Causation and etiologic diagnosis

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Norwegian law: To systems of compensation for occupational disease

- Social security act [Folketrygdloven] (1967)
- Act on occupational injury insurance [Lov om yrkesskadeforsikring] 1989

- From 1990: Compensation of income loss (sometimes millions of kroner)
- Profitable field for lawyers
- Active public debate

Two main topics

General causation: Concepts and models

Etiologic diagnosis: Specific causation (causal analysis in single cases)

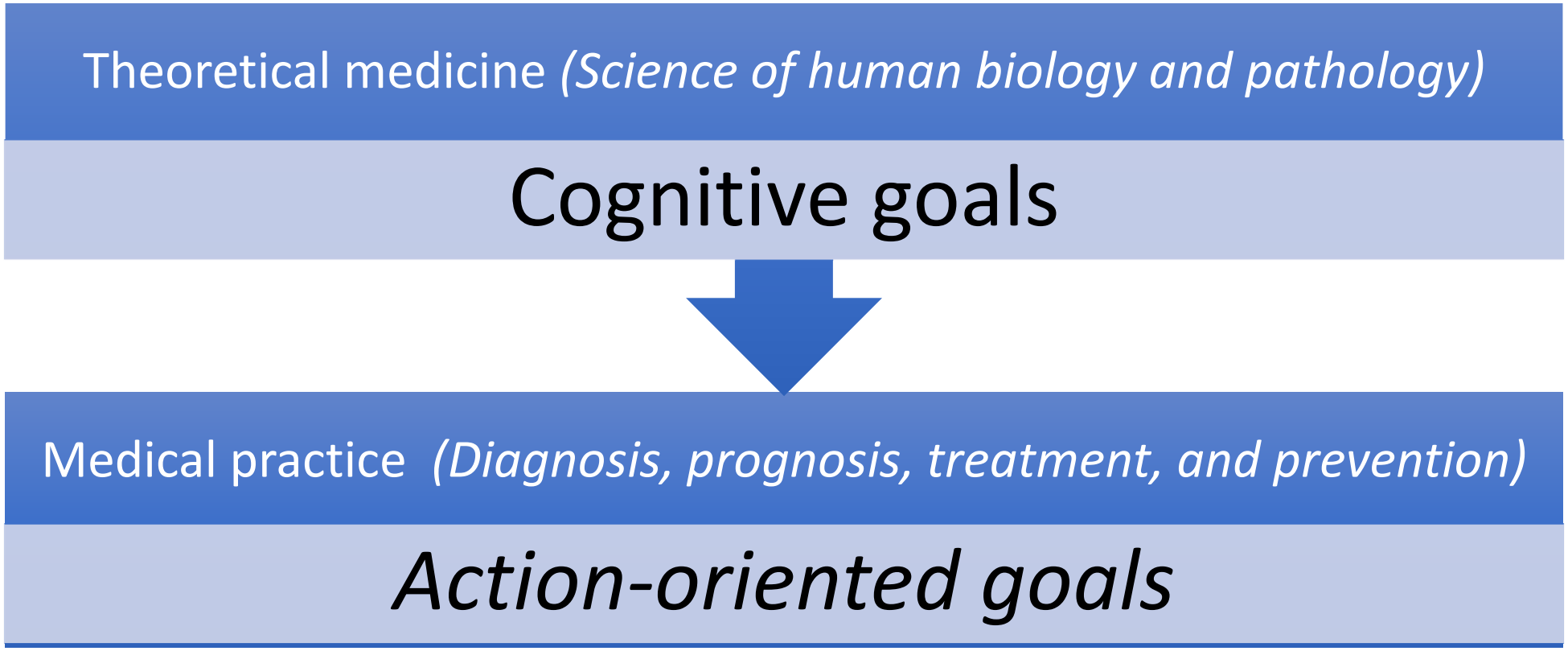
Understanding of causation in medicine: three necessary basic disciplines

MEDICINE: IN PARTICULAR - EXPERIMENTAL MEDICINE AND EPIDEMIOLOGY

PHILOSOPHY OF SCIENCE: ANALYTIC TOOLBOX

LAW: LEGAL FRAMEWORK

Medicine: two main aspects



Active decisions in Occupational Medicine based on causal knowledge

Prevention

Retrospective evaluation of cause in compensation

Causal judgements in occupational medicine: are they (really) evidence-based?

Do we have a sufficient base for correct decisions?

Do we confidently identify causes of disease?

Main challenges of causality in medicine

General causality

Groups of events

Knowledge of hazards

Primary prevention

Specific causality

What is the cause of this event?

- Prognosis and treatment (e.g. Specific etiology of pneumonia)
- Compensation (e.g. work-related diseases)

Approaches to causal reasoning

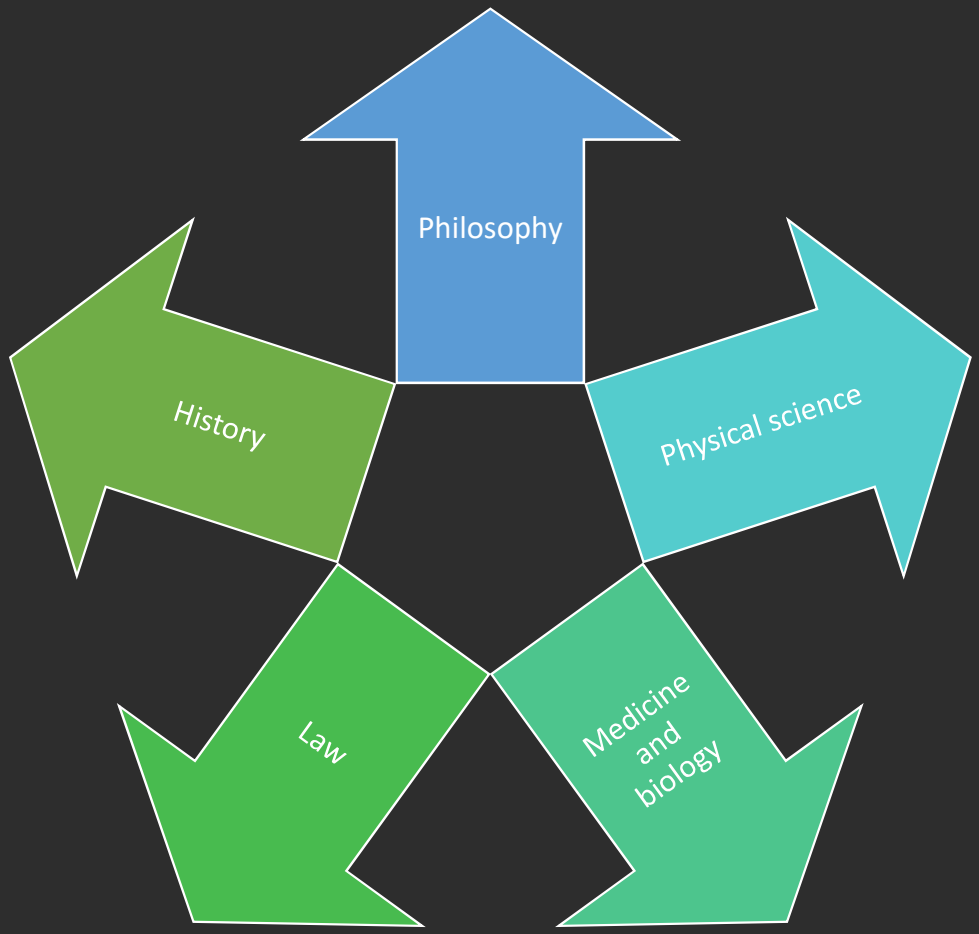
What do you mean by ‘’a cause’’? - (semantics)

How do you recognize causes? (epistemology)

How do you handle them? (pragmatics)

What is «really» a cause? (metaphysics)

Causes in different fields of knowledge



Ultrabrief history

- Philsosophy
  - Pre-Socratic Greek philosophers:
    - Thales of Miletus (c. 624 – c. 546 BC)
      Democritus (c. 400 BC)
  - Aristotle (384–322 BC)
  - David Hume (1711-1766)
  - John Stuart Mill (1806-1873)
  - John Mackie (1917-1981)
- Epidemiology
  - Austin Bradford Hill & Kenneth Rothman
- Law
  - Herbert Hart & Tony Honoré
  - Richard Wright

David Hume

1. “a cause to be an object followed by another and where all the objects similar to the first are followed by objects similar to the second.”
2. “...or, in other words, where the first object had not been the second would never exist.”

<u>But also:</u>

“Observation can only tell us that certain events regularly follow other events. The rest is subjective inference. “

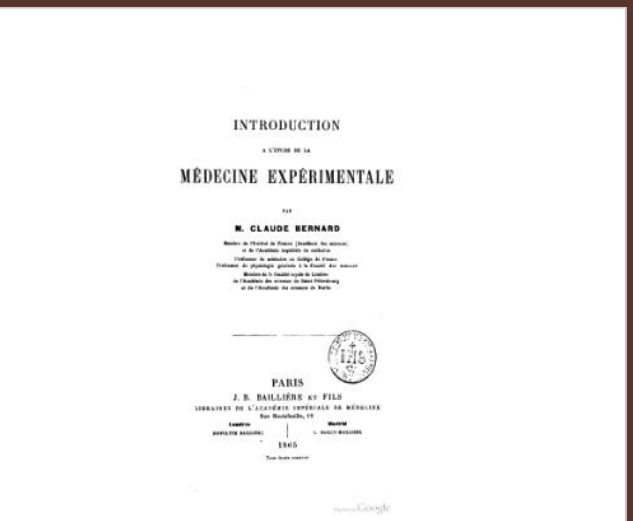
Hume D. An Enquiry Concerning Human Understanding (1748), Section VII, Part 2

David Hume:
To different concepts of causality

1. Regularity theory of causation
   - “a cause to be an object followed by another and where all the objects similar to the first are followed by objects similar to the second.”
2. Counterfactual theory of causation
   - “...or, in other words, where the first object had not been the second would never exist.”

Production	Causes are conditions that play essential parts in *producing* the occurrence of disease.
Necessary causes	A necessary cause is a condition without which the effect cannot occur. For example, HIV infection is a necessary cause of AIDS.
Sufficient-component causes	A sufficient cause guarantees that its effect will occur; when the cause is present, the effect *must* occur. A sufficient-component cause is made up of a number of components, no one of which is sufficient on its own but which taken together make up a sufficient cause.
Probabilistic cause	A probabilistic cause increases the probability of its effect occuring. Such a cause need not be either necessary or sufficient.
Counterfactual causes	A counterfactual cause makes a difference in the outcome (or the probability of the outcome) when it is present, compared with when it is absent, while all else is held constant.

Definitions of causation from the epidemiological literature (M Parascandola, D L Weed 2001)


INTRODUCTION

MÉDECINE EXPÉRIMENTALE

N. CLAUDE BERNARD

PARIS

J. B. BAILLIÈRE ET FILS

1865

Two main lines of research to establish causes of disease

- Experimental medicine
  - ❖ Claude Bernard: Introduction à l'étude de la médecine expérimentale, 1865.
    « Le milieu intérieur »
- Epidemiology
  - ❖ John Snow, (cholera and the mystery of the Broad Street pump)
  - ❖ Semmelweiss (childbed fever)
  - ❖ Bradford Hill

Evidence of causality

Mechanistic Evidence

Probabilistic Evidence

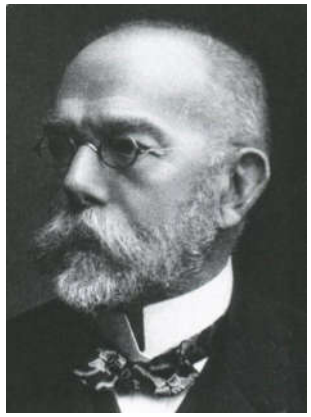
Necessary causes

Koch's postulates

Evidence required to establish etiologic relationship between microorganism and disease:

1. **Microorganism must be observed in every case of the disease**
2. **It must be isolated and grown in pure culture**
3. **The pure culture, when inoculated in animals, must reproduce the disease**
4. **Microorganism must be recovered from the diseased animal**

Koch og Loeffler 1884



Robert Koch

Sufficient-component causes

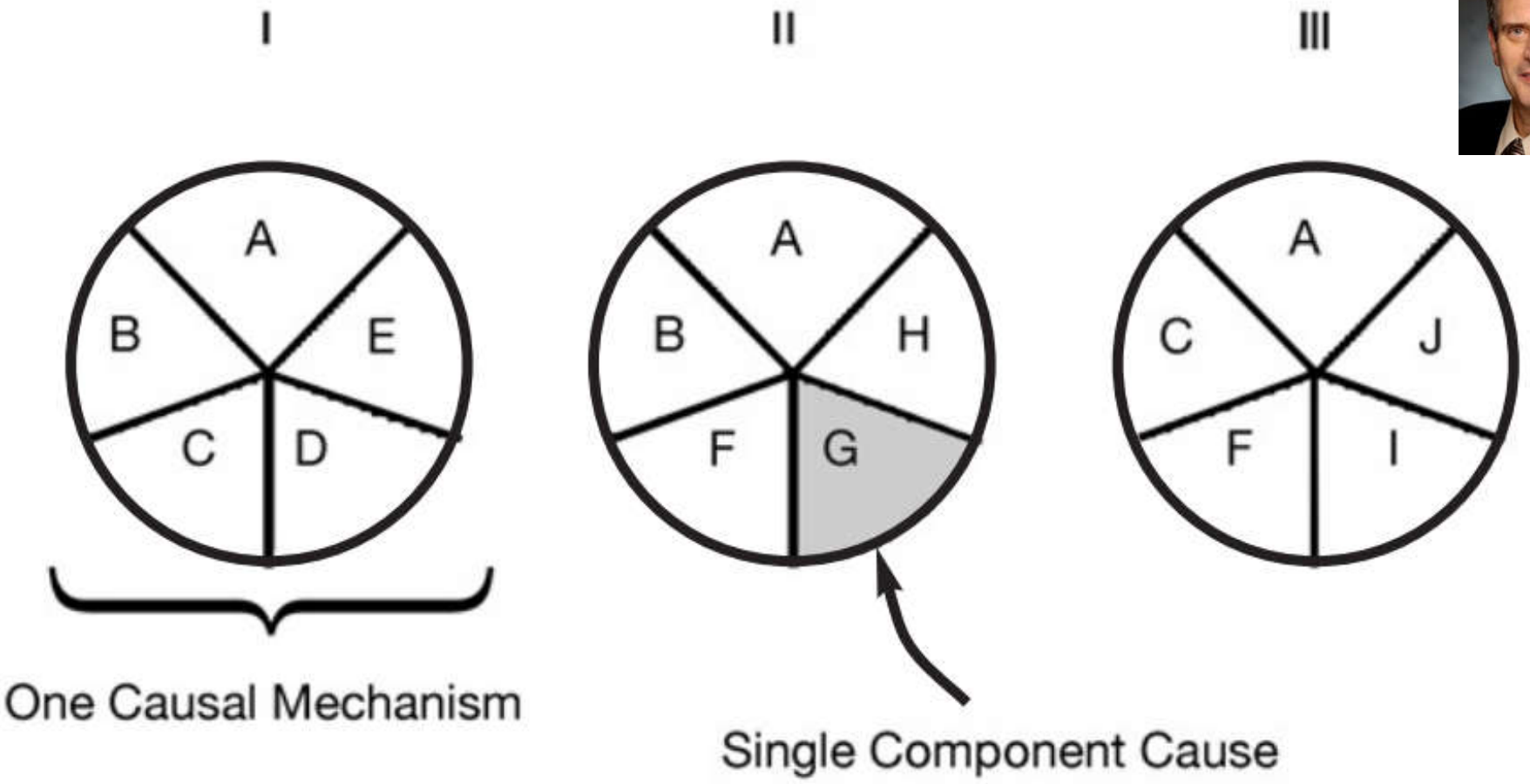
Sufficient cause, means a complete causal mechanism and, can be defined as a set of minimal conditions and events that inevitably produce disease.

A given disease can be caused by more than one causal mechanism, and every causal mechanism involves the joint action of a multitude of component causes.

Rothman & Greenland 2005

Kenneth J. Rothman 2005

Sufficient-component causes: Rothman



Sufficient-component causes: similar theories

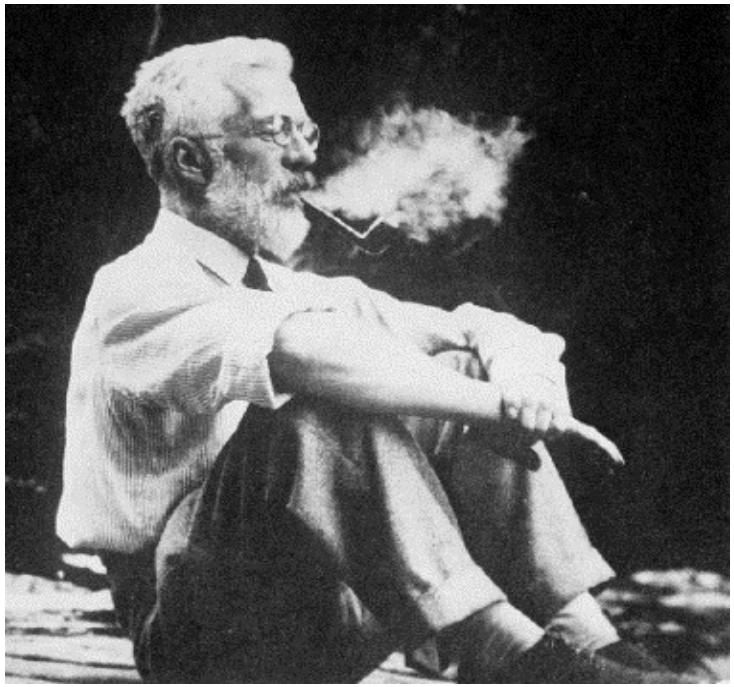
J.L. Mackie: INUS

- INUS conditions (insufficient but non-redundant parts of a condition which is itself unnecessary but sufficient for the occurrence of the effect). (philosphy)

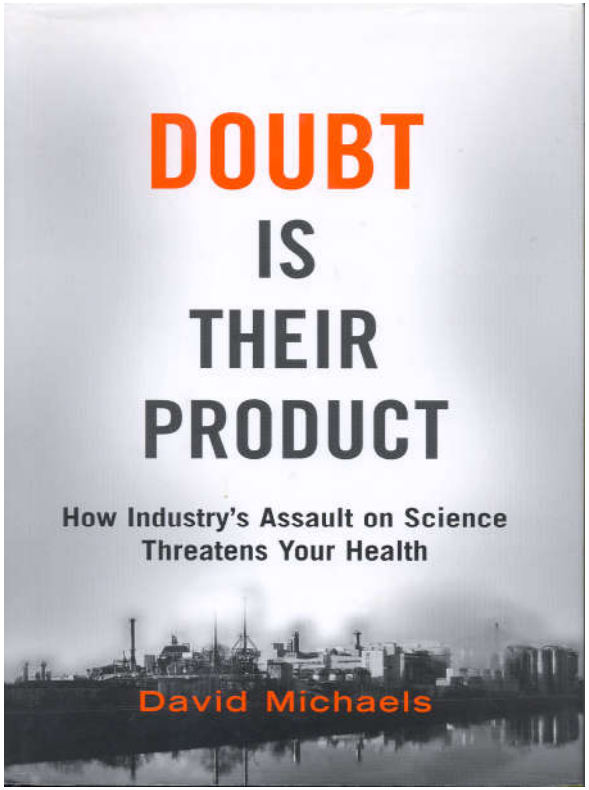
Wright: NESS

- NESS' test [necessary element of a sufficient set] (law)

What is valid medical knowledge? Associations vs. causality



R.A. Fisher smoking a pipe .



Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Ioannidis JP. Why most published research findings are false. PLoS Med 2005; 2: e124

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and the misinterpretation is widespread. However, here we will target

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2×2 table, one gets $PPV = (1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus

US Surgeon General Luther Terry addressing press conference at release of the 1964 Report on Smoking and Health

Hill AB. The Environment and Disease: Association or Causation?".

Proceedings of the Royal Society of Medicine. 58 (5): 295–300.

1. **Strength**
2. **Consistency**
3. **Specificity**
4. **Temporality**
5. **Biological gradient**
6. **Plausibility**
7. **Coherence**
8. **Experiment**
9. **Analogy**

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 and conditions of work may discuss their prob-

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 change exerts that influence may call for a great

Featured Article

Statistics in Medicine

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(wileyonlinelibrary.com) DOI: 10.1002/sim.6825

Exposure-wide epidemiology: revisiting Bradford Hill

John P. A. Ioannidis[a,b,c,d*†]

I argue that of the nine criteria, **experiment** remains important and **consistency** (replication) is also very essential.
Temporality also makes sense, but it is often difficult to document.
strength mostly does not work and may even have to be inversed
There is little evidence for **specificity** in causation in nature
Biological gradient is often unclear how it should it modeled and thus difficult to prove.
Coherence remains usually unclear how to operationalize.
Finally, **plausibility** as well as **analogy** do not work well in most fields of investigation, and their invocation has been mostly detrimental, although exceptions may exist.

(1) Strength
(2) Consistency
(3) Specificity
(4) Temporality
(5) Biological gradient
(6) Plausibility
(7) Coherence
(8) Experiment
(9) Analogy:

Approaches to Causal Inference in Public Health

- The classic approach to causal inference
  - US Dep. Health Educ.Welf. (DHEW). 1964. Smoking and Health. Report of the Advisory Committee to the Surgeon General. Rep. DHEW Publ. No. [PHS] 1103. Washington, DC: US Gov. Print. Off.
  - Hill AB. 1965. The environment and disease: association or causation? Proc. R. Soc. Med. 58:295–300
- Potential outcomes framework (POA)
  - Judea Pearl
  - James Robins et al.

Pearl

Robins

Potential outcomes approach (POA)

The traditional counterfactual theory of causation according to which a ***cause is something such that, had it been absent, the effect would also have been absent*** (for at least some individuals)

Epidemiologists should restrict their attention to well-defined causal hypotheses, whose hallmark is well-defined interventions.

Counterfactual contrasts are adequately well-defined if and only if we can specify a corresponding adequately well-defined intervention on the putative cause, by which the counterfactual contrast would be (or would have been) brought about

Except for randomization, observational studies should emulate all aspects of experimental studies because doing so restricts observational studies to investigating well-defined causal hypotheses.

The potential outcomes approach

Hernan MA Ann Epidemiol. 2016 October ; 26(10): 674–680

Causal contrasts

Questions about the causal effect of a treatment A on an outcome Y in a particular population can be expressed in terms of counterfactual contrasts.

The potential outcomes approach is used to estimate the numerical value of average causal effects like $E[Ya=1] - E[Ya=0]$. A non-zero average causal effect $E[Ya=1] - E[Ya=0] \neq 0$ can be viewed as a sufficient, but not necessary, condition for A to be "a cause".

Interventions

Declaring a version of treatment sufficiently well-defined is a matter of agreement among experts based on the available substantive knowledge.

Quantitative counterfactual inference helps us predict what would happen under different interventions, which requires our commitment to define the interventions of interest.

The potential outcomes approach provides a vehicle for rigorous quantitative causal

inference.

associational concept:

can be defined as a joint distribution of observed variables

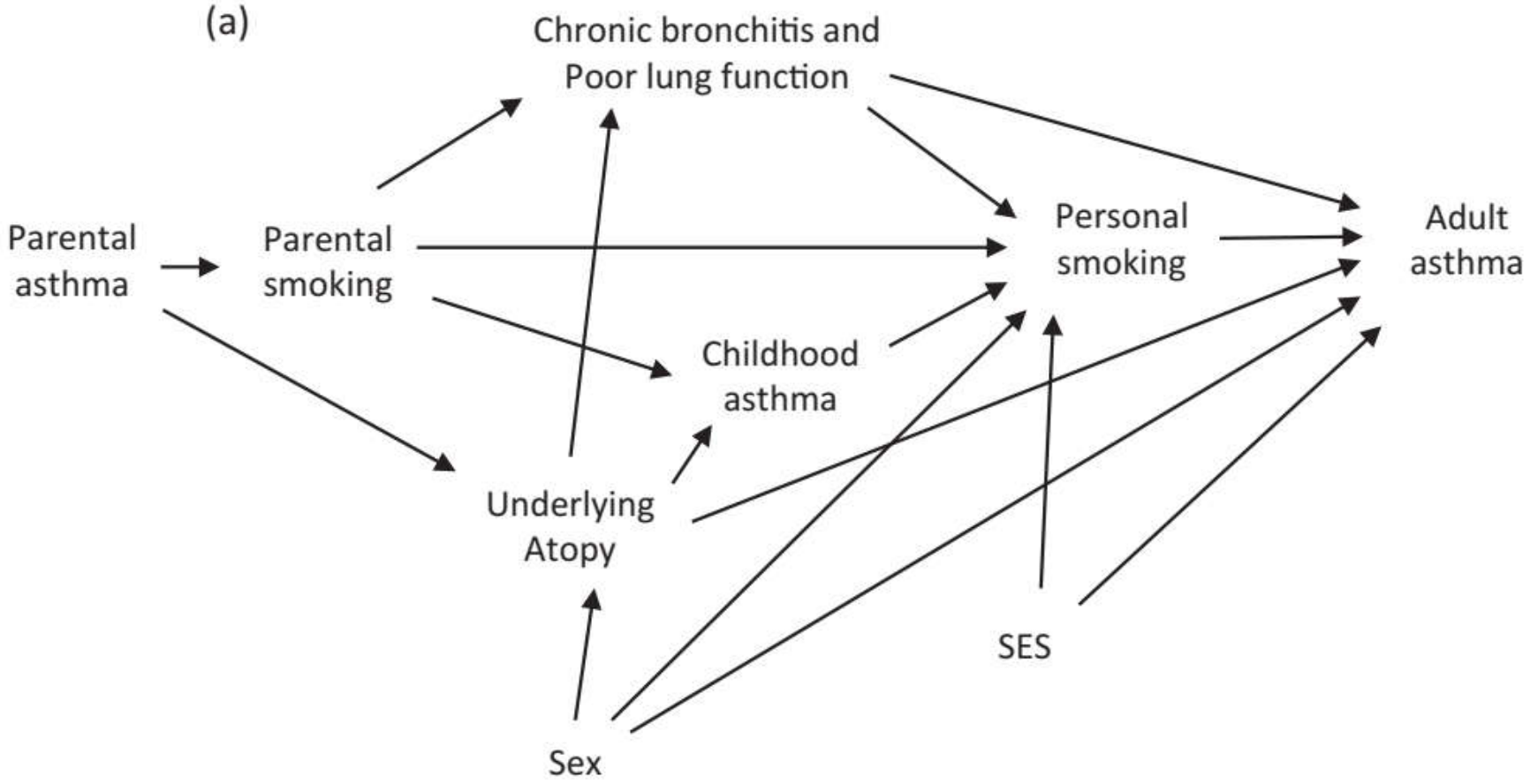
- correlation
- regression
- risk ratio
- dependence
- likelihood
- conditionalization
- "controlling for"

causal concept:

- influence
- effect
- confounding
- explanation
- intervention
- randomization
- instrumental variables
- attribution
- "holding constant"

Figure 1 Pearl: causal & statistical languages.

Use of causal diagrams (directed acyclic graphs-DAG)



Proposed causal diagram to investigate the hypothesized causal effect of personal smoking on subsequent adult asthma. (Williamson EJ et al 2014 Respirology)

Diagnostic precision in occupational disease

Illness	An absence of well-being as perceived:
	(i) by the affected individual (in the form of one or more symptoms); or
	(ii) by others (from an abnormality of function, or from an abnormality of behavior for which the affected individual cannot be held responsible)
Pathology	Abnormality of tissue structure or of biochemical or physiological function that has the potential to cause illness or death
Disease	A combination of pathological abnormalities that are thought to be inter-related
Disorder	A broader term encompassing both illness and disease
Pathogenesis	A sequence or combination of pathological abnormalities that gives rise to a specified disorder

Coggon D, Martyn C, Palmer KT, Evanoff B. Assessing case definitions in the absence of a diagnostic gold standard. IntJEpidemiol. 2005;34(4):949-52

Need of abandoning the Osler paradigm for disease classification?

- Phenotypes and endotypes in obstructive airways disease
- Overlap between asthma and COPD
- Network medicine and systemic biology
- Personalized medicine

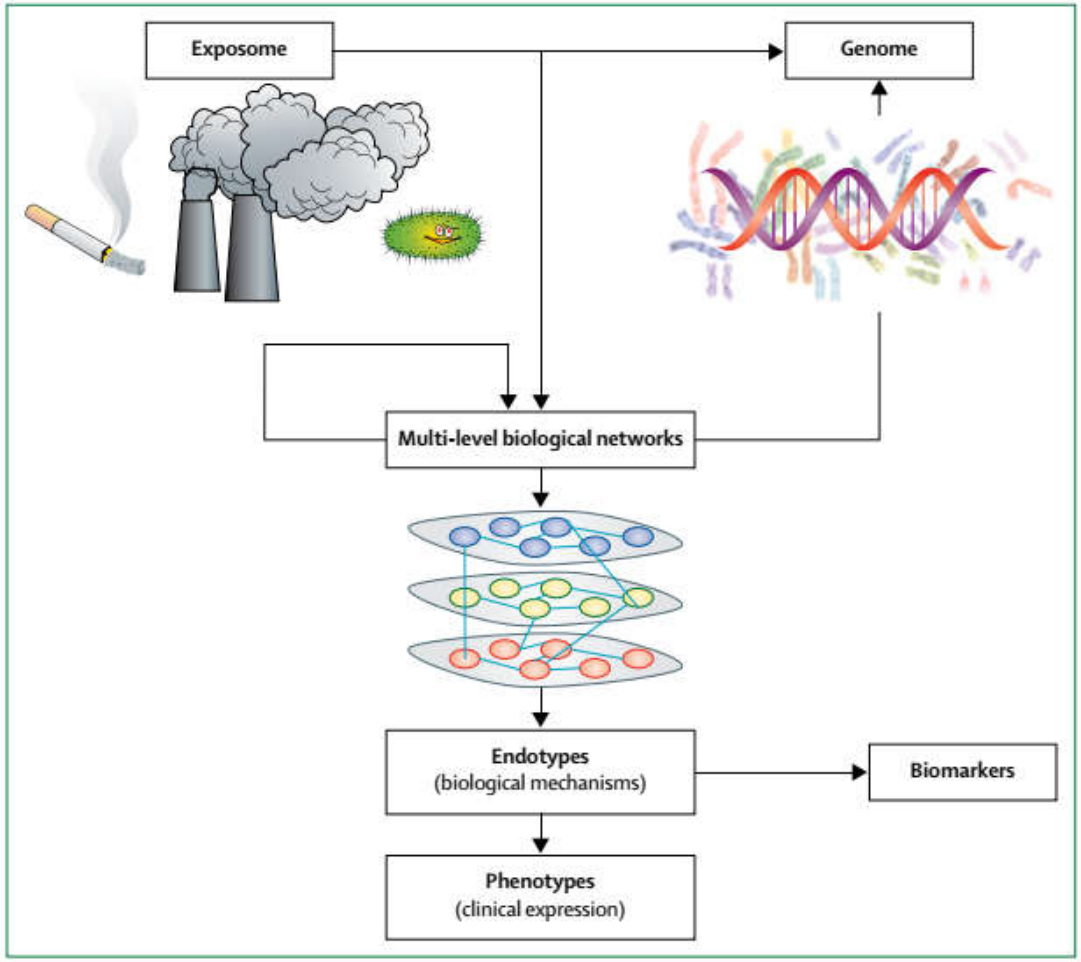


Figure 1: Associations between genes, environment, endotypes, biomarkers, and phenotypes

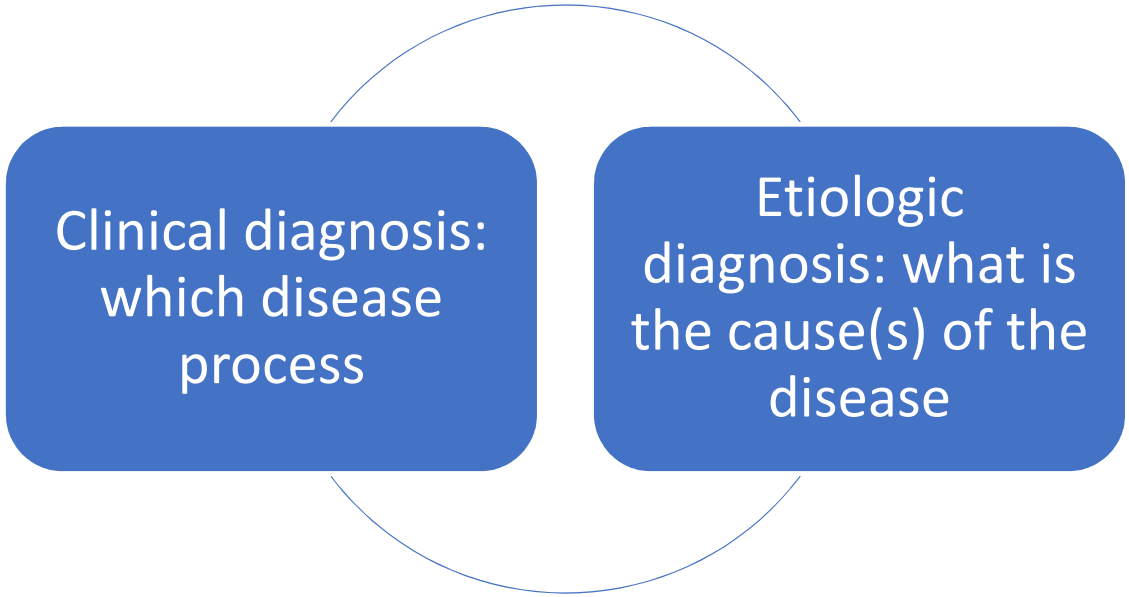
Agusti A, Celli B, Faner R. Lancet. 2017;390(10098):980-7.

General causality: Literature sources (systematic reviews) (some examples)

- Cancer:
  - International Agency for Research on Cancer (IARC) https://www.iarc.fr/
- International medical organizations:
  - European Respiratory Society
    - Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, et al. Guidelines for the management of work-related asthma. Eur Respir J. 2012;39(3):529-45.
    - Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. Eur Respir J. 2014;43(6):1573-87.
- National agencies
  - Arbejdsskadestyrelsen (DK)
    - Omland O, Wurtz ET, Aasen TB, Blanc P, Brisman JB, Miller MR, et al. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health. 2014;40(1):19-35.
- National regulations:
  - List of accepted causes of specific diseases (UK: «prescribed diseases»)

Part II
Specific causation-etiologic diagnosis

Diagnostic evaluation of patients in occupational medicine



Practical relevance of etiologic diagnosis

Base for prevention: primary, secondary and tertiary

(Prospective risk)

Base for evaluation of compensation

(Retrospective risk)

Specific causation – etiologic diagnosis

Possibility of etiologic diagnosis

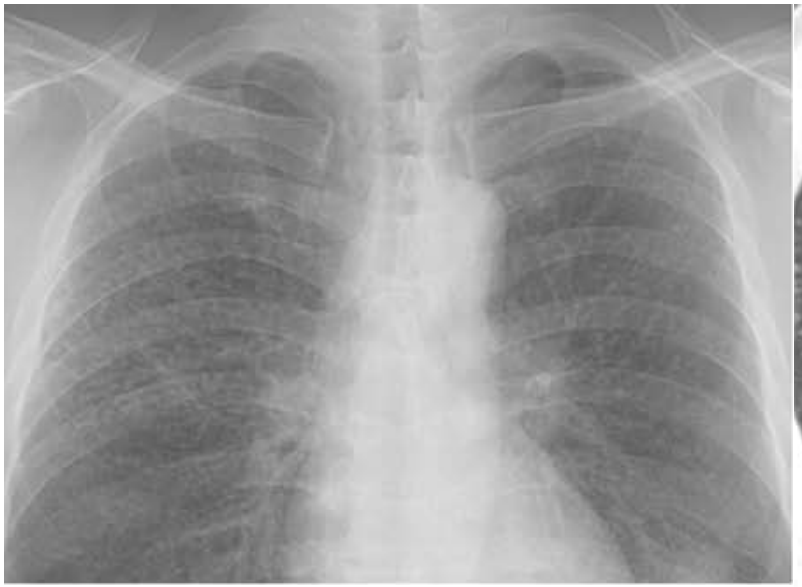
- Pathognomonic (or compatible) clinical picture
- Specific marker of disease
- Use of epidemiological evidence

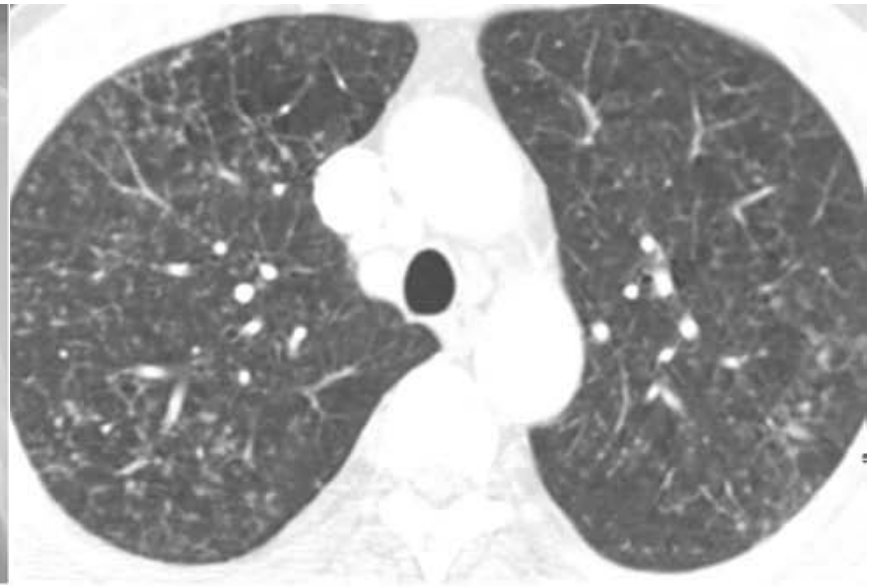
Important considerations in etiologic diagnosis uncertainty

What are the consequences of false positive and false negative diagnosis, for example interventions in occupational asthma:

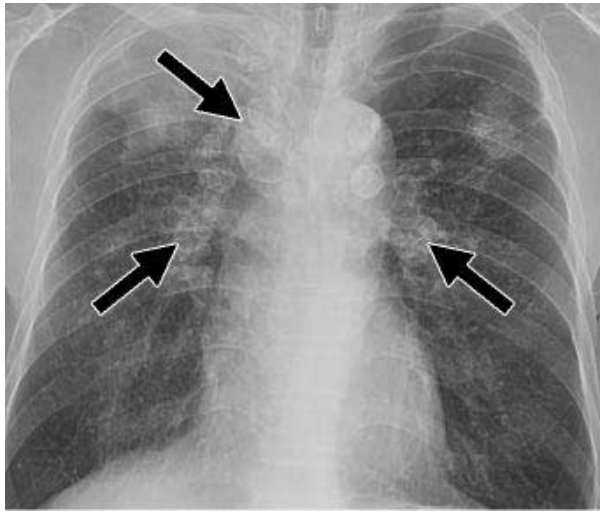
- False positive diagnosis: change to non-exposed occupation → financial loss (or compensation to the wrong applicants)
- False negative diagnosis: Continued exposure → worse prognosis

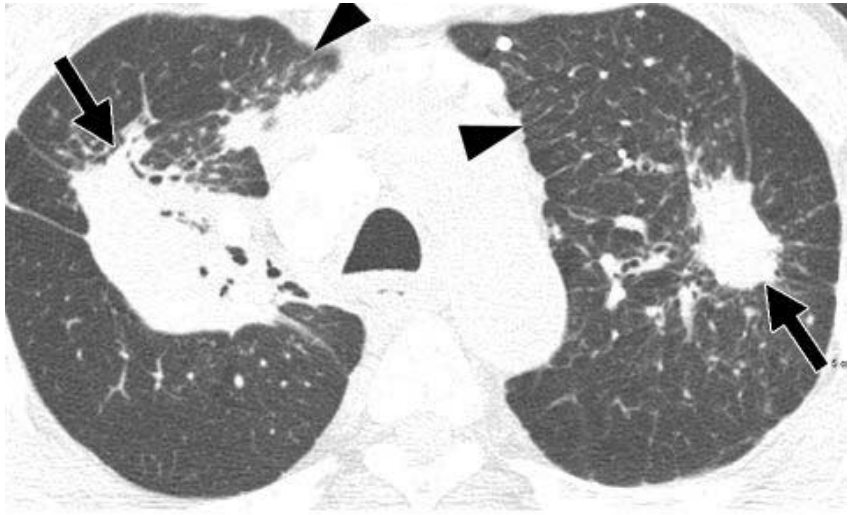
Interstitial lung disease I



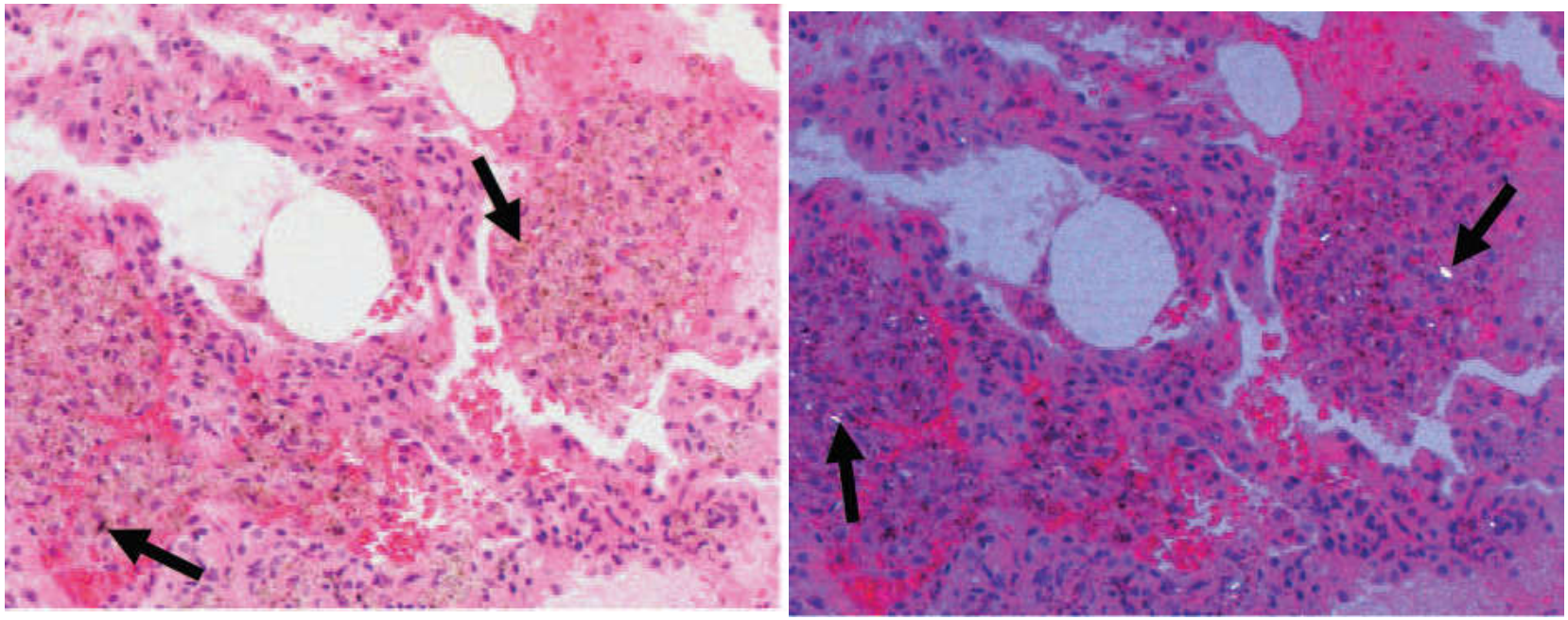


Interstitial lung disease II





Interstitial lung disease III



Silicosis in Swedish workers

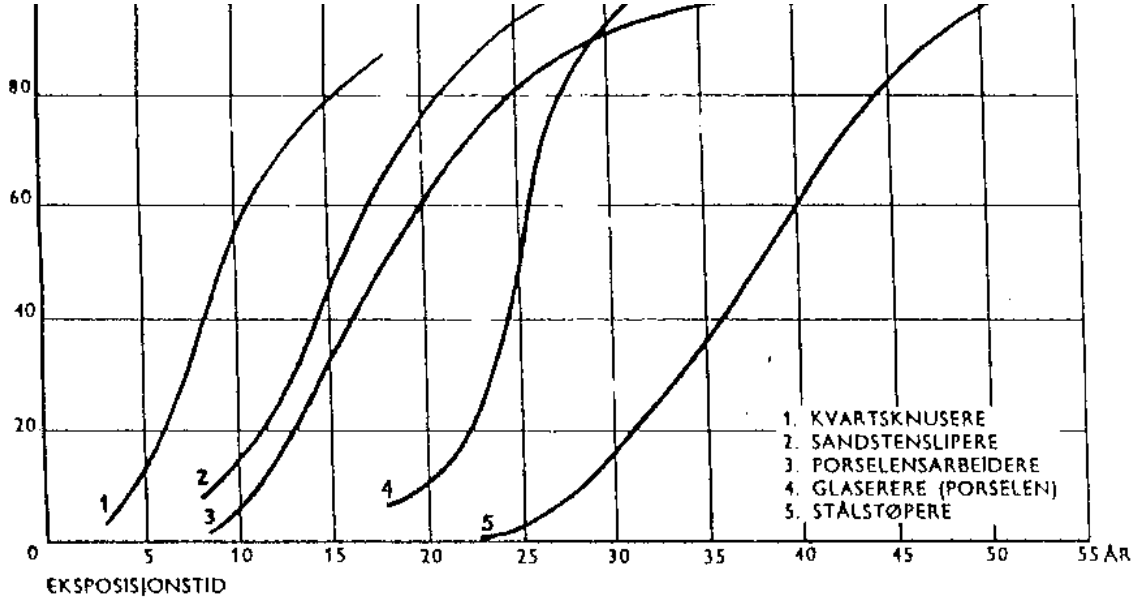


Fig. 94. Silikosefrekvensen hos arbeidere i forskjellige yrkr. Etter ca. 8 års eksposisjon har halvparten av kvartsknusere allerede fått silikose, mens halvparten av stålstøperne først får silikose etter ca. 37 års eksposisjon.

(Etter Ahlmark & Öhman.)

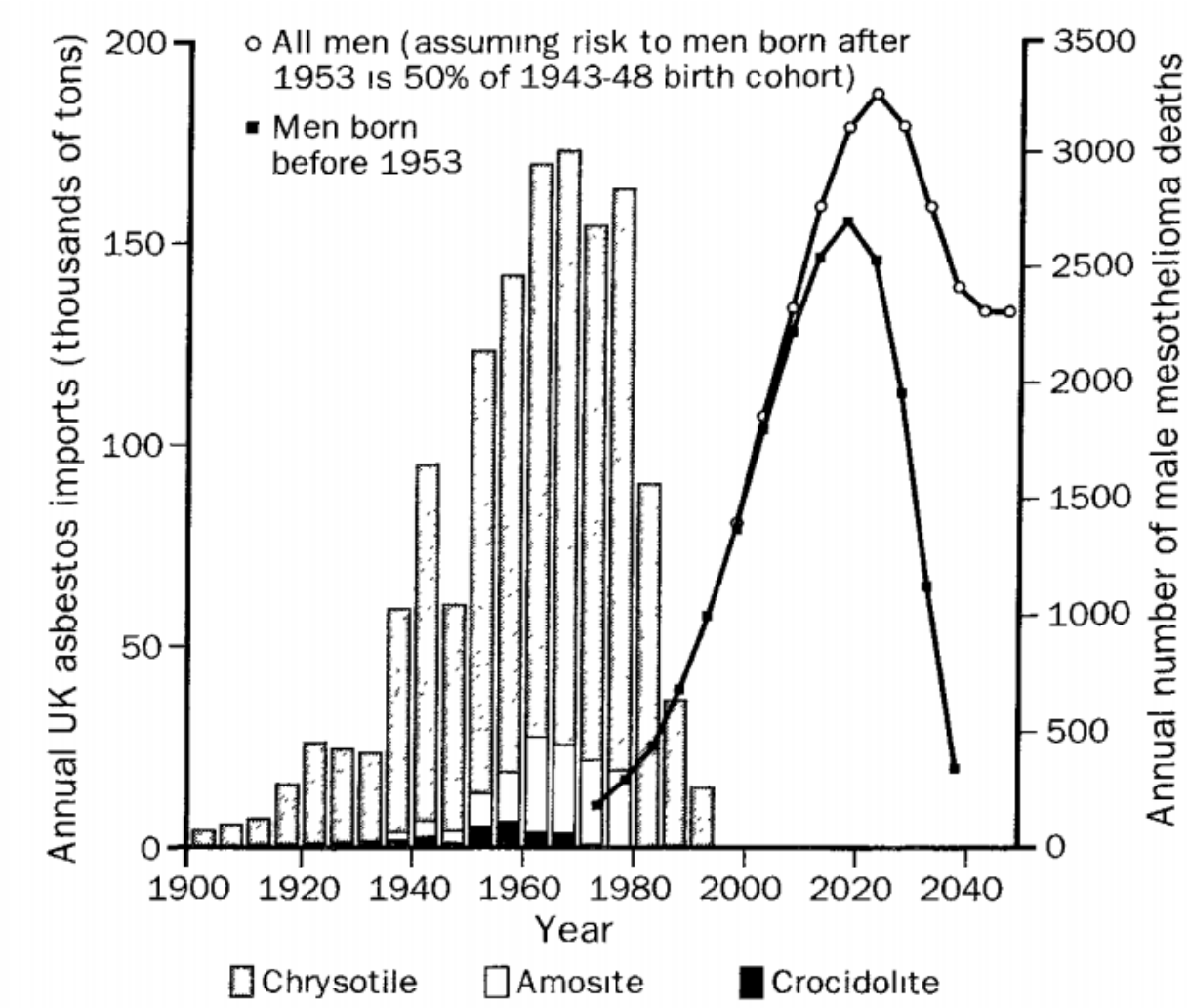


Figure 2: **Predicted mesothelioma deaths in British men and UK asbestos imports**

Peto J, Hodgson JT, Matthews FE, Jones JR. Continuing increase in mesothelioma mortality in Britain. Lancet. 1995;345(8949):535-9

Table 1. Classification of carcinogenetic agents according to the International Agency for Research on Cancer.

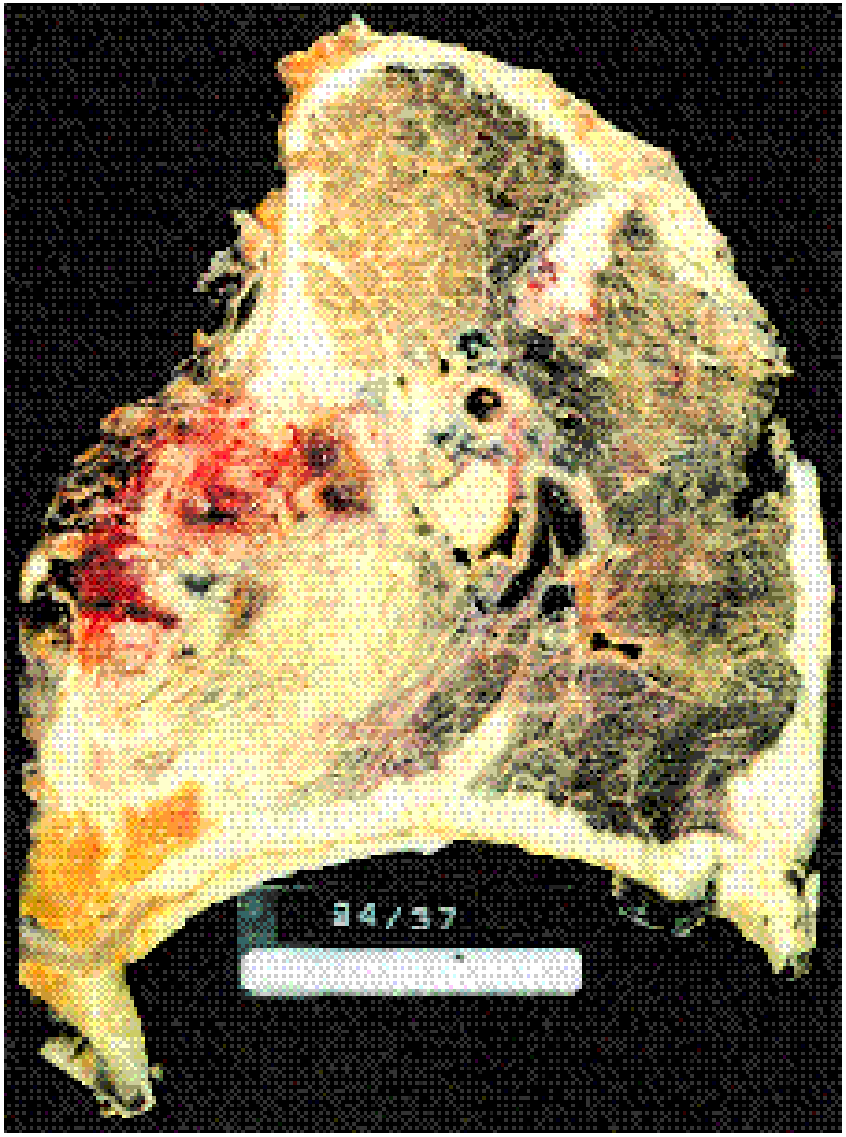
Group	Classification	Parameter	Number of agents
1*	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans and in experimental animals	111
2A	Probably carcinogenic to humans	Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals	65
2B	Possibly carcinogenic to humans	Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals	274
3	The agent is not classifiable as to its carcinogenicity to humans	Inadequate evidence of carcinogenicity in humans and in experimental animals	504
4	The agent is probably not carcinogenic to humans	Evidence suggesting lack of carcinogenicity in humans and in experimental animals	1

*An agent can be included in Group 1 in the absence of sufficient evidence for carcinogenicity in humans but there is sufficient data of carcinogenicity in experimental animals and strong evidence that the agent acts through a similar mechanism of carcinogenicity in humans.

Table 2. Carcinogenetic agents related with development of lung cancer according to IARC (first column: with sufficient evidence in humans; second: with limited evidence).

1. Aluminum production	1. Acid mists, strong inorganic
2. Arsenic and inorganic arsenic compounds	2. Art glass, glass containers and pressed ware (manufacture of)
3. Asbestos (all forms)	
4. Beryllium and beryllium compounds	
5. Bis (chloromethyl) ether; chloromethyl methyl ether (technical grade)	3. Biomass fuel (primarily wood),indoor emissions from household combustion of
6. Cadmium and cadmium compounds	
7. Chromium(VI) compounds	4. Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing
8. Coal, indoor emissions from household combustion	
9. Coal gasification	
10. Coal-tar pitch	5. Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work
11. Coke production	
12. Engine exhaust, diesel	
13. Hematite mining (underground)	
14. Iron and steel founding	6. Carbon electrode manufacture
15. MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	7. alpha-Chlorinated toluenes and benzoyl chloride (combined exposures)
16. Nickel compounds	
17. Painting	8. Cobalt metal with tungsten carbide
18. Plutonium	
19. Radon-222 and its decay products	9. Creosotes
20. Rubber production industry	10. Frying, emissions from hightemperature
21. Silica dust, crystalline	11. Insecticides, non-arsenical (occupational exposures in spraying and application)
22. Soot	
23. Sulfur mustard	
24. Tobacco smoke, secondhand	12. Printing processes
25. Tobacco smoking	13. 2,3,7,8-Tetrachlorodibenzopara-dioxin
26. X-radiation, gamma-radiation	
	14. Welding fumes

Spyratos et. Journal of thoracic disease. 2013;5 Suppl 4:S440-5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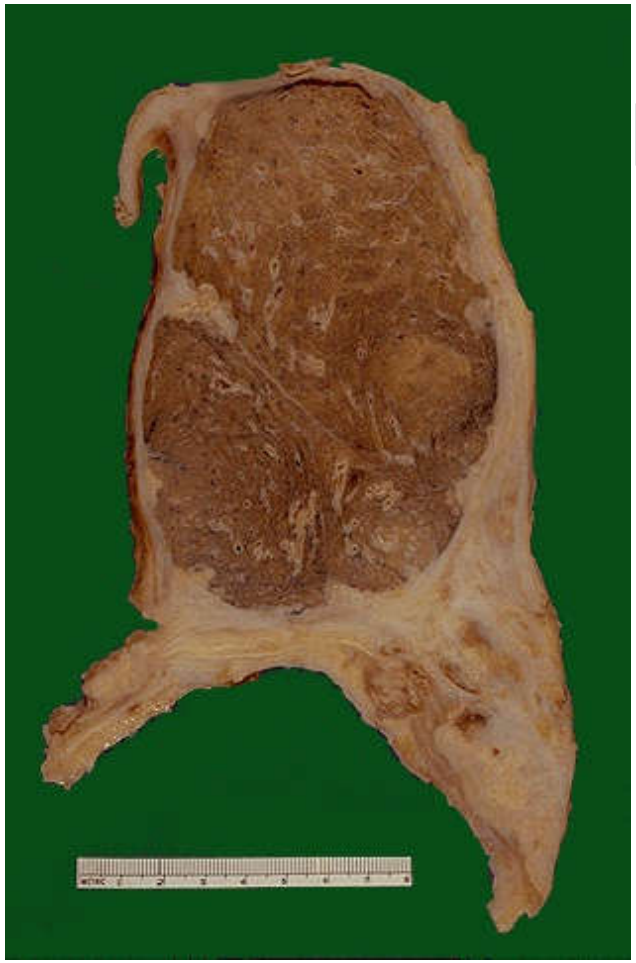
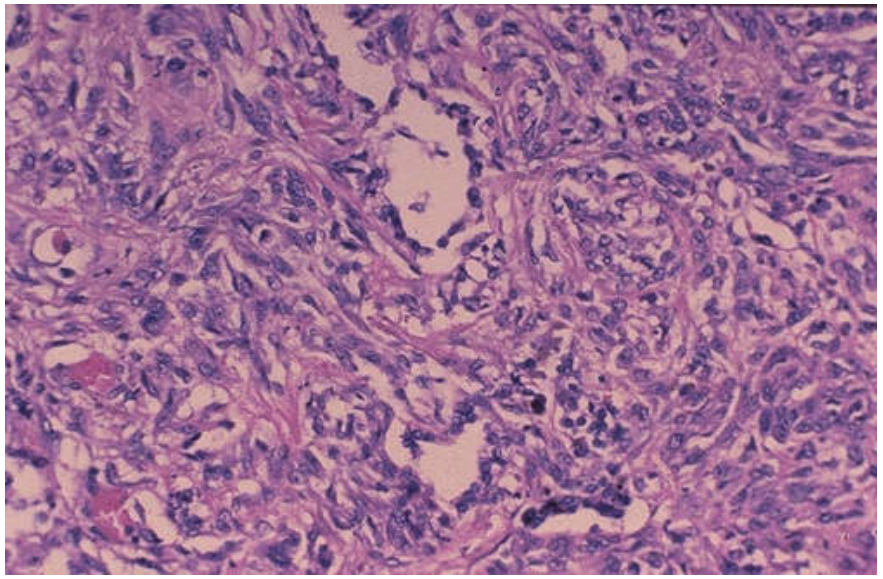


Mesothelioma



Work history

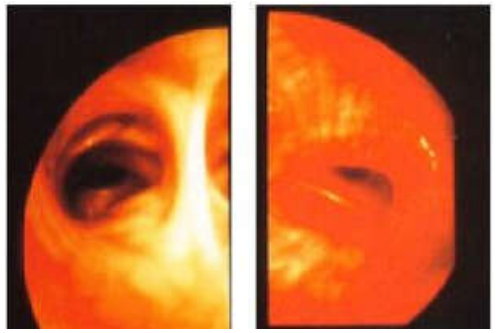
Measurement of airway calibre (at work and at home): Peak flow measurement

Allergy diagnosis

SIC – specific inhalation challenge

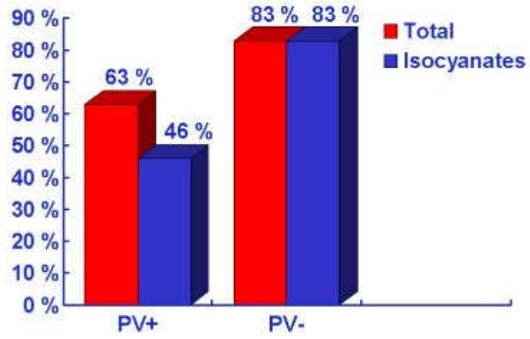
Etiologic diagnosis of asthma

Is the clinical history a satisfactory means of diagnosing occupational asthma?

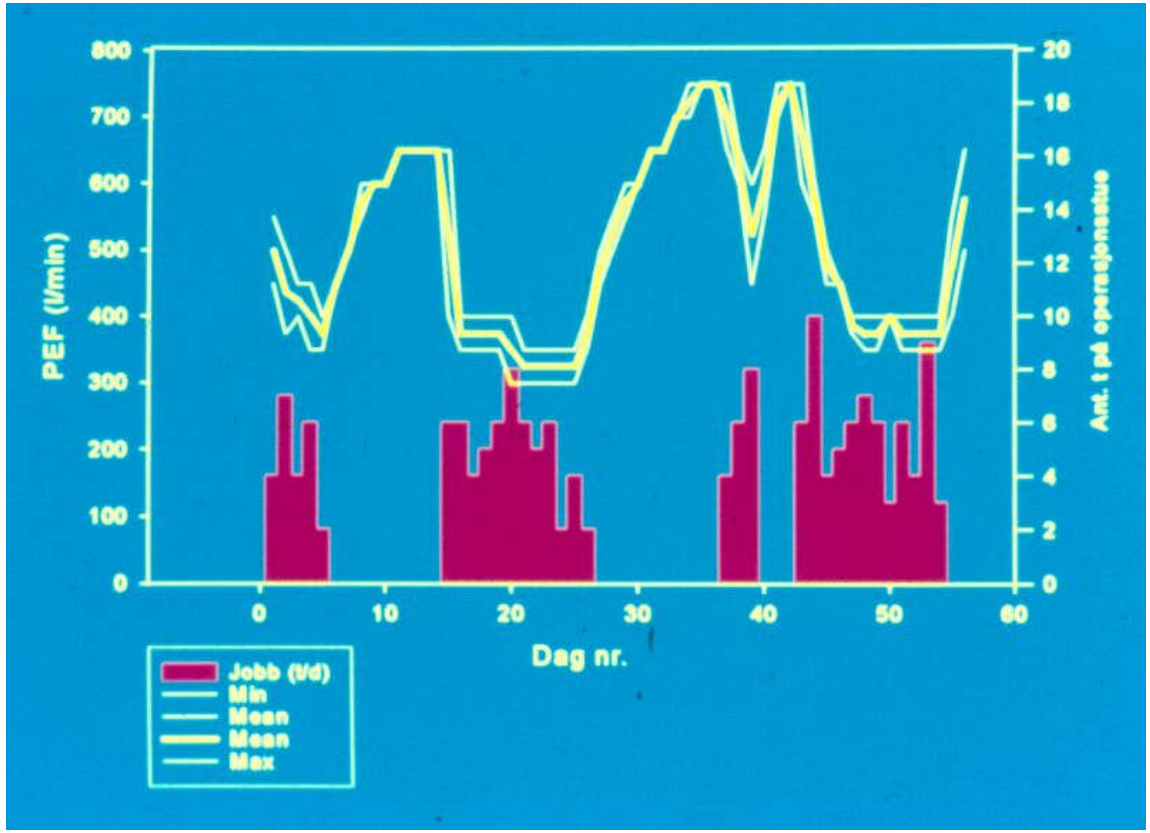


The predictive value of the clinical history (by experts) compared to objective methods

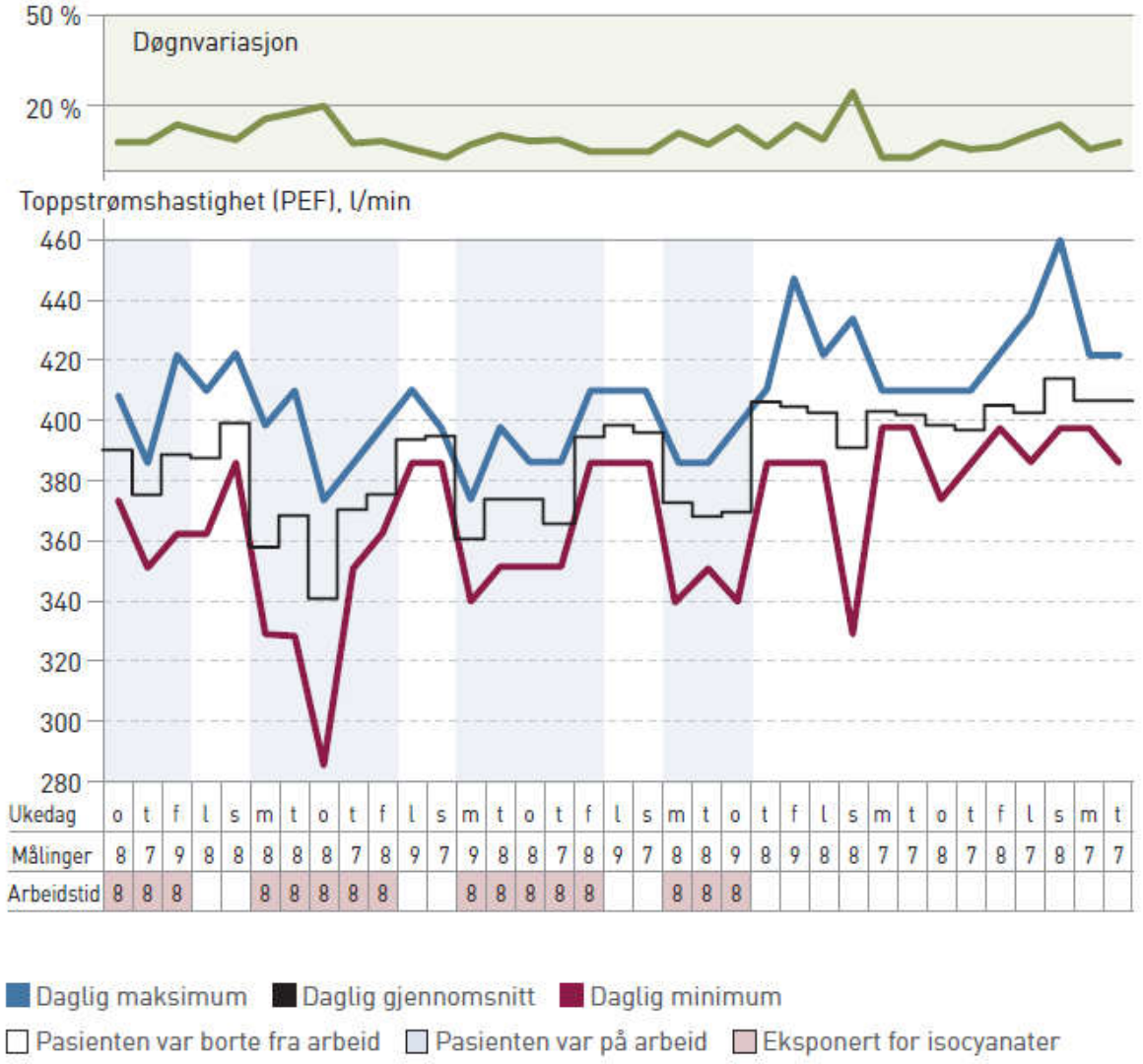
- Positive predictive value:
  - Total 63% (isocyanates 46%)
- Negative predictive value:
  - Total: 83% (isocyanates 83%)



Malo etal: Am Rev Respir Dis 1991;143:528-32


PEF (l/min)
800
700
600
500
400
300
200
100
0
20
18
16
14
12
10
8
6
4
2
0
Ant. t på operasjonsstue
0
10
20
30
40
50
60
Dag nr.
Jobb (t/d)
Min
Mean
Mean
Max

Aasen TB, Kongerud J. Arbeidsrelatert astma - diagnostikk og oppfølgning. Tidsskr Nor Laegeforen. 2014;134(20):1955-9.

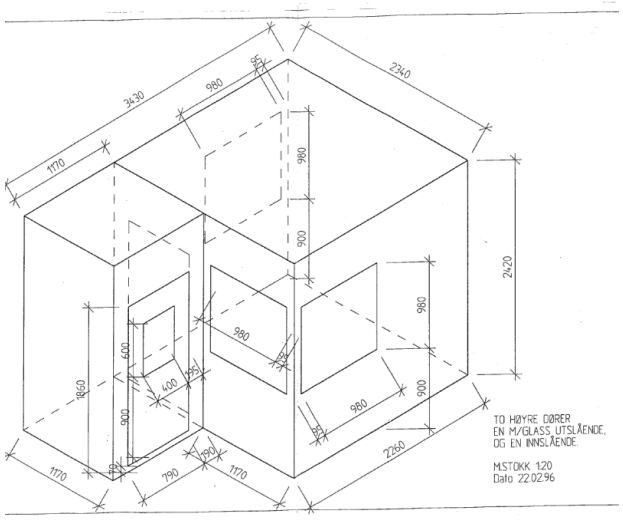


Figur 2 *PEF-registrering hos pasient som var eksponert for isocyanater. Her er markert høyeste, laveste og middelverdi for hver dag samt døgnvariasjon. Øverst er angitt døgnvariasjonen i prosent. Dager i arbeid er skravert. Registreringen taler for at det er en sammenheng mellom eksponering i arbeidet og PEF-variasjon. PEF-data er analysert med OASYS-programmet (16)*

National laboratory for SIC (specific inhalation challenge) in Norway

Yrkesmedisinsk Avdeling, Haukeland universitetsykehus, Bergen

Volum: 12,8 m^3



Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement

Olivier Vandenplas[1], Hille Suojalehto[2,17], Tor B. Aasen[3], Xaver Baur[4], P. Sherwood Burge[5], Frederic de Blay[6], David Fishwick[7,8], Jennifer Hoyle[8], Piero Maestrelli[9], Xavier Muñoz[10,11], Gianna Moscato[12], Joaquin Sastre[11,13], Torben Sigsgaard[14], Katri Suuronen[2], Jolanta Walusiak-Skorupa[15], Paul Cullinan[16,17] and the ERS Task Force on Specific Inhalation Challenges with Occupational Agents

Vandenplas O, Suojalehto H, Aasen TB, Baur X, Burge PS, de Blay F, et al. Specific inhalation challenge in the diagnosis of occupational asthma: consensus statement. Eur Respir J. 2014;43(6):1573-87.

When there is no test available for etiologic diagnosis, can we use attributable fraction as a measure of probability of causation?

Vurdering av årsaksforhold ved yrkesrelaterte lungesykdommer

En epidemiologisk tilnærming

Kjuus H, Hauge OA, Kongerud J, Aasen TB. Vurdering av årsaksforhold ved yrkesrelaterte lungesykdommer. En epidemiologisk tilnærming. . Tidsskr Nor Laegeforen. 1996;116(6):736-8.

En kvalifisert vurdering av årsaksforhold ved yrkesbetingede lungesykdommer forutsetter en korrekt medisinsk diagnose, en detaljert arbeidshistorie og oppdatert kunnskap om aktuelle årsakssammenhenger fra litteraturen. I slike vurderinger vil lungeleger og arbeidsmedisinere ha en komplementær ekspertise. Utredning av yrkesbetingede lungesykdommer i trygdemessig og forsikringsmessig sammenheng nødvendiggjør i tillegg eksplisitte metodevalg for årsaksberegninger før man meningsfylt kan gjøre forsøk på å vektlegge årsaksfaktorer i og utenfor arbeidsmiljøet. Dersom tilstrekkelig epidemiologisk kunnskap er tilgjengelig, kan årsakssannsynlighet, basert på «etiologisk fraksjon blant eksponerte» (tilskrivbar andel), være et egnet utgangspunkt for slik vektlegging.

Manifestasjoner ved yrkesrelaterte lunge-

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5460 Husnes

Johny Kongerud
Lungeavdelingen
Rikshospitalet
0027 Oslo

Tor B. Aasen
Yrkesmedisinsk avdeling
Haukeland Sykehus
5021 Bergen

Kjuus H, Hauge OA, Kongerud J, Aasen TB.
Work-related lung disorders
An epidemiological approach
to the assessment of causal relationships
Tidsskr Nor Lægeforen 1996; 116: 736–8

neringsspesifikk arbeidshistorie, samt oppdatert kunnskap av relevans for den aktuelle problemstilling.

Dette bildet kan gradvis bli endret i de kommende år. Sammenhengen mellom f.eks. asbesteksponering og lungekreft er godt dokumentert, der det med basis i epidemiologisk litteratur også skulle være mulig å foreta en grov bedømmelse av *økningen av risiko* forbundet med eksponeringen i et aktuelt tilfelle. I den grad slike data foreligger, vil man i tillegg til en rent skjønnsmessig vurdering, kunne foreta en vurdering basert på tilgjengelig epidemiologisk kunnskap om *kvantitative* sammenhenger mellom eksponering og effekt.

Dette kan i prinsippet gjøres på to forskjellige måter. Enten ved at man gjennom en samlet omfattende litteratur, kan fremskaffe tall for økning i risiko ved det eksponeringsnivå og den eksponeringslengde som er relevante for det aktuelle tilfellet (1). Eller at man med utgangspunkt i en gjennomført epidemiologisk undersøkelse med (semi)-kvantitative risikoestimater, foretar en vur-

Legal attitudes toward the use of epidemiological evidence in proof of specific causation: (use in British and American courts)

- that epidemiological evidence is irrelevant to proof of specific causation;
- that where only epidemiological evidence is available, normal causation rules may sometimes be relaxed, so increase in risk can satisfy the causation element;
- that the threshold for proof of specific causation using epidemiological evidence is RR > 2.

Broadbent A. Epidemiological evidence in proof of specific causation. Legal Theory. 2011;17(04):237-78.

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Reviews and Commentary

CONCEPTUAL PROBLEMS IN THE DEFINITION AND INTERPRETATION OF ATTRIBUTABLE FRACTIONS

SANDER GREENLAND[1] AND JAMES M. ROBINS[2]

Attributable fraction vs. excess fraction
(After: Greenland & Robins 1988)

R_e : risk of disease in exposed persons

R_u : risk of disease in unexposed persons

RR: relative risk $RR = \frac{R_e}{R_u}$

EF: excess fraction $EF = \frac{R_e - R_u}{R_e} = \frac{RR-1}{RR} = 1 - \frac{1}{RR}$

AF: attributable fraction is the fraction of cases that can be attributed to the exposure, consisting of:

1. Excess cases
2. Etiologic cases: cases where the exposure contributes to the disease, but that probably had occured finally without the exposure (but later)

Generally: AF≥EF

Problems with the attributable fraction

- The Exclusive Cause Fallacy:
  - The assumption that the number of cases caused by an exposure is exactly equal to the excess fraction: $EF=\frac{RR-1}{RR}$
- The Counterfactual Fallacy:
  - The assumption that if, hypothetically, an exposure was removed entirely, then the reduction of level of risk in the exposed population would equal EF.

What can epidemiological evidence prove??
(after Robins and Greenland)

Standard of evidence in many countries: probability of causation >50%

- It is wrong to hold that RR>2 as a necessary condition for and that RR<2 is evidence against specific causation
- However: RR>2 might be sufficient to prove specific causation («more likely than not»)

Yrkesskadetrygdens hovedårsakskrav og fordelingslære

Av Magne Strandberg og Tor Brøvig Aasen

Tidsskrift for erstatningsrett, forsikringsrett og velferdsrett. 2013;10(3):148-72.

Magne Strandberg (f. 1978) er førsteamanuensis ved Det juridiske fakultet, Universitetet i Bergen. Han underviser der i erstatningsrett og sivilprosess. Han disputerte i 2010 på avhandlingen «Beviskrav i sivile saker – en bevisteoretisk studie av den norske beviskravslærens forutsetninger». Han ga i 2005 ut boken «Skadelidtes hypotetiske inntekt – om erstatningsutmåling og bevis».

Tor Brøvig Aasen (f. 1946) er spesialist i lungesykdommer og indremedisin. Han er avdelingsdirektør ved Yrkesmedisinsk avdeling, Haukeland Sykehus.

A. Newman Taylor: The Prescription of Disease, 2006

The Hierarchy of Attribution

Causation		Example
• Accident	→	Acute inhalation accident
• Disease with specific clinical features	→	Occupational asthma
• Epidemiological evidence: By inference from population studies to individual case ("more likely than not")		
Easy	→	Mesothelioma
Difficult	→	Asbestos and lung cancer Coal and COPD

Rothman & Greenland 2005

Philosophers agree that causal propositions cannot be proved, and find flaws or practical limitations in all philosophies of causal inference.

Hence, the role of logic, belief, and observation in evaluating causal propositions is not settled.

Causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as a criterion-guided process for deciding whether an effect is present or not.

Am J Public Health. 2005;95:S144–S150

Conclusions

There are many different concepts of cause in use

The literature abounds with (statistical) associations. These are in general of limited practical use if they are not proven causal.

Knowledge of general causation is established for many exposures and disease in occupational medicine, but controversies persist.

Demonstration of specific causation is in general difficult and often controversial (with a few exceptions)