Introduction to

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Mechanisms in medicine
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1 What is EBM+?

EBM+ is a research programme which explores why and how evidence of mechanisms should have a more prominent role in evidence-based medicine (EBM).

Currently, EBM+ has two projects related to evidence of mechanisms:

Evaluating evidence in medicine. Funded by the UK Arts and Humanities Research Council. Kent, UCL, Amsterdam, Cambridge, Leiden, NICE and IARC.

Grading evidence of mechanisms in physics and biology. Funded by the Leverhulme Trust. Kent.

You can find us at http://ebmplus.org.

Project team:

Brendan Clarke. History and Philosophy of Medicine, University College London

Donald Gillies. Philosophy of Science and Mathematics, University College London

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Also PhD students and other network members.

A ‘mechanism’ might be:

- **A complex-systems mechanism**.

  IE Entities and activities organized in such a way that they are responsible for the phenomenon (Machamer et al., 2000; Illari and Williamson, 2012).

  EG The mechanism by which the heart pumps blood.

- **A mechanistic process**.

  IE A spatio-temporally contiguous process along which a signal is propagated (Reichenbach, 1956; Salmon, 1998).

  EG An artificial pacemaker’s electrical signal being transmitted along a lead from the pacemaker itself to the appropriate part of the heart.

- **A combination of the two**.

  EG The complex-systems mechanism by which the heart pumps the blood, the complex-systems mechanism of the individual’s pacemaker and the mechanistic process linking the two.

NB In a mechanism, organisation is often crucial:

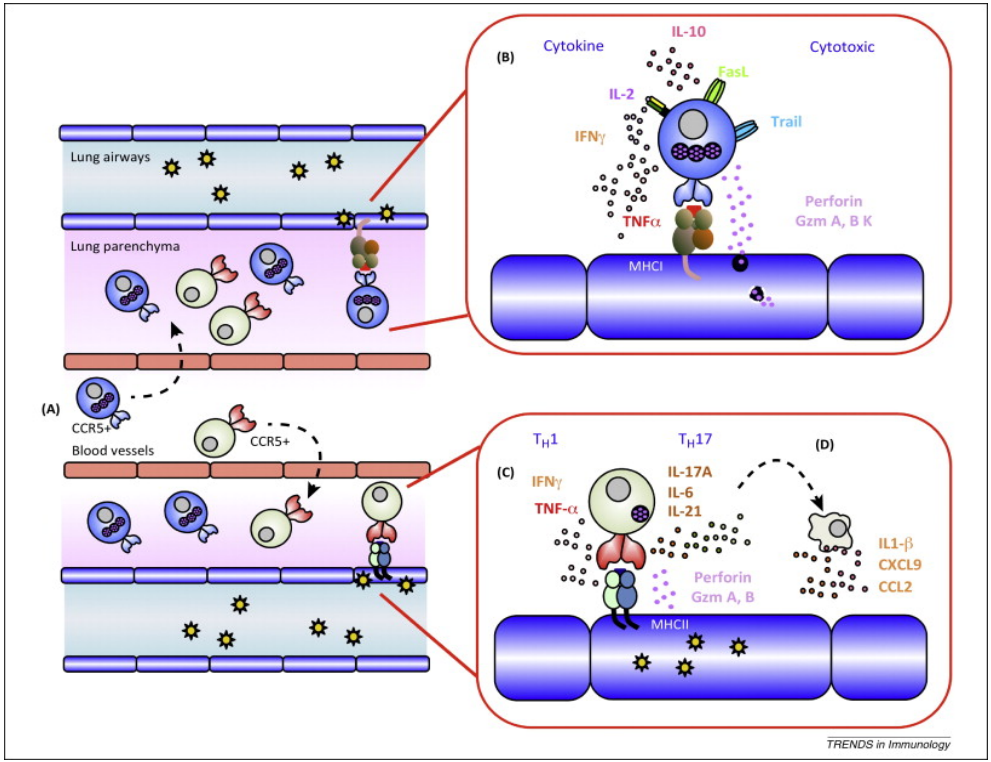


Table 1: Examples of sources of evidence of mechanisms in medicine

Direct manipulation: e.g., in *vitro* experiments
Direct observation: e.g., biomedical imaging, autopsy, case reports
Clinical studies: e.g., RCTs
Confirmed theory
Analogy: e.g., animal experiments
Simulation: e.g., agent-based models

> Evidence based medicine is the conscientious, **explicit**, and judicious use of current best evidence in making decisions about the care of individual patients. (Sackett et al., 1996)

Present-day EBM:

Hierarchies of evidence make the evaluation of evidence explicit:

- These value **clinical studies**.

NB A clinical study for the claim that A is a cause of B repeatedly measures A and B to estimate the extent to which they are correlated, conditional on potential confounders.

Evidence of mechanisms from other sources tends to be either:

- Ignored, or
- Relegated to the bottom of the hierarchy.

Figure 1: SUNY Downstate Medical Center.

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

Figure 2: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (OCEBM Levels of Evidence Working Group, 2011).

2 Why take evidence of mechanisms seriously?

Evidence of mechanisms is useful when:

- Evaluating efficacy,
- Evaluating external validity,
- Drawing inferences about a single individual (for treatment and personalised medicine),
- Commissioning new research and devising new research funding proposals,
- Designing clinical trials and interpreting their results,
- Suggesting and analysing adverse drug effects,
- Designing drugs and new devices,
- Modelling cost effectiveness of a health intervention,
- Deciding how surrogate outcomes are related to outcomes of interest.

Efficacy. Correlation is not enough on its own; a correlation between A and B might be due to:

Causation	A is a cause of B.
Reverse causation	B is a cause of A.
Confounding (selection bias)	There is some confounder C that has not been adequately controlled for by the study.
Performance bias	Those in the A-group are identified and treated differently to those in the $\neg A$-group.
Detection bias	B is measured differently in the A-group in comparison to the $\neg A$-group.
Chance	Sheer coincidence, attributable to too small a sample.
Fishing	Measuring so many outcomes that there is likely to be a chance correlation between A and some such B.
Temporal trends	A and B both increase over time for independent reasons. E.g., prevalence of coeliac disease & spread of HIV.
Semantic relationships	Overlapping meaning. E.g., phthiasis, consumption, scrofula (all of which are TB).
Constitutive relationships	One variable is a part or component of the other.
Logical relationships	Measurable variables A and B are logically complex and logically overlapping. E.g., A is $C \wedge D$ and B is $D \vee E$.
Physical laws	E.g., conservation of total energy can induce a correlation between two energy measurements.
Mathematical relationships	E.g., mean and variance variables from the same distribution will often be correlated.

If it is genuinely the case that A is a cause of B, then

- There is some combination of mechanisms that explains instances of B by invoking instances of A and which can account for the magnitude of the observed correlation.

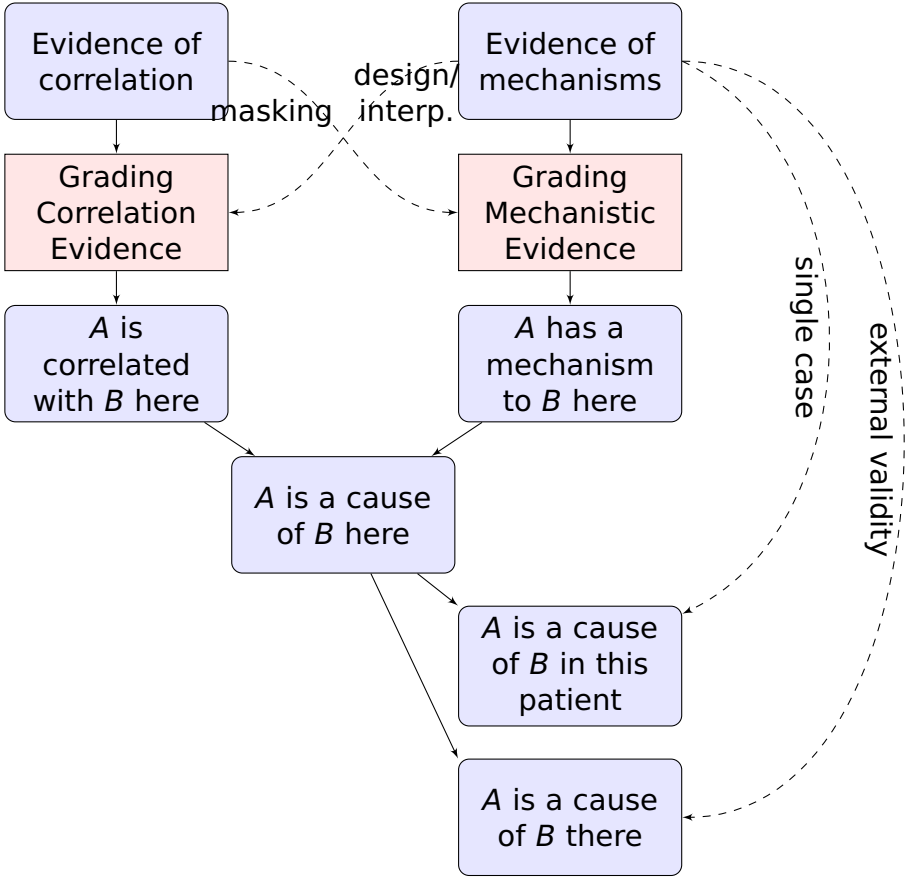
$\therefore$ In order to establish efficacy one needs to establish both:

- The existence of an appropriate correlation.
- The existence of an appropriate mechanism that can explain that correlation.

More generally, evidence of mechanisms can help rule in or out many of the possible explanations listed in the above box.

EG It can help to determine:

- The direction of causation,
- Which variables are potential confounders,
- Whether a treatment regime is likely to lead to performance bias,
- Whether measured variables are likely to exhibit temporal trends.



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Some of our research

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Michael Wilde & Jon Williamson: Models in medicine, in H. Kincaid, J. Simon & M. Solomon (eds), The Routledge Companion to Philosophy of Medicine. In press.

3 How can one take evidence of mechanisms seriously?

Procedure:

1. Identify evidence of mechanisms in the literature.
2. Evaluate evidence of mechanisms.
3. Use evidence of mechanisms to evaluate efficacy and external validity.

See the next talk . . .

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