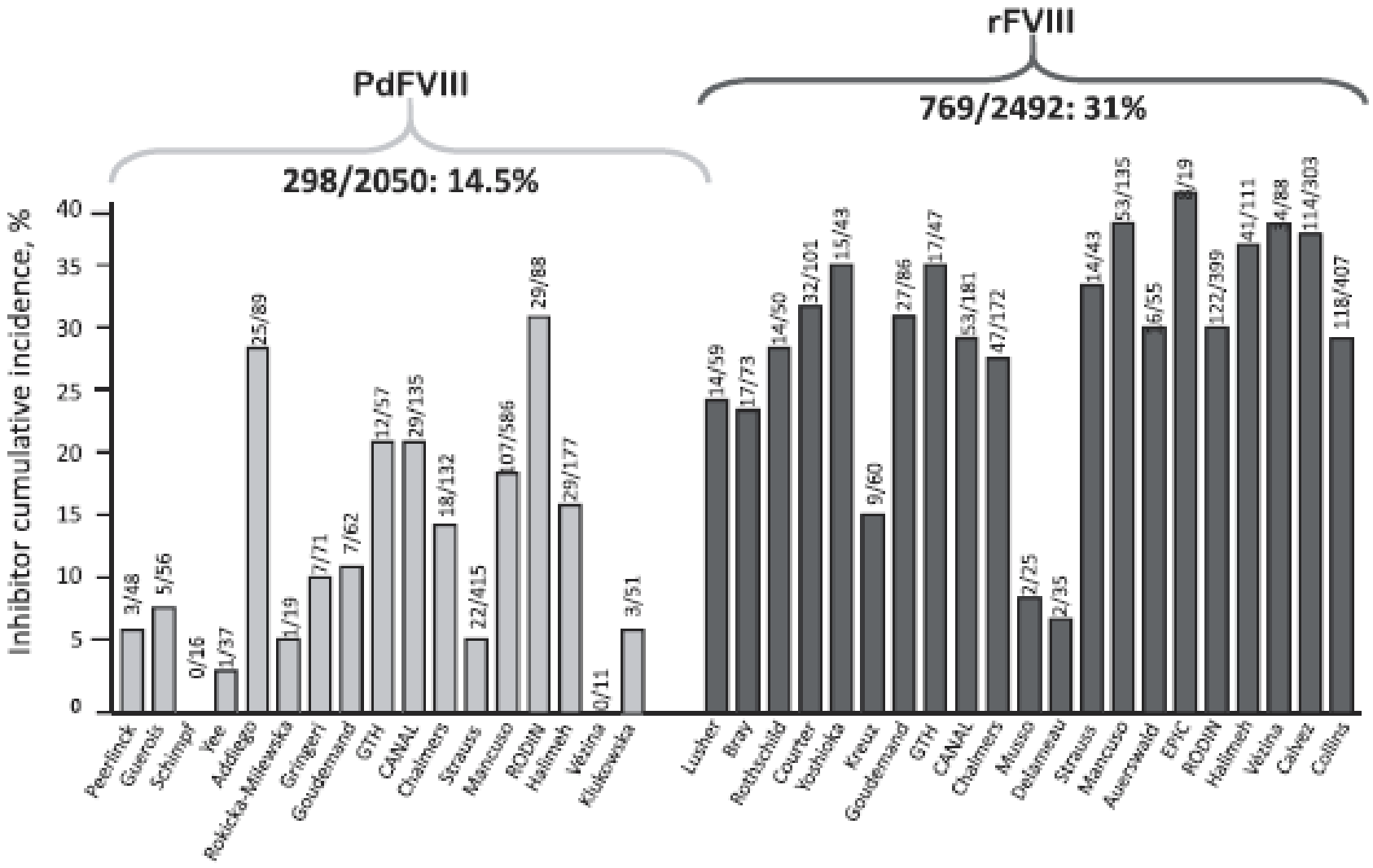
- physician ties treatment to prognosis
- many subtle factors, adjustment ineffective
- randomisation nearly always required

studies on side-effects (‘unexpected effects’)

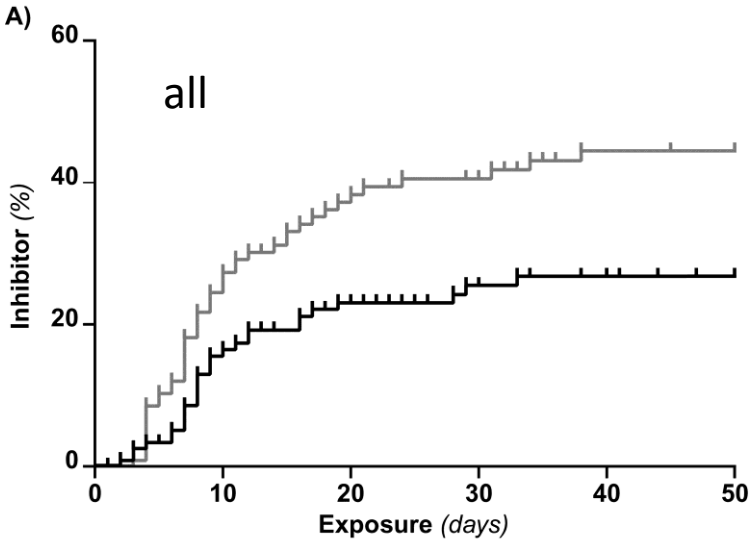
- treatment unrelated to risk profile
- no or adjustable confounding
- observational studies often valid
- but if randomised, always superior

Example: recombinant vs plasma-derived FVIII

Observational studies unclear



SIPPET: RCT of rFVIII vs pdFVIII



44.5% (CI95 34.7-54.3)

26.8% (CI95 18.3-35.2)

HR = 1.87

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

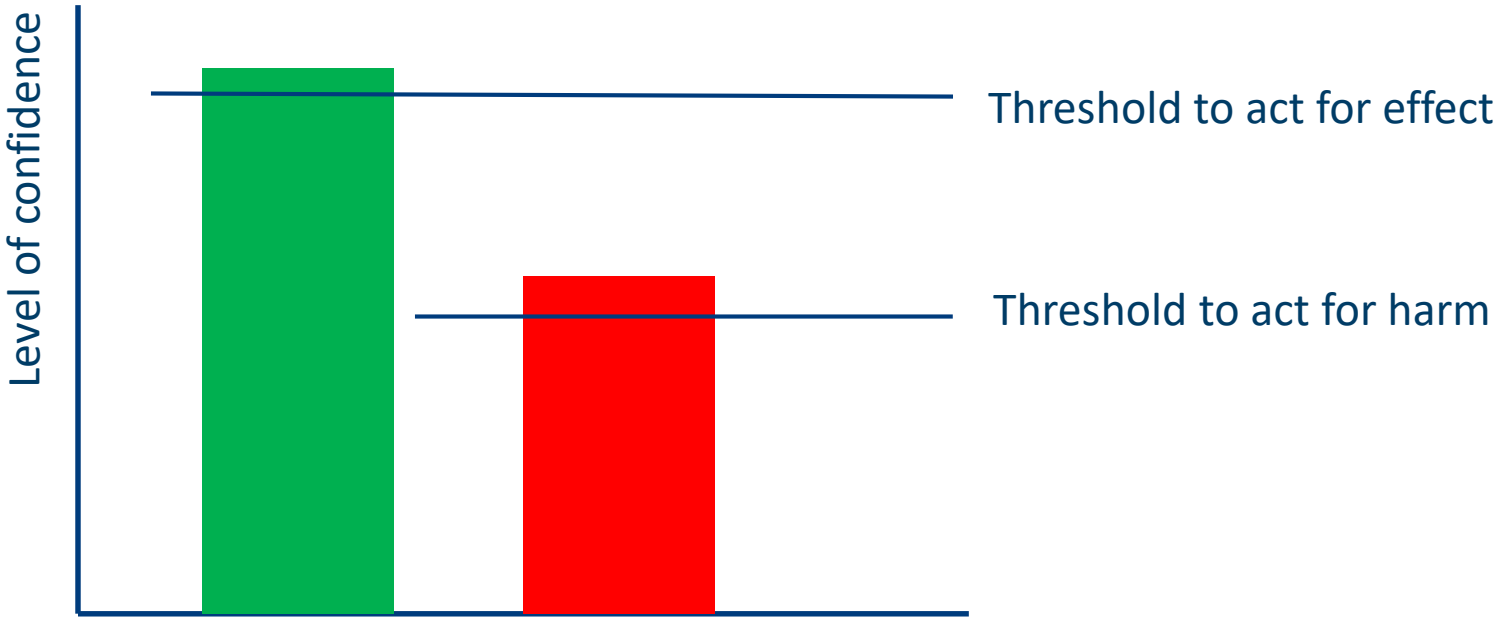
Two levels of thinking

- level of confidence about the evidence
  - study design
  - prior likelihood
  - plausibility of outcome

- which level of confidence is required
  - harm versus benefit

When to act: effect versus harm

- Less certainty required to act on signal of harm than of benefit



Example

- this brand of car uses the least petrol

versus

- this brand of car tends to explode spontaneously

General conclusions

- optimal design choice requires methodological expertise
- studies of efficacy
  - randomisation required
- studies of side-effects
  - observational studies under assumptions valid
  - randomised studies rarely feasible, but superior
- signals of harms should be viewed differently
  - Paradoxical reluctance to take action by physicians, industry, regulators

Monitoring side effects in haemophilia

optimal design

- must take into account low prevalence
- independent studies by independent researchers

- attempt randomised trials when necessary

- when observational studies are possible
  - include unselectively all patients in a region
  - include patients early (inception cohort)
  - start registers that allow cohort and case-control analyses
  - harmonise data collection
  - keep it simple
  - act