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Small Leaps or Giant Steps

By Scott Gottlieb

New drug treatments often take time to prove their effectiveness, and medical progress will slow if the lack of immediate and dramatic results disqualifies new drugs from further research and usage.

There are seldom eureka moments in health care. Few new drugs or medical devices save scores of lives or cure diseases when they first hit the market. New technologies rarely translate into immediate life expectancy gains, and it is uncommon that results of a single study will transform how medicine is practiced.

Medical progress is not magic, and sudden discoveries do not lead to dramatic cures, although a new book by Marcia Angell, a former editor of *The New England Journal of Medicine*, would lead you to think all of our gains in health have been achieved from just a handful of the most potent new medicines.

Instead, medical breakthroughs unfold over time, and gains in life expectancy and health are realized only after a series of small technological advances are collected into new ways of practicing medicine or attacking a disease. The practice of medicine unfolds not in a series of certainties, but in a series of doubts.

The advent of lipid-lowering statin drugs alone did not immediately lead to the dramatic 20-percent drop in death rates from heart disease observed between 1990 and 2000. And neither did the introduction of less invasive ways of opening clogged heart arteries with new drugs such as streptokinase or with tiny catheters inserted into the heart.

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Other new drugs and more aggressive approaches aimed at lowering blood pressure also played an important role. So did reductions in smoking and improvements in diet, not to mention new knowledge on how to integrate all of these different technologies and treatments into a more effective overall approach to healing.

Fatalities from breast cancer fell from 32.3 deaths per 100,000 women in 1980 to 25.4 in 2000, while over that period the risk that a woman with breast cancer would develop an aggressive level of the disease dropped from 40 percent to 15 percent.

The improvements that enabled these gains were not achieved with the approval of a single breakthrough medicine like Roche's drug Herceptin or the promising class of breast cancer drugs known as aromatase inhibitors. Rather, they were the result of research to identify better diagnostic technologies that could achieve earlier diagnoses, clinical approaches that could target new treatments to specific tumor types, and efforts to combine all of these innovations into strategies where the sum of the parts proved far more effective than the individual treatments.

More Than "Me-Too" Drugs

Marcia Angell, a pathologist by training, takes principal issue with "me-too" drugs—new medicines that she regards as not much better than drugs already available. And her views provide ammunition to drug industry critics inside political

circles. The industry, she argues, has become "a marketing machine to sell drugs of dubious benefit," and she calls on the government to take over the testing of new drugs and require that they be tested, not against placebos, but against other drugs for the same condition.

This mandate for "comparative effectiveness" studies, where new drugs are compared to old drugs, is a standard that is used in Europe. But the European data generated from these kinds of head-to-head trials are often ignored by clinicians here, who argued to me when I was at the Food and Drug Administration that head-to-head trials are often underpowered and therefore do not take full stock of subtle but clinically important benefits such as improved dosing schedules that lead to better compliance or better side-effect profiles, which, in turn, allow safer administration of medicines.

Underpowered head-to-head trials do not reveal the small but important benefits offered by incremental advances in medicine. They often end up proving the null hypothesis, that there is no difference between two drugs, even when clinically important differences exist. Nonetheless, the policy change Dr. Angell and others advocate would reduce the total number of drugs approved, as well as the availability of back-up drugs that provide alternatives to medicines and create competition that lowers prices.

That may be the point.

But while Dr. Angell and other critics focus on the list price of medicines, the truth is that companies compete ferociously to get their drugs placed on the preferred lists of many drug plans, often offering deep discounts if the plans accept a battery of products. Ample evidence demonstrates that having a lot of different companies selling similar drugs in the same category only accelerates this price competition. In fact, the most expensive medicines, and the ones least likely to be discounted, are those that face no category competition.

More important is the patient, who often needs the therapeutic variety that Dr. Angell scorns. Not all similar molecules hit every patient in the same way, and drugs that appear to be small advances when first approved end up proving themselves over time, as doctors and patients gain knowledge and experience in using them. Many of the most important uses of new drugs were uncovered only after the medicines were widely available and administered to tens of thousands of different patients—a breadth of clinical experience that no reasonable clinical trial can replicate.

Promising New Treatment

The class of anti-inflammatory drugs known as tumor necrosis factor inhibitors was billed as a promising new treatment for arthritis long before people discovered just how potent it could be in attenuating the course of a bowel ailment known as Crohn's disease, psoriatic arthritis, and now colitis. The angiotensin-converting enzyme (ACE) inhibitors were just another treatment for high blood pressure, in many cases a less potent one, long before they solidified their role in helping the heart muscles reshape themselves after a heart attack or in stalling kidney disease in diabetics. And the breast cancer drug tamoxifen, used alone, reduced the risk of recurrent cancer. Only when it was combined with another drug, years after its approval, did its risk reduction rise to a dramatic 40 percent.

It is tempting to look at the small improvements initially offered by any single drug as a failure of the investment in health care, but viewing medicine this way loses sight of the decades of incremental progress that has put us where we are today.

Painstaking Progress

Looking at medicine through its appropriate prism of painstaking progress reminds us that we cannot lose our willingness to approve and integrate safe and effective new drugs, even if they seem at first blush to be no more effective than the next best thing. If every new drug needs to prove that it is a significant advance over its close cousin before patients and doctors can give it a try, we will lose a lot of medical progress before it ever has a chance to germinate.

That is not to suggest that we should be writing blank checks to medical research. Companies that develop new drugs must fulfill an obligation to patients that use these medicines to continue to collect evidence about drugs in order to substantiate their benefits and define their limitations.