Evidence-based Medicine and Progress in the Medical Sciences.

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Abstract

The question what scientific progress means for a particular domain such as medicine seems importantly different from the question what scientific progress is in general. While the latter question received ample treatment in the philosophical literature, the former question is hardly discussed. I argue that it is nonetheless important to think about this question in view of the methodological choices we make. I raise specific questions that should be tackled regarding scientific progress in the medical sciences and demonstrate their importance by means of an

s of what EBM has, and has not, to offer in terms of progress. I show how critically

favoured methodologies in the right perspective. My conclusion will be that blindly favouring certain methods because of their immediately tangible short term benefits implies that we parry the important question of how best to advance progress in the long run. This leads us to losing sight of our general goals in doing research in the medical sciences.

Introduction: Progress in medicine

What is meant by progress in medicine? This is an important question that cannot easily be answered. It also did not yet attract much attention in the literature. Philosophers of science have written a lot about scientific progress in general but it is not always straightforward to see how these general philosophical approaches apply to specific scientific domains or what the implications are for everyday scientific practice in these domains. The question what scientific progress is for a particular domain such as medicine seems importantly different from the question what scientific progress is in general. Traditional philosophical approaches to scientific

progress start from a historical point of view: they look at the history of science and try to discern the general patterns that constituted progress in science. Some think we have come ever closer to the truth in the history of science, others think that we have accumulated ever more knowledge, and still others think that the history of science teaches us that we have become ever better in solving problems and that this is the essence of progress in science [1,2].

Very generally, one could possibly develop the argument that for the medical sciences, given its importance for clinical practice, scientific progress should be defined in terms of problem-solving capacities rather than in terms of aiming for truths or accumulating knowledge (which also implies that different kinds of scientific progress might be relevant for different sciences).

gh it might be an interesting exercise for philosophers of science to see how far they get hey start arguing from the point of view of a specific scientific domain such as the medical sciences in defending this stance on the essence of scientific progress in general, I do not think an abstract answer in terms of "solving problems" suffices for the more down-to-earth goal of critically considering what kind of progress one should rationally aim for in the medical sciences and what choices should be made in view of that. Much more need to be said and thought about then what the general approaches in philosophy of science have to offer.

Additionally, a view on scientific progress should not only be derived from what happened in the past, but should also help us in choosing directions for the future:

(...), the theory of scientific progress is not merely a descriptive account of the patterns of developments that science has in fact followed. Rather, it should give a specification of the values or aims that can be used as the constitutive criteria for "good science".

(...) it can be argued against the naturalists that progress should not be defined *by the actual developments of science: the definition of progress should give us a normative standard for appraising the choices that the scientific communities have made, could have made, are just now*

making, and will make in the future. [1]

We probably even have different normative expectations regarding progress in different sciences. At least for the medical sciences, we expect the progress to lead to concrete, future improvements. This demand for tangible improvements is probably more central for the medical sciences than for some other sciences, given the importance and centrality of the medical sciences' subject in the daily life of human beings. The medical sciences are closely related to clinical practice, and by consequence the scientific results are of a higher pragmatic importance. Future findings should add to our ability to intervene (through prevention or treatment) in people' s individual health states such as to improve the health of people in general. This is not only the ultimate goal

esearch process, but this should also guide the research in certain directions from the very beginning. By consequence, it is very useful and necessary also to think critically beforehand about what we conceive of as progress and how best to aim for it.

Hence, the question is what are progressive developments in the field of medicine? What methods can lead to progress in the medical sciences? As I just said, we try to prevent or intervene in disease states in order to improve human health in general. However, this is a much too general description of the kind of progress one could aim for in medicine. A lot of questions remain open. For example, do we want to achieve these improvements (primarily) at the individual level? Or do we need to focus also at the group level? Should we focus (solely) on prevention, amelioration and cure, or is it as - or even more - important also to think about care for the quality of life?

All this is also related to the goal of the medical sciences. What is this goal? Also here we have no clear answers and much to think about. The goal of the medical sciences seems many-sided, and is possibly even contradictory at some points [see e.g. 3]. This means that not only different sciences might have different kinds of progress as their aim (as I suggested above), but that even

different sub domains of a same scientific domain might have different goals, and hence, are in need of different projects to make progress.

It is not the goal of this paper to give decisive answers to all the questions that I have just brought up, or to develop a comprehensive theory about scientific progress in medicine. That should be the long-term goal. In what follows, I will take a small first step by focussing on one central and important tenet that is guiding current medical science, namely the paradigm of evidence-based medicine (EBM). A lot has been written in the literature about the pros and cons of evidence-based medicine. Most writings focus on problems resulting from epistemological presuppositions underlying EBM, on methodological problems for the implementation of the preferred methods, the gap between the ideals of EBM and the applicability in practice. In this paper, I ly analyze the value of EBM from the point of view of progress. I deal with the following kind of questions: What kind of progress drives EBM? What kind of knowledge results from EBM? Does this knowledge add to the progress we want medicine to make? What should be our progressive aims in medical science and is EBM helping us in achieving these aims? I do not pretend to present final answers, but my aim is rather to show that critically thinking about EBM from the point of view of progress might help us in putting EBM in the right perspective. Further, this analysis should be read as a case-study which demonstrates the importance of reflecting, from the point of view of progress, on the methodological choices that are made in the medical sciences in general.

EBM, complexity and progress

I do not have to introduce the readers of this journal to EBM, its characterization as “ the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients” [4, 71] or its evidence hierarchy which puts the evidence from (meta-

analyses of) RCTs on top. I suppose that most of the readers are also acquainted with the traditional criticisms on the evidence-based approach: that it oversimplifies complex problems, that it is of limited usefulness in the grey zones of medicine where scientific evidence is incomplete or conflicting, that the evidence from RCTs is almost exclusively derived from ideal patients, that there are common failures in the application of RCTs, that the meta-analytic reviews are unreliable, etc. [see e.g. 5-8]. I believe that these criticisms are important for recognizing the limits of the evidence-based approach, but it does not necessarily follows that the baby should be thrown out with the bath water. Hence, let me focus on what EBM can achieve in terms of medical progress.

ral, the strength of the methods that are highly valued in EBM is that they create the lity to find useful knowledge about (causal) relations apart from deep understanding of the underlying causal mechanisms. They offer us the possibility to deal with the complexity of diseases and to give some certainties where there would otherwise only be uncertainties.

Complexity

Some authors [e.g. 9] use the complexity of humans as an argument against evidence-based approaches, particularly in psychiatry, presupposing some kind of intangible, unique individual make-up to follow from it which would make us unable to find useful causal generalizations. However, since the complex make-up of humans is always involved, even in the development of diseases that we understand well, this argument of complexity is not convincing: in full detail, a lot of causal factors and influences are always necessarily present and interacting in a specific way in order to lead to a disease state. However, for some diseases, this general complexity of humans did not form an obstacle to gaining useful causal knowledge that is used to successfully prevent, treat and/or intervene otherwise in these diseases. How can it be explained that

complexity is a bigger problem in some cases than in others? I am convinced that this should be explained in terms of the complexity of the explanatorily *relevant* causal structures.

Let me explain this. It is not the goal of the medical sciences to give the full and complex description of the whole causal setting that leads up to a disease. As I already pointed out, the medical sciences are closely related to clinical practice and therefore focus primarily on manipulable causes [cf. 10]. This means that medicine makes selections of *relevant* causal factors instead of focusing on the whole causal history leading to diseases. Hence, whether (a) certain cause(s) should be selected as *the* difference-making cause(s) between a healthy and an unhealthy state is decided on the basis of their *explanatory relevance for medicine*. Only those that are

t in view of the medical goal of explaining and intervening will attract the attention of the l sciences. Now, in some cases, it is rather easy to select a limited amount of causes for a disease which also guides us in a successful way to prevention and intervention by showing us which causes to target, for example in the case of bacterial diseases. For other diseases, we do not have a clue (yet) for this selection of explanatorily relevant causes. Some might be caused by a very complex constellation of causal influences that will never be disentangible or reducible to a surveyable number of explanatorily relevant causes that make us able meticulously to understand and intervene in the disease. In the ideal future, we gain enough knowledge of all the explanatorily relevant causes of all diseases. However, the current, factual situation is that we do not (yet) have enough knowledge of a lot of "complex" diseasesto even start developing very precise, directed interventions into their causes.

Moreover, complexity plays at different levels: at the level of the proximate causes of the disease as such, at the level of the more distant causes (e.g. the causal influence of risk factors), and at the level of the possible interventions in the symptoms of the disease. Even if one has a thorough understanding of the proximate causation of a disease, it remains a question whether medical

practitioners really can directly intervene in the proximate causes. This will not only depend on the complexity as such, but also on, amongst others, the stance of the medical know-how. If an intervention in the proximate causes of the disease is impossible (e.g. when we cannot stop the out-of-control cell growth in the case of cancer), one can turn to the more distant causes (which will nonetheless often offer only preventive measures and no adequate treatment options), or to the symptoms (to relieve the effects of the disease rather than to treat the disease itself). Additionally, while knowledge of the role of a limited amount of causal factors might suffice to understand a disease and to know how to intervene in it, one might need further and more complex causal knowledge to understand, for example, the differences in effect between (slightly) different ways of intervening. This is for example the case when we want to compare the workings of different kinds of (similar) drugs.

This is precisely where the methods that are favoured by evidence-based approaches come in handy. These methods are strong in dealing with complexity. They form very handy tools to circumvent gaps in our causal knowledge. They are able to find generalizable knowledge about causes and effects, interventions and outcomes, in such a way that we are not pushed to deal with the whole complex picture. In other words, they help us search for explanatorily relevant causes of diseases, and for efficient ways in dealing with these diseases, for which we lack the insight into the (details of) the causal mechanisms that can further explain these relations. This is precisely their strength: they can offer useful (causal) knowledge where deeper insights in the complex underlying causal mechanisms are missing. The role of the pressure of practice in medicine is further not to be underestimated in this success story. The "black box" methods give us some certainties where there would otherwise only be uncertainties. Their evidence clearly helps practitioners, who feel obliged to do at least something about the disease states that they are confronted with in practice, even if they do not have full understanding of it:

(...), I feel more confident in my medical decisions when I can say "the data show this" or "the data show that". Even when I have to say "there are no data for this," I feel my decision is more valid. [11]

To conclude, complexity can also be seen as a reason *for* the use of the favoured EBM methods, rather than as an argument against them.

EBM and progress

What kind of progress results from the EBM approach? I use a distinction made by Pearce [12, 682]: the progress that EBM is after is a kind of progress that is based on *measurement* rather

derstanding. EBM prefers measuring the impact of (causal) factors to aiming for further anding of how these factors influence diseases. This way of searching for progress is driven by pragmatic aims rather than theoretical ones: the best way to get forward in the medical sciences according to the EBM paradigm is by getting to know what works rather than how it works. Such knowledge also adds to decisiveness with respect to the care for patients, which can be seen as progress in the care for people. All this fits in with a problem-solving approach rather than a knowledge gaining approach to scientific progress. The direct relevance for everyday medical practice drives the evidence-based approach and the progressive results are little gains in piecemeal knowledge about the best solutions rather than important gains in thorough understanding. This means that also the discovery of small differences in outcomes are within an EBM approach presented and interpreted as interesting knowledge that can lead to important steps forward, e.g., when comparing the effects of a new drug with the effects of a similar, existing one. As Mittra argues:

"(...) surely, we do not expect the RCT to deliver a therapeutic breakthrough by itself, in the same way that we would not expect a weighing machine, no matter how sophisticated, to deliver a

miraculous drug that will abolish obesity. It is equally clear that if indeed there were to be a revolutionary drug or intervention, the RCT would be neither ethically permissible nor required. [13, 504-505].

Hence, results from EBM lead primarily to small steps in pragmatically useful knowledge. But these are small progressive steps where we might otherwise not have any clue at all about the possible, or the best, interventions due to our lack in detailed causal knowledge. In that sense, EBM indeed adds to the best care on the basis of the best possible evidence.

However, this is no reason for medicine to canonize the methods that are highly valued by EBM. We should be careful for at least three, related reasons. First, there is the difference between the

nd the real. While these methods can be very helpful and useful, it is just as much

int to recognize that their evidence is also very assailable. The literature on EBM has plenty of critical comments showing the limitations of this approach. They demonstrate that we should also be humble and careful when using these methods and when applying their evidence. Ironically, the more complex the disease state we try to get understanding of, and hence, the more we seem to be in need of methods that can circumvent causal knowledge gaps, the more assailable the evidence that results from these methods will be. In other words, where we are most in need of these methods that are highly valued by EBM, they also seem the least reliable.

Secondly, although RCTs can bring us pragmatically useful knowledge, we should also recognize that the impact of the findings in practice is all together often limited. A lot of the RCTs that are currently carried out only detect small differences and/or only answer very specific questions. Further, the fact that a considerable part of the RCTs is currently commercially driven, leads to even less reasons for hope for unexpected interesting results. Consequently, although we cannot know to what extent we will ever be able to get a better grip on (the complexity of) diseases by alternative methods, it is clear that we should not expect that too much of the pioneering

knowledge will come from RCTs [cf.13]. Therefore, also the reflex to promote only more RCTs in response to our limited knowledge [cf.14] is shortsighted.

Lastly and probably most importantly, if we not only turn to EBM' s favourite methods in cases where we miss important causal knowledge to understand what happens, but just prefer these methods in general at the expense of the use of methods that can lead to deeper understanding (as actually is the case for EBM), than we start creating knowledge gaps, rather than circumventing them when this is our best hope for making any short term progress. And since in the end, the RCT and observational methods should be based themselves on the available theoretical knowledge for their set-up and the interpretation of their results, this reversal not only limits what

gain from the other methods as such, but also what we can gain in the long run by means s and observational studies themselves.

Causal mechanisms and progress

What kind of methods and consequently, what kind of progress is discouraged by EBM? Towards the bottom of the evidence hierarchy stands the evidence from the basic sciences. These are much more occupied with the question *how* diseases develop and *how* interventions can change these developments. Basically, this concerns knowledge of lower-level causal mechanisms. But also the importance of higher-level causal mechanisms, mainly coming from the social sciences, is not recognized by the EBM approach.

Lower-level causal mechanisms

The basic sciences such as pathophysiology give us insights into the detailed causal mechanisms that are at work in the development of diseases. These "lower-level mechanisms" underlie and explain the causal relations that we can measure using RCTs and observational studies. EBM' s

emphasis on the importance of the latter methods, which just measure the role of certain biological and/ or individual factors, goes at the expense of the interest in basic research into the pathophysiological mechanisms. This leads to an increasing impact of statistical results in clinical practice, apart from what I call "deep causal understanding" in the (causal) relations we intervene in. This can create a situation in which statistical results are uncritically accepted. One cannot set up or interpret a trial or an observational study without any knowledge of (possible) causal mechanisms. In the background, knowledge of causal mechanisms and hypotheses about possible causal mechanisms always play a role. However, the problem is that what guides the researchers in setting up a trial and interpreting the results is often just the conviction that it is *plausible* that mechanisms (of which they do not know the details) are at work. The finding that an intervention works nonetheless does not imply that it works through the presupposed plausible mechanism. Also, the finding that a certain correlation holds, does not need to imply that it concerns a causal relation that arose through the supposed, plausible causal mechanism. Although it is clear that we often can make efficient use of our findings from randomized trials and observational studies without having the full knowledge of the underlying causal mechanisms at our disposal, it can also be important to try to get a grip on which causal mechanisms are really at work. More, not having the knowledge of the underlying pathophysiologic processes might hinder the development of novel and potentially more efficacious interventions, as van der Wilt and Zielhuis [15] pointed out. They give the example of breathing retraining as treatment for panic attacks. According to the hyperventilation model, the plausible mechanism was that hyperventilation led to a reduced amount of carbon dioxide in the blood which then caused the panic attacks. However, it turned out that hyperventilation did not reduce the carbon dioxide in the blood. Now it is assumed that breathing retraining leads to a greater level of skilled control which reduces the panic attacks. The latter insight led to new therapies which would not have

been developed without the research into the underlying causal mechanism.

Higher-level causal mechanisms

Randomized controlled trials and observational studies not only rely on background knowledge about causal mechanisms, their results can also point to possible causal mechanisms that can be surveyed in further research. However, this will always concern lower-level causal mechanisms. After all, EBM fits in with the dominant biomedical, reductionist paradigm. The methodology is not appropriate for studies that require a consideration of the historical and social context, as Pearce (1996, 682) points out with respect to epidemiological research:

"The danger is that attempting to eliminate the influence of all other causes of diseases - in an attempt to control confounding - strips away the essential historical and social context, (...) Thus, the tendency to only study factors that fit the clinical trial paradigm should be resisted, and appropriate study designs should be chosen (or developed) to fit the public health question that is being addressed. (...) We seem to be using more and more advanced technology to study more and more trivial issues, while the major population causes of disease are ignored." [12, 682].

Causal mechanisms and progress

I argued that EBM limits the role of the research into causal mechanisms in two ways: by underrating the usefulness of thorough knowledge of lower-level causal mechanisms and by underrating the usefulness of knowledge of higher-level causal mechanisms. Now, what kind of progress can this knowledge offer? These methods offer in the first place detailed *understanding*. At first sight, these additional insights might not be important in our aim for better care and might only be of importance for progress in terms of accumulation of knowledge. However, as van der Wilt and Zielhuis' example of breathing retraining demonstrates, in some cases the research into

the underlying causal mechanism can play an important role as a catalyst for the development of better treatments. Additionally, having a better grip on how an intervention influences the body might make it easier for a clinician better to help individual patients whose bodily state does not conform to that of the ideal patients in the trials. Further, contrary to EBM' s favourite methods, basic research seems better suited to lead to big progressive steps forward in the long run, as Mittra argues:

"Clearly, we need to bring the individual investigator back to the center stage of biomedical research and to provide him with ample funding and opportunities to pursue the much neglected hupothesis-driven, patient-centric, innovative research, because the history of medicine shows bedside doctor can be a passionate man of action capable of catalyzing remarkable ries and innovations of far-reaching therapeutic consequence." [13, 511].

However, also these expectations should not be idealized, as Mittra is inclined to do. After all, there are also examples of interventions that entered medicine without benefit of the numerical method and had to be rejected afterwards. One of them is the use of antiarrythmic drugs after myocardial infarction, which was found in a trial to lead to excess mortality in the treated group (example from Swales [16, 404]). Lastly, research into higher-level causal mechanisms can lead to important progress by means of knowledge on possible group level preventive measures. Although this does kind of knowledge is not always helpful for individualized clinical care, it is clear that it can add to progress in medicine by meeting the more general, long-term goals of the medical sciences.

Progress again, goals and limits

Some argue that the medical sciences did not make any interesting progress in the last decades [13,17]. The high value placed on the randomized controlled trial by EBM is pointed at as one of

the most important causes. However, the answer to the question whether we made any progress of course also depends on the kind of progress we expect the medical sciences to make. Ideally, we want the medical sciences to gain full insight in all relevant causal factors for all diseases and in how to intervene in them. However, to what extent it is possible to meet this ultimate goal in the future remains to be seen and is unpredictable now. In the end, we will also have to look back from a future point in time to judge whether our current enterprises have added to fulfilling this goal. At this point in time, however, we can set ourselves the more humble aim of trying to take some steps forward in defeating diseases and caring for diseased people and thereby just be happy with any small steps forward that we take.

Howe[illegible]er, what is clear from what precedes, is that the resolute choice for the EBM paradigm can us badly and is likely to stop progress in certain ways. Even more problematic is to keep on making such a resolute choice without reflecting on whether the investments are still worth the gains in terms of progress:

Over 16,000 RCTs were reported in the literature in 2005 alone, yet few questions are asked as to their purposefulness or impact on the progress of medicine (Zwarenstein and Oxman 2006). It seems that the RCT, simply because it provides the highest level of clinical evidence, is to be performed for its own sake, like an ideology that is to be blindly followed and not questioned. (...) [13, 504-505].

My analysis in terms of progress adds additional reasons for not favouring RCTs (and observational studies) at the expense of other methodologies. Instead, it is clear that we should value each method that might contribute to the progress of medicine equally. Meanwhile we should recognize that none of the methodologies is ideal, and that each of them needs the knowledge resulting from others in order to gain further new insights.

Additionally, we should try to ameliorate our methodologies and use them in other ways in order

to encourage medical progress. It would, for example, be useful to pay more attention to the survey of long-term effects of interventions by means of statistical methods. In view of progress, we should also more consciously try to merge evidence-based and "mechanism-based" medicine, by bringing both kinds of knowledge together in our further search for knowledge, such as is done explicitly in the EME programme (Efficiency and Mechanism Evaluation Programme, http://www.eme.ac.uk/) [15]. All this should make it possible to aim more efficiently for advances in cure and both short term and long term care, for advances in meeting both our direct and indirect goals, and hence for making both short term and long term progress. However, aiming for progress also means learning to live with the limits of our current methods and knowledge. Recognizing them will teach us to value RCTs as one of the possible methods to progress, rather than *the* preferable one.

To conclude, blindly favouring certain methods because of their immediately tangible short-term benefits implies that we parry the important question of how best to advance progress in the long run. This leads us to losing sight of our general goals in doing research in the medical sciences and does not accord with what we hope the medical sciences to bring us in the future.

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