Mechanisms in Medicine

Phyllis Illari

What is a mechanism?

The idea of mechanisms, and how they are used in the sciences, is something that has been explored since 1993 in what is often regarded as the core mechanisms literature, focusing on the life sciences and the sciences of mind and brain (Bechtel & Richardson 1993; Glennan 1996; Machamer, Darden and Craver (MDC) 2000), and since 1983 in philosophy of social sciences (Elster 1983, Hedström & Swedberg 1998).

Probably the most well-known current characterization of a mechanism is: "Mechanisms are entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions." (Machamer *et al*., 2000: 3.) The paradigm mechanism that MDC discuss is that of protein synthesis, which explains how cells make proteins. For this case, they say, entities include "the cell membrane, vesicles, microtubules, molecules, and ions," and activities include, "biosynthesis, transport, depolarization, insertion, storage, recycling, priming, diffusion, and modulation." (Machamer *et al*., 2000: 8.) There have been various alternative characterizations (Glennan 2002; Bechtel & Abrahamsen 2005), and Illari and Williamson offered the following simplified account: "A mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon." (2012: 120.) Illari and Williamson argue that this captures an emerging consensus within the mechanisms literature, and show how the account can be interpreted fairly broadly to avoid excluding key mechanisms (compare the closely similar formulations of Craver 2007, and Glennan 2008, 2009).

Simply put, then, finding a mechanism explains a phenomenon by finding local parts, and discovering what they do and how they are organized to produce the phenomenon. In medicine, we seek to discover mechanisms of disease and of cure. A great deal of this work

depends on our existing knowledge of bodily mechanisms, of which protein synthesis is an important example.

What is evidence of mechanism in medicine?

To explain disease, we seek at least some *evidence* of mechanisms of disease and of cure. A paradigm kind of evidence of mechanism is probably use of breakthrough technologies, such as Franklin's X-ray crystallography photograph of DNA, which help us study entities we could not study directly before and understand their activities and how they are organized. Franklin's work was famously used by Watson and Crick to describe the structure of DNA, which is now central to our understanding of thousands of cellular mechanisms. In general, finding and understanding new entities and their activities, of which bacteria and viruses may well be the most famous examples, has been important in the history of medicine, and no doubt will continue to be so.

Finding entities might be important, but a huge variety of other scientific work might count as finding evidence of mechanism: anything that helps us identify or better understand entities, activities, and their organization, including simulating organization of complex mechanisms, might count as finding evidence of mechanism. (See Bechtel & Richardson 1993 and Darden & Craver 2013 for extensive discussion.) It is worth noting that the literature often recognises two kinds of mechanisms. The first kind is mechanisms that consist of entities and activities *underlying* a phenomenon of interest (called 'constitutive' by Craver 2007; and 'vertical' by Kincaid 2011, 2012). For example, we observe that cells make proteins and identify the activities of DNA, RNA, and ribosomes as the mechanism underlying this phenomenon. The second kind is mechanisms that consist of intermediate *links* between a posited cause and its effect (called 'etiological' by Craver 2007; and 'horizontal' by Kincaid 2011, 2012). Taking the example of protein synthesis again, we might suspect that an

alteration in DNA affects which proteins are produced, and try to identify the intervening entities and activities by which the cause leads to the effect. This distinction in kinds of mechanism can be important for some purposes (see Kincaid 2011, 2012), but in some cases it might not much matter: if we cannot really tell what kind of mechanism we are examining given what we know. Suppose we are investigating little known mechanisms of protein synthesis, trying to identify new entities or activities, then we might make the same methodological choices whether we think of ourselves as identifying a constitutive/vertical mechanism underlying this phenomenon, or finding an etiological/horizontal mechanism linking cause and effect. It might only be possible to use this distinction in practice for cases where the mechanisms in question are unusually well known.

In the face of the variety of kinds of evidence of mechanism, I will simplify this short piece by focusing on a single case: that of breast cancer. This case is unusual, in that evidence of mechanism is used very intensively, but, for this reason, it serves well to illustrate the points, so that they can be applied to thinking about less clear cases.

Although the breast cancer population is large, it is non-homogenous. Not all breast cancers develop in the same way, or respond to treatment in the same way. There is no single mechanism of disease. There are important differences among cancerous cells, differences among tumors as to how they develop and grow, and, as is common, differences in individual patient positive response to treatment versus toleration of toxicity. These differences are crucial to our understanding of the disease, to understanding that there are multiple related mechanisms of breast cancer, with different prognoses.

We can now get effective evidence of these different mechanisms at the cellular level, even in individual patients. Most notably, we can take biopsies and type breast cancer cells according to the proteins expressed on their surfaces. This has been enormously helpful in

understanding possible mechanisms of *cure* (or inhibition). Designing drugs that target particular proteins has led to enormously improved treatment in 80-85% of cases of breast cancer, because it helps to get drugs to harm cancerous cells and not healthy cells. The protein targets become a crucial access point for an effective mechanism of cure.

The other side of this success story is the remaining 15-20% of cases, called 'triple negative breast cancer' (TNBC). Clinically, "[t]riple--negative breast cancers are defined as tumors that lack expression of estrogen receptor …, progesterone receptor …, and HER2." (Foulkes *et al*.: 1938.) Although TNBC is more common in younger women, it has a poor prognosis, as we have no drugs that will effectively target it. The search to better understand these mechanisms of disease, and design effective mechanisms of cure, will continue. Improving treatment of breast cancer is dependent on this ongoing, extensive, largely laboratory-based, determination of mechanism.

Integrating evidence of mechanism with other evidence in medicine

Explaining disease is of course intellectually valuable, but it is not the only aim of medicine. As in breast cancer, in wider medicine we want to act. In this section, I will draw attention to the many things we want to know in medicine in order to act effectively, and begin to illustrate how this leads us to use evidence of mechanism alongside other evidence, most notably randomized controlled trials (RCTs, see chapter 19).

In medicine, we want to know what causes disease, certainly, but this is not simple, nor is it the only task (see interesting details in Dawid 2000; Kincaid 2011, 2012). Notice that we also want to know how we can treat people, to prevent disease or cause cure, which is not quite the same as knowing what causes disease. Further, we frequently want to know *how* a particular agent causes a disease, or how a drug works, which is often explicitly described as finding the mechanism of disease causation, or of cure.

We also want to know other things, which may be more or less important under varying circumstances. In many cases, quantities matter. For example, we need to know effective dosage of drugs, or what levels of radiation are safe. We also want to know various things about the human population we intend to treat. Are some people more at risk? For example, some drugs must not be given to pregnant women. Ultimately, patients and their doctors have to assess what is the best treatment for one particular person.

Mechanisms are directly involved in explaining how disease is caused, but knowledge of mechanisms can also help with these other tasks. To succeed in these tasks, we use evidence of mechanism alongside other sources of evidence. Many philosophers have advocated something like a requirement of 'total evidence' (Carnap 1962; Hempel 1965) in science more broadly. This requires us to bring to bear all available evidence on scientific problems, and acknowledge that, in science, any study is fallible. All studies have some weaknesses. This means that the best we can do in investigating any particular disease, or possible treatment, is use a variety of kinds of studies, kinds of experimental work, and different sources of evidence. We hope that, at the very least, they have *different* kinds of weaknesses, and should not all display the *same bias*. When this is true, and a variety of different studies agree, we can have much more confidence in the outcome (Haack 1993; Wimsatt 2007).

This requirement of total evidence does not seem to accord with privileging a single kind of tool or study. Randomized controlled trials (see chapter 19), where the study population is randomized to treatment and control groups, are often treated as our 'gold standard' of medical evidence (Cartwright & Munro 2010). RCTs are rightly valued for careful protocols, which, if carefully followed, restrict the influence of bias and unknown confounders on the outcome, both accidental (perhaps due to doctors and patients having faith in the new treatment), and non-accidental (such as fraud). RCTs are an important tool, although, for practical or ethical reasons, they cannot be used in many cases.

Important tool that they are, as we noted above, RCTs, like any evidence, should not be used alone. And indeed they are not. Whether running an RCT (or indeed an observational study), you have to make a variety of decisions that cannot themselves be decided by an observational or experimental clinical study. You have to decide what variables you will include in your study and how you will measure them – many medical studies depend heavily on decisions about diagnosis of disease, and judgment of cure or of disease progression. You have to decide how long to run a trial for: 12 weeks, 6 months, or 5 years? When these questions are raised, they are often treated as either simply part of the RCT, or as based merely on 'preclinical trials' or on 'background knowledge.' But we can do better than this – we can recognize that justified choices of these kinds can be based on our best evidence for the mechanism of disease causation, and possible mechanism of cure. That understanding should inform diagnosis, judgment of cure or disease progression, and decisions about how long patients need to be followed up for.

To illustrate, these kinds of decisions had to be made to run a Phase 2 trial of iniparib as an initially promising treatment for TNBC. Diagnosis of disease was performed by typing cells from biopsies, but judgment of successful treatment was difficult for this trial. Sadly, unambiguous complete cure was not expected, which meant the trial designers had to define what they would count as relevant outcomes. The authors explain: "Primary end points were the rate of clinical benefit (defined as the percentage of patients who had a complete response, a partial response, or stable disease for at least 6 months), as well as safety and tolerability of iniparib. Secondary end points were the overall rate of response and progression-free survival, defined as the time from randomization to confirmation of disease progression or death. Overall survival (defined as the time from randomization until the date of death) was not prespecified as an end point but was analyzed to explore the potential effect of iniparib on survival." (O'Shaugnessy et al., 2011: 207.) The study required, of course, a

way of assessing progression-free survival: "Tumor response was based on investigator assessment of target and nontarget lesions and was assessed by means of computed tomography or magnetic resonance imaging at baseline and every 6 weeks thereafter, in the absence of clinically evident disease progression." (O'Shaugnessy et al. 2011: 207.) The variety of outcomes specified was based on our knowledge of the usual mechanisms of disease progression, and what could reasonably be hoped for from the treatment being tested. Further, the trial used what technologies it could to track the underlying mechanisms of disease progression, such as the growth of the tumor, by examining the tumor using computed tomography or magnetic resonance imaging to give an assessment of patient response that was as objective as possible. Evidence of mechanism of disease progression was used here on an individual patient basis.

Evidence of mechanism can also be very helpful for an important group of tasks once trials have been completed: extending the results of studies to non-study populations. This can include wider patient populations, overseas populations, important sub-populations, or even decisions about one single case. An observational study or even RCT does not in itself contain information about *who else* the results of that study might – or might not – apply to. (Steel 2007 discusses the 'extrapolator's circle'; Cartwright 2012 presses the worry of 'external validity', see chapter **.) Evidence of mechanism cannot solve these problems entirely, but it can help us make judgments.

For example, in the case of breast cancer, evidence of mechanism tells us how crucial the cellular differences are to treating sub-populations of cases. This lets us know that typing the cells from a biopsy is likely to be more important to whether a patient will respond to a treatment designed to target that particular protein than whether a patient lives in the UK or the US. Of course, this does not exclude other differences being relevant to patient response.

In sum, there are multiple tasks in assessing disease causation in medicine, and in choosing sensible treatments. Evidence of mechanism is frequently helpful. In general, it is not possible to make really justified choices for all of these vital decisions without investigating what evidence there may be of mechanism of disease causation or cure.

Assessing evidence of mechanism

All these tasks are involved when putting together kinds of evidence to decide, overall, what to conclude on the basis of multiple studies about any possible treatment, which is the responsibility of many public bodies worldwide. For example, in the US, the Food and Drug Administration is the agency responsible for assessing drugs for safety and efficacy to decide whether their sale should be permitted in the US. The National Institute for Care and Health Excellence in the UK is responsible for assessing treatments for effectiveness versus cost, to say which treatments will be paid for by the UK National Health Service (see National Institute for Care and Health Excellence 2014). The International Agency for Research on Cancer is tasked with categorizing carcinogens (see International Agency for Research on Cancer 2006). These and many other agencies convene panels or committees to assess all the evidence available on particular medical treatments.

Knowledge of mechanisms can help us perform this kind of assessment. But we do not simply either know a complete mechanism, or know nothing whatsoever about the mechanism. We need to assess in a more nuanced way than this what kind of evidence of mechanism we have. In this section I will illustrate how we can have different amounts of evidence of mechanism by describing three different 'levels' of evidence of mechanism one might have. I draw heavily on collaborative work with Brendan Clarke, Donald Gillies, Federica Russo and Jon Williamson (summarized in Clarke *et al*. 2014).

The main point is that *evidence* of mechanism must amount to more than a hypothesis about a possible mechanism, but need not amount to complete knowledge of a mechanism. Suppose you are on an evidence panel assessing whether a particular drug (*Drug)* causes a cure (*Cure*) of a particular disease. Consider that there are at least three different levels of evidence of mechanism you might have:

1. Evidence that there is a particular mechanism explaining a link between *Drug* and *Cure*.
2. Evidence that there is some kind of mechanism or other explaining a link between *Drug* and *Cure*.
3. Evidence that there is no mechanism explaining a putative link between *Drug* and *Cure*.

We are very seldom in the position where we know the complete mechanism in medicine. However, all three levels above are feasible, and they can all be incredibly useful.

In reverse order, homeopathy is often considered a case of level 3. Ultimately our major reason for considering homeopathy ineffective is that everything that we understand of the physical chemistry of water suggests that homeopathy's posited mechanism of action cannot work; that water does not have a 'memory' in the relevant sense. Notice that this evidence is not narrowly of the posited mechanism, but is much broader, as the physical chemistry of water structures what we know about many other mechanisms in the domain. Ultimately, of course, this is an application of other scientific knowledge, which should not be treated as permanently infallible. We cannot know how our understanding of the physical chemistry of water will develop in the future.

A particularly important case of level 2 is the discovery of the mechanism of the disease tetanus. Tetanus was puzzling, as the disease seemed to involve infection at a wound site, causing effects distant in the body. When we discovered that the mechanism of action was due to a protein that travelled around the body, and isolated the protein, it was an enormous

leap forward, even if we did not know the full mechanism. Faced with a different puzzling disease, it is then sensible to ask whether there might be another mediating protein, and search in turn for evidence of its action. This is reasoning from analogy. Isolating that protein, and identifying other entities and activities in the mechanism, shifts the evidence from level 2 to level 1.

Whether you require evidence of level 3, 2 or 1 is highly contextual. It depends heavily on how much you know about the domain in question, and on your purposes. In a public health emergency involving a largely unknown domain, a public body might regard level 3 as enough to proceed to trials. When considering a very well-known domain, a drug company might require something closer to level 1, such as identification of a drug target in a well-known mechanism of disease causation, and laboratory evidence that the drug is effective against that target, before funding expensive trials.

Ultimately, both scientists and evidence panels put evidence of mechanism together with evidence from clinical trials to make decisions about treatment. I will illustrate the use of evidence of mechanism through the rest of this chapter by looking in more depth at two trials of iniparib as a treatment for TNBC: the earlier trial seemed promising (O'Shaugnessy *et al*. 2011), while a later and larger trial showed no significant benefit (O'Shaugnessy *et al*. 2014).

The reason to test iniparib as a possible treatment was dependent on lab-based evidence of mechanism: in this case, pretty well known general mechanisms of cancer causation, combined with reasoning from analogy from the mechanisms successfully designed to target 80% of cases of breast cancer, to search for a drug which may be effective on at least some cases of TNBC. The broad outline of cancer causation is well known. DNA is constantly subject to damage, but cells have multiple DNA repair mechanisms. The ultimate defense

against cancer is when unrepairable cells undergo programmed cell death. Only when this, too, fails, do cells begin replicating out of control, which is to say, become cancerous.

The standard treatment used for TNBC is chemotherapy, which aims to kill cancerous cells, but has significant toxic effects on healthy cells. Iniparib was designed as a possible new mechanism of cure, to try to increase the effectiveness of chemotherapy. Cancerous cells also have to repair their own DNA to stay alive when they are under attack by treatments such as chemotherapy. Iniparib inhibits PARP (poly(adenosine diphosphate–ribose) polymerase), and inhibiting PARP was found to increase the frequency of double-strand breaks in DNA (Carey and Sharpless 2011: 277). TNBC cells were thought to be particularly susceptible to double-strand breaks killing them (O'Shaugnessy et al. 2011: 205). Finally, lab evidence suggested that iniparib would work well with chemotherapy drugs: "Although the full mechanism of its antitumor activity is still under investigation, iniparib enhances the antiproliferative and cytotoxic effects of …[chemotherapy drugs] in in vitro models of triple-negative breast cancer." (O'Shaugnessy et al. 2011: 206.)

What was hypothesized here was a way to interrupt a known mechanism of disease causation (level 1), piggybacking on known mechanisms of cure (level 2-1), using a new substance, iniparib, the action of which had been confirmed in lab-based preclinical trials (level 2). Put simply, available evidence and reasoning about mechanism were used to design iniparib to set up the cancerous cells so that the chemotherapy would wipe them out – making the chemotherapy far more toxic to cancerous cells than to healthy cells.

This illustrates, then, how useful evidence of mechanism can be, in this case for the task of continuing the search for treatments of a disease that currently has a very poor prognosis. It also illustrates how evidence of a solitary mechanism is not generally used in an isolated way, but integrated with other availably mechanistic knowledge. In the final section, we will turn

to examining problems of evidence of mechanism, and looking more carefully at how evidence of mechanism is put together with evidence generated by clinical trials. Iniparib will also be used to illustrate this – promising as it seems, as of 2014, iniparib does not work in clinical trials.

Problems with evidence of mechanism

So far in this chapter we have seen how mechanisms are used to explain disease, and developed thinking about how evidence of mechanism can be useful for many of the different tasks of medicine. In this final section, I will sound a note of caution. Some might be tempted to regard evidence of mechanism as conclusive about whether, say, *Drug* causes *Cure*. However, evidence of mechanism is itself fallible (see Howick 2011). In this section I will examine two common problems with evidence of mechanism, and argue that evidence of mechanism is best used in integration with other sorts of evidence, such as that coming from clinical studies such as RCTs.

Recall that I claimed in the previous section that we seldom if ever have complete knowledge of a mechanism. The three levels of evidence I have described and defended as useful are all levels of less than complete knowledge. It is in this, the usual context, where two common problems of evidence of mechanism arise. Again, suppose we are assessing whether *Drug* causes *Cure*.

1. **Complexity**: The mechanism explaining the link between *Drug* and *Cure* is too complex to allow us to estimate an overall, average effect.
2. **Masking**: The mechanism explaining the link between *Drug* and *Cure* is masked by an undiscovered mechanism which also links *Drug* and *Cure*. The undiscovered mechanism may have the *opposite* effect to the known mechanism.

Suppose you have level 1 evidence of a mechanism that explains a link between *Drug* and *Cure*. Perhaps you have isolated some crucial entities on the pathway from *Drug* to *Cure*, and established novel activities that explain the action of *Drug*. It can be tempting to suppose that you can now be certain that *Drug* causes *Cure*.

Notice, however, what you most want to know given the task of medicine: you want to know that the drug will work to cure disease in real human populations. Real populations, the human body, and even individual cells, are very complex, interactive entities. This means that identifying one mechanism connecting *Drug* and *Cure* does not tell you what else might connect or otherwise affect *Drug* and *Cure*. You might have a problem of complexity, which means that you have pretty secure lab-based or even *in vivo* evidence of mechanism, but are unable to estimate effect size attributable to that mechanism, perhaps even be unable to decide whether its overall effect will be positive or negative. Further, you might have a masking problem: however detailed your knowledge of the known mechanism is, other mechanisms may exist connecting *Drug* and *Cure*, that are completely unknown to you, and mask (or alternatively enhance) the action of the known mechanism.

To address these problems, to help decide what will work in real human populations, what we need clinical studies. These studies cannot entirely solve the problems at hand, but they can be very helpful. On the one hand, if they are also positive, we have excellent evidence for the effectiveness of *Drug*. On the other hand, it is quite common for a new treatment that appears promising in the lab or in animal studies to turn out ineffective in human populations – due perhaps to toxicity, but also sometimes due to not working, for no reason that we can detect.

I will illustrate the importance of using trials alongside evidence of mechanism by examining how work on iniparib proceeded at the trial stage. The later 2014 trial concludes: “The

efficacy results from the phase III study did not confirm the promising results of the phase II [2011] study." (O'Shaughnessy et al. 2014: 3846.) So the first thing to note is that however good the lab studies of iniparib looked, the phase 3 trial did not support its effectiveness in a real human population.

I will now suggest that evidence integration goes beyond simple ideas of weighing evidence. It is not the case that positive preclinical evidence is a plus, while negative RCTs or other trial evidence is a minus, and we generate the overall assessment of evidence by simply adding up the pluses and subtracting the minuses. In the case of iniparib, the negative Phase 3 trial trumps the positive lab evidence for decisions about treatment, while the lab evidence remains strong enough to support further lab work. Evidence of mechanism and evidence from RCTs inform each other in important ways. This is because, used in combination, evidence of mechanism and evidence of correlations in populations found in trials can help with the weaknesses of each other, as I will now show. Consider the chart below, which illustrates the relation between the advantages of each kind of evidence, and the weaknesses of the other (updated from Illari 2010):

Evidence of *C-E* correlation (such as from clinical studies)

- *Weaknesses*: confounding, non-causal correlations, and bias.
- *Advantages*: can reveal masking, and can help assess the net effect of a complex mechanism.

Evidence of *C-E* mechanism (such as from lab or animal studies)

- *Weaknesses*: masking, and being too complex to assess a net effect.
- *Advantages*: can reveal confounding and non-causal correlations.

On the one hand, suppose we have identified – even at level 1 – a mechanism explaining the link between *Drug* and *Cure*, but we are concerned that its action will be masked, either in a real human body, or in a real human population. Then our best evidence that we can put aside this concern is evidence of a correlation between treatment with *Drug* and *Cure* in a real human population, coming from an RCT or other trial.

On the other hand, if we are concerned that the correlation found in a trial is due to bias or confounding by a common cause of treatment and recovery, evidence that the mechanism of action of the treatment really works *in vitro* or in animal studies helps ameliorate that concern.

In these ways, evidence of mechanism, and evidence of correlation in real human populations, are both essential in assessing total evidence of whether medical treatments really cause cure.

The intertwining of evidence is important to our assessment of iniparib. First, we do not know why it did not work in the 2014 trial. The trial report says: "There is not a strong biologic hypothesis that can explain the discrepancy in the iniparib efficacy results in the first- versus second-/third-line cohorts." The trial designers could find no difference in patient populations, either. (O'Shaughnessy *et al*. 2014: 3846.) It is not clear whether the mechanism of action of iniparib did not work, or was masked. An editorial comment published at the same time as the 2011 trial illuminates how much we do not know: "We cannot tell whether the benefit from the PARP inhibitor accrued to all triple-negative tumors equally or whether the benefit preferentially accrued to a subgroup of BRCA-deficient tumors, with less effect in those without the deficiency." (Carey and Sharpless 2011: 278.)

Specifically, Carey and Sharpless seem to be suggesting that there may be relevant but unknown sub-populations in TNBC, and iniparib might work only in a sub-population we

cannot yet clearly define. Recall that, to run any clinical study, you have to decide what counts as disease, and what counts as cure or desirable outcome. You have to choose how long to run the trial for, and how to *measure* both disease and outcome. I claimed above that justified decisions on these issues should be based on evidence of the mechanisms of disease and of cure.

To find effective treatments for breast cancer, it is crucial to recognize that there is not one homogenous disease 'breast cancer.' The classification 'Triple-Negative Breast Cancer' is already very interesting. It is a diagnostically important classification because it affects prognosis and identifies some treatments as useless. Yet the classification TBNC depends on what we know of the disease mechanisms – and also on known mechanisms of cure.

Carey and Sharpless are drawing our attention to the fact that sub-populations are likely to be central to ongoing development of breast cancer treatments, and hopefully identifying these populations will lead to effective treatments for cases which are now classified together simply as 'triple-negative.' In sum, breast cancer illustrates how evidence of both mechanism and of correlation are used in assessing overall evidence of medical treatments. As we have seen, the complete mechanism is seldom known, but there are at least three levels of evidence of mechanism that may be useful. We have also discussed the problems of masking and of complexity for interpreting evidence of mechanism, and noted that what level of evidence of mechanism is needed depends both on what else is known, and the purposes of inquiry.

We have seen throughout this chapter how important evidence of mechanism has been in our much improved ability to treat 80-85% of cases of breast cancer, even when 'gold standard' RCTs are being used. Well known mechanisms of cancer causation and progression are used as a background to design new targeted mechanisms of cure. In treatments of other diseases,

the use of such evidence may be far less obvious. However, in so far as any trial has to decide what variables to include, how to measure them, how long to run, and what populations the trial results apply to, all trials have to be run based on decisions that the trial itself cannot validate alone. These decisions thus must often be based on evidence of mechanisms.

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Most closely related chapters:

- Holly Andersen: Reduction in the biomedical Sciences (Chapter 9)
- Julian Reiss: Causality and causal inference in medicine (Chapter 7)
- Adam La Caze: The randomized controlled trial: internal and external validity (Chapter 19)
- Robyn Bluhm: Systematic review, meta-analysis and the evidence hierarchy (Chapter 21)
- Mael Lemoine: Explanation in medicine (Chapter 29)

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Keywords: Mechanism; Explanation; Causal inference; Medical evidence; RCTs; Randomised controlled trials.

Recommendations for further reading:

- William Bechtel and Robert Richardson (1993): *Discovering complexity*, Princeton University Press: Princeton. (Classic statement of modern mechanism, and extended exploration of mechanism discovery.)
- Nancy Cartwright (2012): 'Will this policy work for you?', *Philosophy of Science*, 9(5): 973-989. (Recent statement of Cartwright's long standing concerns about applying results of randomized controlled trials to other populations.)
- Brendan Clarke, Donald Gillies, Phyllis Illari, Federica Russo, and Jon Williamson (2014): 'Mechanisms and the Evidence Hierarchy' *Topoi* (online first), DOI 10.1007/s11245-013-9220-9. (Summary of how mechanisms can be used in evidence integration in medicine.)
- Jeremy Howick (2011): *The philosophy of evidence-based medicine*. BMJ Books. (Extensive discussion of evidence-based medicine, including criticism of uncritical use of mechanistic reasoning.)
- Steel, D. (2007): *Across the boundaries: Extrapolation in biology and social science*, Oxford University Press: New York. (Classic recent treatment of mechanisms and the extrapolation problem.)

References

Bechtel, W. (2008): *Mental Mechanisms*, Routledge, Oxford.

Bechtel, W. and Abrahamsen, A. (2005): "Explanation: a mechanist alternative," *Studies in the History and Philosophy of the Biological and Biomedical Sciences*, 36: 421–441.

Bechtel, W. and Richardson, R. (1993): *Discovering complexity*, Princeton: Princeton University Press.

Carey, L.A. and Sharpless, N. E. (2011): "PARP and Cancer – If It's Broke, Don't Fix It," *New England Journal of Medicine*, 364(3): 277-9.

Carnap, R. (1962): *Logical Foundations of Probability* (2nd ed.), University of Chicago Press: Chicago.

Cartwright, N. and Munro, E. (2010): "The limitations of randomized controlled trials in predicting effectiveness," *Journal of Evaluation in Clinical Practice*, 16(2): 260-266.

Cartwright, N. (2012): "Will this policy work for you?" *Philosophy of Science*, 9(5): 973-989.

Clarke, B., Gillies, D., Illari, P., Russo, F. and Williamson, J. (2014): "Mechanisms and the Evidence Hierarchy," *Topoi* (online first), DOI 10.1007/s11245-013-9220-9.

Craver, C. (2007): *Explaining the Brain*, Clarendon Press: Oxford.

Darden, L. and Craver, C. (2013): *In Search of Mechanisms*, University of Chicago Press: Chicago.

Dawid, A.P. (2000): "Causal inference without counterfactuals (with comments and rejoinder)," *Journal of the American Statistical Association* 95: 407–448.

Elster, J. (1983): *Explaining Technological Change*, Cambridge University Press: Cambridge.

Foulkes, W. D., Smith, I.E., and Reis-Filho, J. S. (2010): "Triple-Negative Breast Cancer," *New England Journal of Medicine* 363:1938-48.

Glennan, S. (2009): "Mechanisms," H. Beebee, C. Hitchcock and P. Menzies (eds.) *The Oxford Handbook of Causation*, Oxford University Press: Oxford, 315-25.

Glennan, S. (2008): "Mechanisms," S. Psillos and M. Curd (eds.) *Routledge Companion to the Philosophy of Science*, Routledge: Oxford.

Glennan, S. (2002): "Rethinking Mechanistic Explanation," *Philosophy of Science*, 69: S342–S353.

Glennan, S. (1996): "Mechanisms and the Nature of Causation," *Erkenntnis*, 44(1): 49-71.

Haack, S. (1993): *Evidence and inquiry: Towards reconstruction in epistemology*, Blackwell: Oxford.

Hedström, P. and Swedberg, R. (1998): *Social Mechanisms: An Analytical Approach to Social Theory*, Cambridge University Press: Cambridge.

Hempel, C. G. (1965): *Aspects of Scientific Explanation*, Free Press: New York.

Howick, J. (2011): *The philosophy of evidence-based medicine*. BMJ Books.

International Agency for Research on Cancer: *Preamble to the IARC Monographs* (amended Jan 2006), available at: http://monographs.iarc.fr/ (accessed November 2015).

Illari, P. M. (2011): "Mechanistic evidence: Disambiguating the Russo-Williamson Thesis," *International Studies in the Philosophy of Science*, 25(2): 139-157.

Kincaid, H. (2012): "Mechanisms, Causal Modelling, and the Limitations of Traditional Multiple Regression," H. Kincaid (ed.) *The Oxford Handbook of the Philosophy of Social Science*, Oxford University Press: Oxford.

Kincaid, H. (2011): "Causal modelling, mechanism, and probability in epidemiology," P. Illari, F. Russo and J. Williamson (eds.) *Causality in the Sciences*, Oxford University Press: Oxford.

Machamer, P. Darden, L. and Craver, C. (2000): "Thinking about Mechanisms," *Philosophy of Science*, 67: 1-25.

National Institute for Care and Health Excellence (2014): *Developing NICE guidelines: the manual*, available at: http://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf (accessed Nov 2015).

O'Shaughnessy, J., Osborne, C., Pippen J. E., Yoffe, M., Patt, D., Rocha, C., Koo, I. C., Sherman, B. M., and Bradley, C. (2011): "Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer," *New England Journal of Medicine*; 364: 205-14.

O'Shaughnessy, J., Schwartzberg, L., Danso, M. A., Miller, K. D., Rugo, H. S., Neubauer, M., Robert, N., Hellerstedt, B., Saleh, M., Richards, P., Specht, J. M., Yardley, D. A., Carlson, R. W., Finn, R. S., Charpentier, E., Garcia-Ribas, I., and Winer, E. P. (2014): "Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer," *Journal of Clinical Oncology*, 32: 3840-3847.

Steel, D. (2007): *Across the boundaries: Extrapolation in biology and social science*, Oxford University Press: New York.

Vandebroucke, J. (in progress): "The potential outcomes model and epidemiology"

Wimsatt, W. (2007): *Re-Engineering Philosophy for Limited Beings*, Harvard University Press: Harvard.