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How Medical Know-how Progresses*

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Over the past several years I have been working with a group at Columbia University studying the progress of medical understanding and practice in several disease areas, and recently also with a group at the University of Manchester with similar research interests. The point of view I will espouse below has been developed in close interaction with my colleagues and their research projects, as well as through my attempts to understand the history of modern medicine more broadly. I believe that most of my colleagues have come to a similar perspective, but I do not want to implicate any of them in the details I will put forward.

The conventional wisdom regarding the sources of the remarkable progress in medical practice that has been achieved over the last century highlights the role of scientific research that has transformed as well as deepened understanding of how the human body works and the nature of pathologies. Under this perspective, new understandings won through research have lit the way to methods of cure and prevention. While there certainly is something to this position, I will argue that the advance of basic knowledge of the human body and disease has been one, but only one, of the important forces enabling progress in medical practice. Further, the role played by scientific research only can be understood properly if other pathways to progress, in particular the advance of the technologies underlying treatment and diagnostic modalities, and learning by doing and using, are recognized.

Among other things, the simplified picture of the advance of medical know-how that is widely held now tends to repress that the advance of practice has been very uneven across diseases. Certainly many diseases that used to be scourges are now preventable or curable – most but not all diseases caused by microorganisms fit that bill. However, little

progress has been made on others – this is the case with many cancers. This unevenness of progress suggests that, at the least, the simple story about science driven progress needs to be disaggregated, and there are important questions about why certain diseases have not been mastered, at least not yet. The obvious response – that progress in practice has been stagnant where scientific understanding has not advanced much - is too simple. As I will argue shortly, there are many cases where ability to treat a disease has increased dramatically without any dramatic improvement in basic scientific understanding of that disease, and other cases where scientific understanding clearly has improved significantly, but has not led to advances in the efficacy of treatment.

More generally, as I read medical history, even recent medical history, there is a somewhat overblown faith in the importance of relatively basic understanding of how the body works or of the nature of a disease in enabling the advance of practice. Of course that argument hinges to some degree on what "basic" understanding means. The discovery and demonstration by Pasteur and Koch that a number of human diseases were caused by microorganisms clearly was a crucially important scientific breakthrough that in a number of cases enabled preventions or cures to be developed. [†] But the discovery that microorganisms caused certain diseases was a long way from the development of understanding of just what the microorganisms were doing that was so harmful to the body. I also note that for many years the search for a mode of treatment invoked by identification of a microorganism that caused a disease was to try to develop a vaccine. But how vaccines actually worked was not understood before many years had passed since the early vaccines were developed.

[†] See the discussion in Porter, 1997

I propose that most of the gain in ability to prevent or cure diseases that have come from research on the cause of disease have been of this sort, quite narrowly oriented. A canonical case in point is Lind's 18th century trial on sailors of different possible ways of preventing scurvy, which identified having citrus fruits in their diets as a mode of prevention. [‡] In more recent times, the discovery that diabetes was caused (at one level) by inappropriate levels of bodily production of insulin, that certain diseases were the result of vitamin deficiencies, and that peptic ulcers often were the result of bacteria, all pointed to more appropriate means of treatment. But these new understandings were not particularly "basic", in the sense that they gave deep or broad new insight into the biology of health or disease. Rather, they were quite local and empirical. [§]

It certainly is true that on a number of occasions new, more basic scientific understandings of how the body works or of what is going on in a disease have lit the way to better medicine. The growth of understanding of the workings of the immune system facilitated the development of vaccines, and other treatments, and illuminated what is going on in diseases like lupus. Understanding of the biochemistry influencing the behavior of the heart provided the illumination needed for the development of various pharmaceuticals that effectively treat high blood pressure. [**] More recently the development of Gleevec as an effective treatment for myelogenous leukemia is a case in which search for a drug was closely guided by scientific knowledge of what was going on in a particular cancer. But I would propose that, for the most part the advances in scientific understanding that have led to advances in practice have been local and

[‡] See the discussion in Porter, 1997
[§] For a similar point of view see Thaggard, 2003
[**] Gelijns, 1991

empirical. Gleevec still is an exception. Most of the developments or discoveries of new drugs that are improvements in the treatment of cancers continue to be made through methods that come close to trial and error learning.

To push the matter further, I would argue that most of biomedical research is incremental and focused narrowly, aimed to learn somewhat more about a particular body function or pathology, or to discover or develop more directly a better mode of treatment. Most proceeds within established accepted paradigms, to use Thomas Kuhn's term. While, as the examples above show, occasionally such research will yield a new way of looking at a disease, this is rare, and even more rare is a scientific breakthrough that changes broad biological understanding. On the other hand, over long periods of time the cumulative result of such research often is a major improvement in ways of treating patients. [††]

I now want to argue that, in addition to mischaracterizing the nature of the advances in scientific understanding that have been behind the advances in practice that has been achieved, the argument that progress in medical practice largely has been the fruit of stronger scientific understanding does not recognize adequately that in many disease areas progress in practice has been largely the result of new modes of treatment – new drugs, new medical instruments and devices – whose discovery, or invention, and development had little to do with any advance in scientific understanding of how the body works or of disease. Put another way, the perceived set of understandings and research methods that orient work aimed to discover or develop new treatments and

[††] See for example Gelijns regarding improvements over time in treatment of high blood pressure, Metcalfe James and Mina on the treatment of cataracts, Bohmer on diabetes, or Mina, Ramlogan Tamputolon and Metcalfe on angioplasty

diagnostic modalities, as contrasted with research aimed to achieve better understanding of a disease, should be understood as having standing as a paradigm, in the sense of Kuhn, in its own right.

Thus in the years after World War II the knowledge of the efficacy of antibiotics, and of how to find and develop them, and more recently the development of recombinant DNA techniques and of combinatorial chemistry, has dramatically augmented the ways that new pharmaceuticals have been created, found, tested, and developed, but these understandings and techniques were not the result of any improved understanding of particular diseases. Similarly with respect to the building blocks for medical devices and instruments, where technological advance not originally oriented to use in medicine has enabled major advances, for example the use of lasers, and of flexible catheters with miniature television or cameras at the tips. Advances in electronics have been the basic facilitating factor behind the remarkable advances in diagnostic equipment that have been achieved over the past half century. [‡‡]

Over the last 30 years great advances have been made in the treatment of cataracts. Now the treatment involves the removal of the clouded natural lens and its replacement with a plastic intra ocular-lens. A wide range of technological developments were involved, but hardly any of these depended in an essential way on better understanding of the eye and how it works. [§§] Similarly, the development of stents largely involved the invention and refinement of new devices, rather than any deepened understanding of what leads to clogged arteries. [***]

[‡‡] See Gelijns and Rosenberg for the histories of a number of important medical instruments and devices that have been developed in the years since World War II.
[§§] See Metcalfe, James, and Mina, 2005
[***] See Gelijns, 1991, and Mina, Ramlogan, Tamputolon, and Metcalfe

Because the base of knowledge and technique used to develop advances in the modalities used in treatment and diagnosis is to a considerable extent separate, these advances can and often do occur independently of any significant increase in knowledge about the disease. The other side of this coin is that, while advances in understanding of a disease may point broadly to a possible treatment or preventions, the capability to develop that treatment may not be there. Thus biomedical scientists have known for some time that cystic fibrosis is the result of a genetic defect that prevents the body from maintaining the appropriate balance of sodium and chloride in its cells. However, this knowledge has not yet led to a cure, and most effective treatments have been arrived at pragmatically. [†††]As another example, while enough now is known about AIDS to suggest that a vaccine would be an extremely valuable preventative, existing techniques for developing vaccines presently do not seem strong enough for an AIDS vaccine to be developed.

While the pathways to better diagnostic and treatment methods often are powered or hindered by factors that are relatively independent of scientific understanding of disease, there clearly are important interactions. Understanding of the body and disease obviously orients the search for better modes of diagnosis and treatment, even though what can be achieved given that orientation may depend largely on factors like the ability to design pharmaceuticals of a particular type, or available electronics technology. I also want to highlight that the interactions often go the other way. New diagnostic technologies and new treatments often provide the basis for the development of improved, or radically different, scientific understanding of the disease. But the principal point I am making here is that the ability to develop new modes of treatment often

[†††] See eg Gawanda, 2006

depends on activities, and paradigms focusing and giving strength to those efforts, that are different from those oriented to advancing scientific understanding of disease.

The theory that scientific research has been the key to advances in medical treatment also ignores the role of learning in practice. In many cases what is deemed promising in research proves not to work well in practice, and even may be seriously deleterious. At the least the treatments to which research results point need to be tested out in practice. Testing in practice not only serves as a screen for proposed new treatments; such experimental practice often leads to significant modification of the conception that came out of research. More generally, I note that even in this era of strong medical research, in many cases considerable progress has been made through learning by doing. ‡‡‡ This is very common in surgical procedures where very major improvements tend to be made as experience accumulates, problems are recognized and dealt with, and routines honed.

Again using Thomas Kuhn's language, it seems clear that at any time there is a paradigm regarding what is appropriate practice to deal with a particular disease which, while connected to the scientific paradigm, has standing in its own right. As with Kuhn's conception of a scientific paradigm, a practice paradigm includes both prevailing understanding of what is best practice, and a number of problem solving strategies and methods that can be invoked when doing the standard thing is not working well. Much of learning in practice proceeds through the problem solving activities used by physicians and their associates in practice.

The scientific paradigm and the practice paradigm of course are related. When the scientific paradigm changes, the practice paradigm generally changes as well. Thus the

‡‡‡ The Gawanda study of cystic fibrosis provides some fine examples

radical changes in understanding of diabetes, peptic ulcers, the sources of high blood pressure, mentioned above led to major changes in the accepted treatment paradigm. But the two paradigms are not the same thing.

At any time, large portions of scientific understanding of a disease will have little bearing on practice. As noted, while scientists know a lot about cystic fibrosis, ability to deal with the disease is still limited. On the other hand, a good deal of prevailing practice may be known to be effective, but with little scientific understanding or just why and how. This is true today for many pharmaceuticals used in the treatment of various diseases. Indeed, these puzzles about why a particular treatment seems to work often provide attractive targets for scientific research.

Obviously the practice paradigm also interacts with the paradigms that guide and enable the development of new or improved treatment and diagnosis modalities. The needs felt by practitioners feed back to influence R and D on new medical artifacts. And experience with new drugs and equipment is an essential part of the process through which these are evaluated and improved.

Generally the development of new treatments involves both off line research and development, and learning in practice, but the roles played by research, and the nature of the interactions of research with practice, differ significantly depending on the modality of treatment being explored, developed, and tested. The discovery and development of new pharmaceuticals tends to be research intensive, much of the work going on "off line" (in a laboratory setting rather than in practice). However, controlled trial in practice is an essential part of the process by which new pharmaceuticals come into use. Also, what is learned in practice often stimulates research to find or design a pharmaceutical that is

more effective and has less negative side effects. And often productive new uses of a drug originally advertised as for one purpose or disease emerge out of practice.

The design work on new medical devices, like specialized catheters, or the stents now used in treatment of clogged arteries, also is done largely off line. However here my reading of the histories suggests that, more than regarding new pharmaceuticals, there is an interactive process involving feedback from use in practice, to efforts to design a more satisfactory device, to more experience in practice…before a satisfactory design is achieved, and improvement through this process can go on for a long time. Learning regarding new medical procedures, like a new mode of surgery, may begin with experimentation on non-human animals, but proceeds largely in practice.

Thus while often ignored in the contemporary discussion, it is apparent that learning by doing and using plays an important role, along with off-line research, in the advance of both medical understanding and practice. But this fact poses something of a puzzle. There clearly are great advantages to being able to learn in off-line research as contrasted with having to learn in practice. For one thing, it is much easier to put tight controls on experiments. And, feedback from experimentation is likely to be faster. Also, for good reasons there are strong restrictions on trying something new on a human patient, unless there is strong evidence that doing so will not be harmful, or that any possible harm is more than balanced out by promise that what is to be done is going to be significantly more effective than present best practice. Obviously there are far fewer constraints on what can be done in experiments in vitro, or using non-human animal models. But why then does such a significant part of the progress made in medical know-how continue to be made through learning in practice?

Clearly a principal reason is that, given the state of scientific understanding, there are limits to what can be learned through in vitro research and the use of animal models. An important reason for the broad truth of the proposition that it has been the advance in scientific knowledge that has illuminated the pathways to better medical practice is that, in many cases, stronger scientific knowledge has enabled the sharp focusing of off-line research, in vitro or on animal models, on treatment modes that have good promise of being effective, whereas when knowledge is weaker such exploration is more random. But it is apparent that our capabilities of learning through research that does not involve experimenting on human subjects remain significantly limited.

But a second reason is that a lot is learned in the course of practice, observation of what seems to be working and what is not working, modifying practice to try to get better results, surprising developments, etc. There are strong constraints on experimenting in practice. However, it is clear that a lot is learned from cumulative observation and from the variation that naturally occurs across patients, physicians, and time. And particularly regarding a new practice, often the lines between observation and evaluation, and experimentation, are blurry, not sharp.

I note that the fact that a lot is learned in practice, and only can be learned that way, calls into question another part of today's conventional wisdom: the idea that formal random assignment trials are the only reasonable way to sort out what works and doesn't work in medicine. By that I do not mean to downplay the importance of random assignment trials. Rather, my argument is that these need to be seen as part of a broader system of experimentation and learning that molds the advance of medical know-how.

In today's world, random assignment trials play two important roles. One is to serve as a screen for proposed new treatment modes, a new pharmaceutical is a canonical example, to test out whether they are safe and effective prior to any movement to get them into general use. The other is to test systematically the efficacy of a treatment mode that has been used in practice but whose efficacy or safety are uncertain and controversial. Both are valuable functions.

However, the ability to screen new modes of treatment through scientific testing before they get into use is limited. [§§§] As argued above, practice itself is the source of many new modes of treatment, from the use of a pharmaceutical in a different way than had earlier been tested and approved, to a new mode of surgery. There is every reason to be careful about these kinds of initiative, but it also is important not to shut them down, and impossible to do so effectively. And given the costs and constraints involved in random assignment testing, only a small percentage of prevailing practice is going to be subject to such an assessment, even when such practice is controversial. A significant share of the evaluation of practice is going to have to be through the assessment by physicians and physician groups of the safety and efficacy of what they are doing, and communication of these judgments to the wider community.

Similarly, given the costs and organizational complexities of doing random assignment testing, use of this procedure for evaluating practices that have been in use whose efficacy is under question is necessarily limited. Again, considerable reliance has to be rested on physician evaluation. And where a practice has been used relatively widely, epidemiological studies, for all their limitations have to play an important role.

[§§§] Much of the following argument is developed in more detail in Murnane and Nelson, 2007, and in Christensen. Gelijns, Moskowitz, Rosenberg, and Talati, 2007

There is a further limitation on modes of evaluation more generally, including random assignment testing, that also must be recognized better than it is. What is being evaluated at any time generally needs to be understood as a snapshot in a moving picture. Particularly if there is a non trivial lag between when a practice is performed, and the time when its efficacy can be reasonably evaluated, at the time of evaluation the practice itself may have changed considerably from what was evaluated. And clearly freezing the practice over the period of evaluation to avoid this problem is usually not a desirable thing to do, even if it could be done.

I think it fair to say that most discussions of the roles of random assignment testing do not recognize these innate limitations, and that therefore that that instrument must be seen as a part of the evaluation system, rather than its sole element, and be understood in a dynamic learning context, not a static one.

To sum up my argument, the advance of medical knowledge regarding a disease needs to be understood in terms of progress within three interacting but partially independent paradigms: one concerned with biomedical understanding of what is going on in the disease, a second with procedures for developing new treatment modalities, and a third beliefs about effective practice in dealing with the disease. The process is evolutionary, in the sense that many new things are tried, some are judged to be effective and are incorporated into the body of practice, and others are judged ineffective or worse. Of the latter, some are abandoned and others modified to try to make them work better. The evaluation-selection process also involves a number of elements, random assignment clinical trials one among them. But formal random assignment testing can cover only a small fraction of new much less prevailing practice, and needs to be understood as one

part of the dynamic learning process, involving a variety of methods of evaluation, through which the medical community, including scientists, practitioners, and policy makers, improve what is done.

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