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Abstract

In this chapter we explore the functions of mechanisms in medical practice. Using a group of six examples of mechanisms in medicine, we present a pluralist epistemological stance about medical mechanisms. We argue that these mechanistic approaches contribute to, rather than constitute, inferential practices in various contexts. We conclude that an over-emphasis by philosophers on the epistemology of clinical trials has concealed the importance of mechanisms in medical practice.

1. Introduction

Our aim in this chapter is to give a 'functionalist account' of the ways that mechanisms are sought, formulated, and used, in medicine. Rather than giving a single analytic account of mechanism, or a review of ways that existing accounts of mechanism fail to describe one or other aspects of medical practice, we instead work from a starting position that one of us has previously called the 'mosaic view' of causality (Illari and Russo 2014). According to this mosaic view, the objective of research by practically- and historically-engaged philosophers of science is not to find *The-One* definition of causality, but instead to understand what role related notions play in our epistemologies and methodologies. In a similar vein, we here focus on exploring the use of mechanisms in the methodologies and epistemologies of medicine. In this we are motivated by (amongst others) Andrea Woody's functionalist account of explanation. Her approach is to:

> "[…] think about where and when explanations are sought and formulated, and subsequently to consider what role(s) they might play in practice." (Woody 2015: 81)

Our aim is to provide a related inquiry, concentrating on the ways that mechanisms are sought, formulated, and used, in medicine. We take the main aims of medicine to be to understand and intervene on the health of individuals and of populations, where those interventions seek to cure, mitigate or prevent disruptions to human health.

Mechanisms, we submit are found to the point of ubiquity in medicine. Because of this, we will use six 'episodes' to draw out some of the role(s) that mechanisms play in making sense of medicine. In section 2, we introduce these episodes in a fairly descriptive way. We then, in section 3, analyse these episodes in order to draw lessons about mechanisms in medicine. Finally, in section 4, we reach some tentative conclusions about mechanisms in medicine. Here, a major job is to answer the following question: if the mechanisms project often or usually looks to the sciences for inspiration, why is there such a mis-match between the high prominence of mechanisms in medical practice, and the much lower level of attention that medical mechanisms have received from philosophers?

2. Examples of mechanisms in medicine

We begin with what seems a simple fact of the matter: talk of mechanisms are nearly ubiquitous in medical practice. This is not to claim that mechanisms are either necessary or sufficient to establish the causes and effects of health and disease, but just to notice that mechanisms enter, very, very frequently, into *several* inferential practices in the medical sciences. The interesting question then becomes what these different uses of mechanisms have in common or in which respects they differ. This is in line with Woody's functionalist approach.

In order to build our argument for this diversity we present some 'episodes' of medical mechanisms at work. We borrow from Chang (2011: 110ff) the term 'episode', rather than 'case study', to emphasize these are selected as exemplary cases of the numerous uses of mechanisms in medicine, rather than unique instances chosen *ad hoc* for the purpose of the present discussion. To develop this point slightly, we intend to tell a diverse group of stories about the practices of the medical sciences, present and historical. Yet we hope that the term 'episode' will suggest that, while each tells a different story about medicine, that these stories have something in common from the perspective of researchers interested in mechanisms.

Recall that we take the main aims of medicine to concern understanding and intervening on the health of individuals and of populations. This means we use the term 'medicine' to include all clinical, scientific, and even political forms of engagement with health and disease (for a detailed discussion,

see Clarke and Russo 2016). We therefore use 'medicine' as an umbrella term with the aim of moving towards a broad and inclusive understanding of medicine which – we hope – will foster a thorough discussion of the role of mechanisms in this broad-church medicine. It is in this sense that, in this chapter, we explore the *applied* epistemology of mechanisms in medicine. We submit that mechanisms are powerful tools for understanding, establishing and intervening on causal relations in medicine. However, we worry that insufficient attention has been paid to the *different* ways that an understanding of mechanisms can contribute to this applied epistemology. *Hence*, our six episodes.

From the discussion of the episodes it will become clear (i) that mechanisms *contribute to*, rather than constitute, several inferential practices in medicine and (ii) that the effects of these contributions are extremely heterogeneous. We will go on to think more analytically about these various contributions in section 3.

As a first case, consider aspirin, which has been widely used as analgesic, antipyretic, and anti-inflammatory since its synthesis by Hoffmann in 1897 (Schrör 1997: 349). Its effects are so well-known that the example of aspirin is often used by philosophers of medicine to argue that mechanisms are not needed to establish causal relations (e.g. Howick 2011: 930). At first sight, the argument seems compelling: the efficacy of aspirin as a pain-killer was known for many decades before its mechanism of action was understood. Many of us, too, will have taken and trusted aspirin to (say) relieve our headache despite (we venture) few of us possessing the knowledge of the relevant mechanisms that explained why it was effective. Yet the analgesic, antipyretic, and anti-inflammatory effects are not the only effects of aspirin of interest to medical practice. Aspirin is widely used because of its effect on platelet function. Giving regular low-dose aspirin improves cardiovascular outcomes (Antithrombotic Trialists' Collaboration, 2002). Yet, we argue, this role of aspirin is not so perspicuous as its painkilling one. Instead, knowledge of this effect was intimately linked to understanding the mechanism by which the drug worked.

We summarise here the main steps of how the effect of aspirin on platelet function was established, based on Schrör's presentation (1997: 349-50). Quick reported that aspirin increased bleeding time (which is a measure of the overall rate at which blood clots) in 1967. This was shortly followed by several reports that low-dose aspirin appeared to inhibit platelet aggregation – in itself, an important part of blood clotting (Weiss, Aledort and Kochawa 1968; O'Brien 1968). This inhibition began within two hours of taking the aspirin, and lasted for several days. The investigation this impressive degree of platelet aggregation in turn lead to the finding that aspirin inhibited prostaglandin synthesis (Vane 1971). Incidentally, this inhibition of prostaglandin biosynthesis was later to provide the roots of the mechanistic explanations of the other actions of aspirin. Smith and Willis (1971) then identified that the inhibition of prostaglandin biosynthesis was "the mechanism of the antiplatelet action of aspirin" (Schrör 1997: 350), which was traced specifically to inhibition of the cyclooxygenase (or COX) enzyme in 1975, and to a specific amino acid residue in the COX-1 enzyme in 1991. Further mechanistic research on COX would reveal routes for future interventions that could capitalize on aspirin's beneficial effects, while hopefully avoiding its adverse effects.

Our second example is HDL-raising drugs. Observational evidence suggests high levels of high-density lipoprotein (HDL) in the blood are inversely correlated with heart disease. But is this correlation due to an underlying causal (preventative) relationship between heart disease and HDL?

How about investigating this question by using HDL-raising as an intervention designed to prevent heart disease? A recently-developed class of drugs called cholesteryl ester transfer protein (CETP) inhibitors seemed to promise just such an investigation. Clinical trials of the drug torcetrapib seemed effective at raising HDL levels (Brousseau et al, 2004). However, it did not improve clinical outcomes. In fact, it severely worsened them, leading to the abandoning of a large phase III clinical trial (known as ILLUMINATE) in 2006, owing to excess deaths in patients receiving torcetrapib. This result was

unexpected – so much so that one commentator suggested that this result should lead us to conclude that "We know so much about the cholesterol pathway, but we never seem to know what matters" (Lehrer 2011). The trial authors (Barter et al) were unsurprisingly more measured in their analysis of the trial result, and responded with some educated speculation as to its cause(s):

> "[…]Clinical trials such as ours are not designed to elucidate mechanisms of either benefit or harm associated with the use of a drug. However, they may provide clues that have the potential to inform future research… There are at least two possible explanations for the observation of increased mortality and morbidity associated with the use of torcetrapib in our study: an off-target effect of torcetrapib, unrelated to CETP inhibition, and an adverse effect of CETP inhibition per se, with the possible generation of dysfunctional or even proatherogenic HDL cholesterol." (Barter et al 2007)

Further research has suggested that the "off-target" mechanism suggested by Barter et al may be correct. It appears that torcetrapib increases blood pressure (Tall, Yvan-Charvet and Wang 2007) – itself, a well-known cause of cardiac death. If that is the case, then the increased mortality and morbidity found in the ILLUMINATE trial appear to be an adverse consequence of torcetrapib specifically, and therefore unlikely to be replicated in clinical research on alternative CETP inhibitors (such as evacetrapib and anacetrapib).

The third example is that asbestos is known to be responsible for fatal diseases such as asbestosis and lung cancer. The biochemical mechanisms that connect exposure to asbestos fibres with the development of cancer have been studied and examined carefully (see e.g. IARC Working Group 2012). However, work remains to be done studying the (largely social) mechanisms by which exposure to asbestos occurs. For example, occupational medicine researchers have been studying the disease from the perspective of the work place. This led to study populations living close to asbestos factories. Examples abound across different geographical locations. We might mention, for instance, Barking in the United Kingdom (Greenberg, 2003) and Eternit in Italy, for which a memorable sentence was issued in 2009 after a long and difficult trial (Mossano, 2011; Allen and Kazan-Allen, 2012): the owners of the asbestos multinational were deemed guilty of fraudulent environmental disaster and omission. In this context, and because of their bearing on legal and policy questions, some aspects of the mechanisms underlying asbestos exposure remain disputed, for instance latency (see, e.g., Terracini et al., 2014; La Vecchia and Boffetta, 2014). The point here is that mechanisms investigated via occupational and environmental epidemiology largely do not concern the way that asbestos causes asbestosis. This, as we shall further discuss later, poses a question for the 'overbiologizations' of diseases, namely the reduction of disease causation to biochemical reactions in the body.

In the philosophy of medicine our fourth example, the discovery of *Helicobacter pylori* as a cause of gastric ulcer, has been used to illustrate how hypotheses are generated in medicine (Gillies 2005; Hutton 2012; Thagard 1998a, 1998b). The same episode has also been used to illustrate the mutual need of evidence of difference-making *and* of mechanisms in establishing causal claims in medicine (Russo and Williamson 2007). This body of literature showcased how the use of mechanisms in given inferential practices *also* depends on the available theoretical framework. In this case, available background knowledge had it that bacteria could not live in acid environments such as the stomach. This tended to preclude the hypothesis that *H.pylori* could be a cause of gastric ulcer, and until the mechanism by which this bacteria could survive in low-pH environments had been investigated, the causal claim could not be properly assessed.

Another stock example in the philosophy of medicine, and our fifth, is the story of Ignaz Semmelweis, a doctor active in nineteen-century Vienna. His notoriety is due to his hypothesis that puerperal fever was due to some infection. The mechanisms had not been clarified at that time, but his suggested preventive intervention was remarkably simple: doctors should wash their hands after performing autopsies and before assisting women in labour. Part of the debate in philosophy of medicine concerns the question whether the scientific community was right or wrong in rejecting Semmelweis' precautionary measure on the basis of available evidence and of the theoretical framework supporting the intervention.

The sixth and final episode we want to present is the *comparison* between approaches to health and disease. This becomes highly relevant in times where the public is showing skepticism and mistrust for so-called 'Western medicine' and increasingly seek advice from 'alternative' approaches. 'Alternative' or 'complementary' medicine is however a basket where too often anything that is 'non-Western' is placed. Instead care is needed in carry out comparisons and non-Western medical traditions ought not to be conflated.

To illustrate the relevance of our point, we rely on the contribution of Hugh Shapiro in the volume *Medicine across cultures* (Shapiro 2003). Shapiro provides an invaluable contextualization of what is usually called 'Chinese medicine', including a brief history of its relation to Western approaches. Shapiro then explains that from a practice of forensic medicine and of dissection, which was common to both Chinese and Western approaches, very different conceptualizations of the body (anatomy and physiology) and of pathology derived. Moreover, this led to very different developments: the study of the living body in Chinese medicine and the study of the dead body in Western medicine. Shapiro illustrates these claims with the case of 'nerves'.

At the beginning of the last century the medical community gathered to translate and standardize terms coming from the West. It became clear that there wasn't a one-to-one correspondence. For instance, Chinese lacked both the concept and the word for 'nerve'. Since the Renaissance, attempts to translate Western medical concepts into Chinese ones had to make recourse to periphrases and to neologisms that would make sense in their conceptual framework. Thus, for instance, nerve was used much as synonymous of sinew, and its function was to transmit the 'vital power'. Chinese doctors have known for long how to intervene on this vital power, using the technique of acupuncture. The lack of a corresponding term for 'nerve' in Chinese testifies, argues Shapiro, to the different conceptions and understanding of the body and of the phenomena of health and disease. This, it should be noted, holds for Western culture too. In fact, Shapiro continues, in the West the understanding of what nerves are and of how they function has been related to the character trait of 'volition', an idea that traces back to Greek medicine. Moreover, this is intimately connected with action and especially volitional actions, which are defining features of identity.

3. Mechanisms contribute to inferences in medicine

After this overview of episodes of mechanisms in medicine, it would be tempting to try and pin down The-One definition that fits them all. In accordance with the 'mosaic view' and the 'functionalist approach' we espoused (see section 1), we will not pursue this objective here. For our purposes, we can safely rely on the working characterization by Jon Williamson and Phyllis Illari:

> "A mechanism for a phenomenon consists of entities and activities organized in such a way that they are responsible for the phenomenon" (Illari and Williamson 2012: 120)

This kind of view is now routinely referred to as 'minimal mechanism' (see also Chapter 1). This characterization avoids equating mechanisms with Cartesian deterministic machines (see Chapter 3). Also, this characterization is flexible enough to accommodate mechanisms that travel across generic, or population-level case and single, individual case. It allows us to deal with bio-chemical, pharmacological, or social mechanisms of health and disease. These and other aspects of mechanisms are discussed next.

Returning to our first episode, aspirin, examples like this are instructive in that they illustrate, in a concrete way, the difficulties that can be experienced in finding effects in medicine. This is hard – effects are complex, and we think that researchers need to know about mechanisms in order to reliably find and measure many effects. While there are exceptions - you need no detailed knowledge to know that an anaesthetic is effective in sending someone to sleep - it can be extremely hard to discover and understand all the clinically relevant effects of an anaesthetic (or, in this case, analgesic) drug. This is also the case when it comes to finding side effects (such as gastric and duodenal ulcers, Reye's syndrome, and exacerbations of asthma in the case of aspirin).

The second example, HDL-raising drugs, shows that medical effects of interest may result from complex systems of mechanisms that are difficult to separate (like the hypertensive effect of torcetrapid). The complexity comes for the interaction of given drugs with a pathology, or rather with *several* pathologies. In fact, cases of co-morbidity (i.e., a patient that has more pathological conditions at one time) are the norm rather than the exception. Knowledge of mechanisms is necessary to explain, predict, and treat, especially in these cases. Differently put, the situation of one drug—one pathology rarely occurs. Knowledge of mechanisms doesn't come from large clinical trials *alone* (as Barter et al noted in their quote given above), but is instead to be complemented with other types of studies, for instance lab experiments.

Cases like the third, asbestos, point to the question whether or not, in the light of the stunning advancement of biomedicine, disease ought to be reduced to biochemical reactions in the body. On the one hand, in the medical sciences, attention *is* given to social mechanisms of health and disease, but these are often considered 'distant', namely as 'adjunct' description of how biological mechanisms of health and disease correlate with socio-economic difference or inequalities across individuals. On the other hand, the sociology of health and the behavioural sciences describe the role that social, psychological, economic, or behavioural factors play in the aetiology of disease. To be sure, this is an area where evidence of difference making (*that* social factors make a difference to the occurrence of disease) exceeds evidence of mechanisms (*how* social factors intervene in the mechanisms of disease causation. The philosophy of mechanisms has a chance there in developing an account of *mixed mechanisms*, where both biological and social factors play an active role (Kelly et al 2014). This is not just to elucidate the aetiology of disease, but also to better plan public health interventions. In fact, while most (non-communicable) diseases have a proper explanation in terms of biochemical mechanisms, successful public health interventions in the past targeted social determinates, lifestyles, and basic hygiene or sanitary measures; to be sure, this is still the case nowadays, as evidenced by major public health interventions in Brazil (see e.g. Barreto et al, 2010 and Barreto and Aquino 2009). In a nutshell, bio-social mechanisms of health and disease are needed to plan, research, and implement interventions. This is because successful interventions need a complex view of what counts as relevantly beneficial or harmful.

The fourth case, *H. pylori* and gastric ulcer, is interesting in that it shows that mechanisms do not function as an 'experimentum crucis' for a theory, nor are they 'deductively' inferred from available theories. The search for explanatory and therapeutic mechanisms requires constant interplay with available background knowledge. Hunting for specific mechanisms, like that linking *H. pylori* infection with stomach ulcers, might confirm, or disconfirm existing background knowledge. It is

undeniable that experiments depend on mechanisms, more precisely on *knowledge* of mechanisms. However, without standards to assess the quality of knowledge of mechanisms, poor-quality assertions and speculation ("the stomach is sterile") appear to fill the gaps that should instead be populated with empirically-based, carefully-researched knowledge about mechanisms. This allows us to introduce a *normative* dimension of the mechanism project in medicine, next to the descriptive one carried out in the previous section. Mechanisms support the infrastructure of medical inference. To be even more precise, they support a *variety* of medical inferences at different stages of the scientific process. They aren't just a way of expressing existing knowledge, but instead actively participate in producing new knowledge. Mechanisms have a vital role in the setup of trials or of lab experiments. And the results of these scientific practices may lend further support to these mechanisms, or they may lead us to significantly revise our knowledge base (as Craver and Darden 2013 suggest).

The fifth case, puerperal fever, is an instructive case for several reasons. One is that we should avoid 'presentism': it is wrong to assess the past with the theories available today. The recent debate on evidential pluralism (such as Broadbent 2011) focuses on whether the scientific community, at the time of Semmelweis, was right or wrong in rejecting his preventive measure. The point here is that this measure was not supported by solid theoretical background, as this was happing well before the germ theory of disease had been developed. Given what we know *today* about bacteria and so on it is too easy a judgment to say that the scientific community at that time was wrong in rejecting Semmelweis. The point here is of course broader than just *this* specific episode. It is a point of philosophical methodology and of how to do philosophy of science, properly informed by the history of science. Yet much is historically disputed – indeed "misleading" (Tulodziecki 2013: 1074) in the Semmelweis case. Another reason why this episode is relevant to us is that, even if the historical quarrel cannot be settled, this can provide important lessons about the present. In particular, examples like these should encourage reflection on what to do when knowledge of mechanisms is incomplete or highly uncertain. What actions are nonetheless justified? This is where proper attention to mechanisms in philosophy of medicine pushes back the frontier of epistemology and of methodology. In fact, exquisitely epistemological questions about the (un)certainty of current medical knowledge quickly turn into ethico-political questions about what justifies the implementation (or refusal) of interventions or preventive measures. A case in point here is the current controversy over vaccination programmes. Apart from the disputed question of the correlation of vaccines and autism, another question concerns the tension of individual freedom not to vaccinate and the public health concern to protect the population at large by imposing vaccines to all individuals.

Health, disease and worldviews, the sixth episode, is an area where *much* work is needed, from a philosophical, historical, and also socio-anthropological perspective. These sorts of comparison are instructive in that they remind us that mechanisms, their entities and activities, are not *given*. They are instead products of our investigations into the phenomena of health and disease. From an epistemological point of view, this means that mechanisms are part of our inferential systems – a point that already arose earlier in the reflection on the case of Helicobacter Pylori. But mechanisms are a part of our inferential system also in another sense, namely different understandings of the phenomena of health and disease may lead to *incommensurable* mechanisms, or to syndromes that are culture-bound (Guarnaccia and Rogler 1999). Thus all these phenomena, as well as the investigations and explanations thereof, are deeply couched into cultural factors, in the East as well as in the West. In our sixth episode, this was shown in the way the nervous system was conceptualised differently in Western and in Chinese medicine, and in the different terms to refer to parts of the body and to its functioning. This should warn us about a scientistic attitude and imperialistic imposition of Western standards in an uncritical way.

4. Evidence and contrastive focus

The septet presented in section 2, and then analysed in section 3, reveal many issues of interest to those thinking about mechanisms. While we would like to follow them with a detailed and exhaustive theoretical discussions of the issues, we will restrict ourselves to a discussion of just two of them. The first – evidence of mechanism – is a hotly disputed issue in the current debate. We will develop our account of evidence of mechanism in medicine from the six episodes will be a useful contribution. The second – contrastive focus – has not (we think) received sufficient attention from philosophers interested in mechanisms. We therefore highlight it here by way of raising interest in it as a research problem more widely.

We begin by considering evidence, reasoning, and narratives in medicine. As the aspirin example suggests, mechanisms do not typically appear as ready-made pieces of knowledge. A great deal of work is needed in order to acquire and establish knowledge of mechanism. Here, the notion of *evidence* plays a crucial role. We borrow from Illari the definition of *evidence of mechanism*. She – and we – take evidence of mechanisms as being

> "[…] evidence of the actual existence of the postulated mechanism linking cause and effect." (Illari 2011a: 120)

While schematic, this definition is sufficiently clear to warrant some initial clarification regarding our thoughts about the use of mechanisms in medicine as evidence. What is at stake, in fact, is a distinction between *evidence* of mechanism and mechanistic *reasoning*, around which substantial disagreement exists. For instance, Howick et al define mechanistic reasoning as follows:

> "[…] the inference from mechanisms to claims that an intervention produced a patient-relevant outcome. Such reasoning will involve an inferential chain linking the intervention (such as antiarrhythmic drugs) with the outcome (such as mortality)." (Howick et al 2010: 434).[i]

We take this to mean that mechanistic reasoning would involve making a clinical decision about the likely efficacy or harms of a medical intervention **just** by thinking about mechanisms. We do not endorse this way of using mechanisms to make medical decisions as a normative aspiration. Nor do we think it is a good description of the generality of medical practice (it seems hard to connect to our episodes). We instead think that reasoning about mechanisms *alone* is highly unlikely to make for reliable clinical inferences. As we have argued in other places (Clarke et al 2013; 2014), a kind of *pragmatic* evidential pluralism featuring some contribution from evidence of relevant mechanisms may instead help make better medical inferences. According to this view, evidence of mechanism participates, along with *other* kinds of relevant evidence such as that produced by randomised clinical trials, in various inferential practices. For the purposes of this chapter, though, it suffices to note that our *evidence of mechanism* is just one kind of evidence (amongst many), rather than the ambitious and free-standing *mechanistic reasoning* discussed by Howick et al. Along with Solomon (2015: 123-4), we therefore note that *evidence of mechanism* and *mechanistic reasoning* cannot be used interchangeably.[ii]

A further distinction that we wish to draw is between evidence of mechanism and *narratives*. While the role of narratives in medicine (see Kleinman 1989; Greenlagh, 1999; Montogomery, 2006) and in science more generally (Roth 1988, 1989) is a topic that deserves more philosophical attention than it actually gets, it is important to note that we think there is a difference between evidence of mechanism and of the *narrative(s) that may be used to* describe, present, discuss, or criticize said evidence of mechanism.

It's possible to use (empirically grounded) narratives to describe mechanisms, but that is not the same thing as saying that mechanisms just *are* narratives (see also Chapter 34). We think that any scientific result that is expressed in ordinary language can be understood as a narrative, without the converse assertion that all scientific results are just narratives. More positively, we think that there are standardized rules that govern the relation between a result and its narratives, which supply rigid structure on the presentation of those narratives. Consider how a scientific article must present a research question, the data, the analyses, and the results.

We turn now to our second main point. One aspect that many mechanisms in the episodes above share is *contrastive focus*. Mechanisms, as also discussed elsewhere in this volume (see Chapter 16), help answer the question '*How* does C cause E?'. Medicine is no exception to this use of mechanisms. Typically, emphasis is given to those characteristics of mechanisms (most notably, *organization*) that participate in explaining *how* C causes (in the sense of *producing*) E.

In this section, though, we want instead to draw attention to another way that we might interpret the question 'How does C causes E?'. Rather than give an answer that highlights the productive continuity that obtains between C and E, we might instead give an answer that explains why our C causes E rather than E_1, or that C, rather than C_1 causes E. This is the question of *contrastive focus*, which has been fairly extensively discussed in relation to causality (Dretske 1972, Schaffer 2005, Northcott 2008). Here, we aim to show that attention to contrastive focus is key to several inferential practices in medicine, and that dealing with questions of contrastive focus often involve thinking about mechanisms, in different ways, also illustrated by the septet of episodes. We highlight here two specific aspects of the contrastive focus: (i) normal vs pathological and (ii) biological vs social. Simply put, the idea is that the aspects of contrastive focus we discuss here concern (i) different mechanisms describing normal or pathological behaviour and (ii) the factors – biological or social – that are at work in such mechanisms.

To begin with, mechanisms that deal with the aetiology of pathology typically do so in a contrastive way with normal physiology (see also Chapter 8). For example, the mechanism that explains how infection with *H. pylori* leads to ulcers does so in a contrastive way with normal physiology (see the extremely thorough review by Kusters, van Vliet and Kuipers 2006 for further details). This means that we need a *generic* mechanism about normal physiology *and* a suitable contrastive model of a mechanism that explains pathogenic behaviour. Many experimental studies in bio-medicine are based on this idea – they effectively compare subjects that do and do not receive some intervention. The very same idea is at the basis of extrapolation from animal studies to humans (see e.g. Steel 2007).

This means that contrastive focus is at the basis of RCTs too. In fact, one way to use RCTs is precisely to differentiate between the effect E_1 rather than E_2, or between the role of C_1 rather than C_2. This adds to the recent debates on the role of mechanisms in RCTs. Specifically, according to EBM-theorisers mechanisms play little if no role at all in establishing causal relations – a view challenged instead by supporters of 'evidential pluralism', namely the view that to establish causal relations one typically needs multifarious evidence (for a discussion, see Clarke et al 2014).

The contrastive focus can also participate in establishing causal relations at the individual, single case, level, precisely using considerations about what is (thought to be) normal and what is not. This, however, is far from being an easy task, as testified by the several challenges of diagnosis. We shall focus here on just one challenge. To make a diagnosis in the single case we need to contrast it with generic mechanism. But how *generic* should a generic mechanism be?

There is no principled answer to this question. One problem has to do with finding mechanisms that are stable in sufficiently homogeneous reference classes. A reference class is homogenous when all its members have the same characteristics. This is usually not the case in medicine – we expect those in the reference class of 'patients with heart disease' to be suffering from a range of different conditions. Homogeneous reference classes – where all individuals have exactly the same conditions - are either very scarce, or very hard to find, in medicine. A notable example in this respect is the study of pathologies that frequently co-occur with other pathologies. As the HDL-raising drug example above shows, it can be extremely hard to unpick the contributions of different conditions with similar effects. In the HDL-raising case, we can presumably assume that isn't just one mechanism at work, but several nested and interconnected mechanisms. This is because people using HDL-raising drugs have very different conditions, and most of the time *multiple* pathologies, not just heart disease. Consequently, the contrastive focus of mechanisms should not simply be in terms of differentiating the effect of a drug against a placebo. Instead, drugs should be tested taking these other mechanisms into account, including interactions with other drugs.

The second aspect related to the contrastive focus is whether only biological factors should contribute to answering the question 'How does C cause E?'. We encountered this issue in the asbestos example, where a relevant question is whether work place or other social factors are appropriate factors to be included in the aetiology of the disease. So, when we check for appropriate contrasts between reference classes we shouldn't just consider bio-chemical factors (i.e. those bio-chemical factors marking normal vs pathological behaviour), but also psycho-demo-socio-economic one. Abestosis is of course not the only case. Another example is epigenetics, which attempts to reconstruct the effect of the environment, including *in utero* events, at the genetic level even one generation later. The contrastive focus here might be with events that happened much earlier on in our lives, if not generations before. So the mechanisms of health and disease may be acting over long time spans, and the causes may reside in events that cannot be assessed at the time of diagnoses. Studies on the 'Dutch famine' of 1944-45 are a good case in point. According to these studies, the children of women that were pregnant during the famine are more susceptible to develop diseases such as obesity, diabetes, cardiovascular conditions, etc. Epigenetics attempts to shed light on the long-term mechanisms that, by affecting women during pregnancy, also affected their offspring even decades after birth (see Roseboom, de Rooij and Painter 2006 for an introduction).

The health sciences (including sociology of health) have recognised since long time that health and disease are not independent of socio-economic factors (for an overview, see Kelly et al 2014). But this recognition is typically explicated in two ways. On the one hand, socio-economic factors are merely correlated with health and disease, and they are used to map which parts of the population are healthier and which are more ill. But here socio-economic factor do not actively participate in the production of health and disease. On the other hand, the action of psycho-socio-demo-economic factors is totally explained away by reducing them the action of bio-chemical factors. Here, a proper understanding of how these factors *actively contribute* to health and disease is missing. Differently put, the mechanisms of health and disease are not just bio-chemical or just socio-eco-psychological. They are most often *mixed*, a blend of those categories, and in need of further investigation within medicine and public health, and philosophy too. Most non-communicable diseases, from obesity to type-2 diabetes, alcohol-related diseases arguably require mixed mechanisms both for understanding and for intervening on their causes and effect (see also Kelly et al 2014). Admittedly, these (and many others) are cases where what we *don't* know exceeds by far what we know. And, precisely for this reason, thinking in terms of how mechanisms contribute to several inferential practices (rather than just working out The-One definition of mechanism) may be of great help.

5. Conclusions

As shown by the above sextet of examples, we have a very broad and inclusive understanding of what medicine is and does. We hope that this will help redress part of the existing debates in philosophy of medicine, particularly for what we call the 'narrow view of medicine', held by a number of authors, both from medicine and from philosophy.

For many philosophers in recent years, medicine has been largely synonymous with evidence-based medicine. This is perhaps an artefact, due to how philosophers of science came to pay attention to medicine. The establishment of evidence-based medicine as a dominant paradigm prompted a peculiar reaction in the philosophical community, which was captured by the iconic paper by John Worrall (2002). He asked: "What on earth was medicine based on before?" This might explain why so much attention was, since then, devoted to this *sub*-field of medicine. There is much more to medicine than evaluating the efficacy and harms of drugs. At the same time, particularly in the way that philosophical work on EBM intersects with other interests of analytic philosophers of science (particularly the philosophy of statistics) we see just why this narrowing might be both useful and comforting. However, when it comes to thinking about mechanisms, we worry about this narrowness, largely because it (we think) has led to the pre-eminence of a narrow set of related questions that are ostensibly about medicine, but are really about statistical inference in the context of the clinical trial: evidence, bias, and so on. In turn, this has led to a caricature of medical practice such that mechanisms are either a) described as playing a negligibly minor evidential role or b) are treated as a simple (but faulty!) alternative method of inference to the clinical trial. Both of these caricatures, we submit, are inaccurate. It is high time to broaden the scope of the debate, by looking at the very many practices in medicine, including, but not restricted, to EBM.

The approach taken in this chapter points to a *pluralistic* account of medicine, and of mechanisms in medicine. This stems from the different ways in which mechanisms contribute to medical practices. It is in this sense that we have explored the *applied* epistemology of mechanisms in medicine. We submit that mechanisms are powerful conceptual tools for establishing and intervening on causal relations in medicine. However, we worry that insufficient attention has been paid to the *different* ways that an understanding of mechanisms can contribute to this applied epistemology. This is all the more important, because the philosophy of mechanisms itself became somewhat specialized, discussing mechanisms in specific, isolated domains: in biology, in psychology, or in sociology. But mechanisms, in medicine or elsewhere, are seldom intrinsically biological, psychological, or sociological. We hope that our approach to mechanisms in medicine will be an encouragement to start crossing the borders of these sub-fields in the philosophy of mechanisms.

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[i] Howick also gave a similar formulation in a later solo article: "Mechanistic reasoning is an inferential chain (or web) linking the intervention (such as HRT) with a patient-relevant outcome, via relevant mechanisms." (Howick 2011: 929)

[ii] A brief clarification is in order here. We do not agree that our previous work (Clarke et al 2013; 2014) endorsed the equivalence of mechanistic reasoning and mechanistic evidence, as Miriam Solomon seems to suggest: "Although there are differences between Howick (2011b), Andersen (2012), and Clarke et al. (2013), they all share the assumption that mechanistic reasoning should be regarded as mechanistic evidence, moreover, evidence that has a place in the hierarchy. This is an assumption that I challenge." (Solomon 2015: 120)