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Discoveries Now and Then

Shifting Incentives and Expectations

Mark V. Pauly, Philip A. Rea, and Lawton R. Burns

Imagine you were transported back in time to the early 1900s – say 1916 – in any large city in the United States: Boston, Philadelphia, Chicago, Minneapolis, San Francisco. Things would look different from today, but much would feel familiar. There would be automobiles with gasoline-powered engines, a telephone service, public transportation, clothing made of wool or cotton, electric lights, and appliances powered by electric motors. The Harvards, Princetons, Penns, and many other colleges would be there, though much smaller in terms of faculties and budgets than today, with much more emphasis on teaching rather than research. A government that sometimes succeeded but sometimes failed in delivering basic public services (trash pickup, police) would be a constant. Travel would be a great deal slower, but that would not matter to most people because they wouldn't be expected to journey as far, or get there as quickly, as people do today. Entertainment would tend to cost less and be performed live, although those new "moving picture palaces" would be opening up all the time. There would be more steam, more smoke, and more noise, but on the whole it would be a world you would recognize.

What would be truly different? One major difference is that since 1916, the US standard of living has gone up enormously. People at the lowest level of today's income distribution actually live better material lives than everyone but the wealthiest in 1916. A reason for this is that much of the population at that time worked on farms and earned notoriously low pay. And although those raising chickens and milking cows represented a much larger segment of the population than the urban workforce crowding the cities, the price of food was still very high relative to what people could afford.

Another major difference – and it is a huge one – is a change in what the average person was afraid of dying of. Today heart disease and cancer

top the list of the USA's major causes of death. But in 1916 you would be most terrified by the thought of catching an infectious disease. (It was a fear validated by the influenza epidemic that would sweep the country three years later, killing an estimated 50 million people worldwide, more than the number who died in World War I.)

That year, tuberculosis was the second leading cause of death (it had just been edged out by heart disease), and was followed at very high rates by other contagious diseases and related complications: pneumonia and influenza, nephritis from scarlet fever or diphtheria, and diarrhea. Cancer was only the eighth leading cause of death, followed by death from premature birth. By our time, heart disease and cancer would be first and second cause respectively, and all of the infections and premature birth would have fallen off the chart.

Also by our time, agricultural productivity has skyrocketed, reducing the relative price of food. (So much so that overabundance and obesity has a lot to do with the modern list of causes of death.) Today, the US population and much of the world is fed (and fueled) by a tiny fraction of the workforce.

Our trip back in time reveals that improvements in agriculture and health – made possible by discoveries in the life sciences – have contributed much to the quality (and length) of life we enjoy today. While it is true that, measured as a percentage of gross domestic product (GDP), 1916's medical care spending is far below today's level, few of us would choose it if what we got in return was only what that era's biomedical technology had to offer. Innovation-driven progress in the biomedical sciences, continually yielding new medicines and cures, is something we have come to take for granted. Our triumphs over disease in this century have been so outstanding that there is almost a "what's taking so long" feeling around the fact that conditions like cancer and diabetes continue to claim lives; we think that something must be amiss in resource allocation or efficiency.

If we extend our look back to the beginning of history, the current pace of improvements in health and food production seems even more anomalous. Discoveries leading to a correct understanding of our bodies, the plants and animals central to our lives, and the threats from disease and pests historically were rare. They tended to appear in bunches (such as in the works of ancient Greek and Muslim writers), and they took a long time to be accepted and to result in changes to what people actually did to avoid and treat illness and pests. It took nearly 200 years – as we shall see – from the discovery of bacteria to the effective prevention and treatment of bacterial infection. It took even longer for hybridization and other forms of selective breeding of crops and domesticated animals to

be implemented by farmers. But now that we've come to expect progress, its failure to appear in a timely way is treated as evidence that something needs to be corrected.

It is important to appreciate how far we have come. And it is humbling to realize that we as citizens, policy makers, businesspeople, and patients still do not really understand where this innovation comes from, how it develops, and how to guide it to maximum advantage or minimum delay.

The question of what determines the pace and cost of progress in the biomedical sciences, a process clearly dependent on invention and creativity, is the subject of this book. We hope to understand these magnitudes and their changes over time. We also hope to evaluate whether the process can, and should, be altered by changes in public and private policies that affect the financing and rewards for innovation in the biomedical sciences.

UNVEILING THE PROCESS OF DISCOVERY

Where do new ideas in the biomedical sciences come from, and why do some get carried forward to the point they become useful? It isn't hard to name the steps in the process. There have to be resources available for a discovery process, which in contrast to creative endeavors such as music or the arts is much more demanding in terms of raw materials. There has to be at least one person, and perhaps many, motivated to worry about why some things are not working well and might be improved. There is almost always a stock of prior knowledge, sometimes about the "basic" building blocks of ourselves and our world, and sometimes about other successes and failures in this particular line of investigation. At this point, any discovery has to be turned into a large-scale activity of application, of implementation, of finishing and polishing, of demonstration and solicitation, and of evidence generation. Once people are convinced that this new thing, or new approach, is truly novel and will on balance do more good than harm, then typically new tools will be needed to produce the thing in quantity, and at a profit. Finally, consumers and those who advise them have to be willing to use the new thing, and be able to pay what is charged.

There are many possible ways of detailing these steps. What we'll do here is try to describe the cusp of innovation (where many preconditions have already been satisfied, but success is far from assured) using some deep concepts from the philosophy of science, not just the life sciences. The philosopher Thomas Kuhn will be our guide on the first part of this journey, because he was the inventor of the concept of "paradigm shift" as a means of rationalizing progress in science.

Although cloaked in deep language, Kuhn's idea is a simple one: at some point in time there exists some way of looking at a particular part of the world – the orbits of the planets in the night sky, the cause of a disease that kills a loved one. This "reigning paradigm" will be used to guide behavior but will be observed over time to fail to predict or explain some crucial phenomenon. The accumulation of such contradictions will be followed by the proposal of a new paradigm that reconciles those contradictions in a new theory or model of the world. This event sets the stage either for the emergence of new contradictions or satisfaction with a new paradigm. It is rare, but sometimes no further progress occurs in a particular setting. For example, the discovery of effective, inexpensive vaccines against smallpox and polio meant there was no need for further progress. But more frequently, progress is incomplete, leading to yet another cycle of contradiction and emergence of another new paradigm.

The actual discovery itself in the life sciences – the insight that X may be a way to affect Y in a useful way – is usually sparked by or occurs to a single individual, although there are often many others involved in the process. The original inventor is often unaware of what he or she has wrought, while co-workers pick up on the breakthrough. Moreover, to turn an insight or hypothesis into an evidence-supported explanation or solution will generally involve many people and organizations and, especially if it is a pharmaceutical or device, high levels of resource allocation for the clinical trials needed to demonstrate safety and effectiveness. So, it is false to propose a contrast between discoveries by individuals and discoveries by groups: it almost always takes both.

Considerable thought has been given to understanding what is conducive to discovery in general, and in the life sciences in particular, by historians, sociologists, philosophers, and economists. But almost all of their conclusions hinge on what we might call "intellectual-social environmental preconditions": things like intellectual freedom, the availability of inventor time and resources, and the propinquity of other people worrying about the same problem. While these are indeed factors necessary for discovery to happen – as we will examine in more detail below – their presence does not guarantee that it will happen. In the language of mathematics, they are necessary but not sufficient conditions.

Searching for some kind of sufficient trigger may be a fool's errand, as we shall see, given the serendipitous and trial-and-error character of successful discoveries, and given the very large number of research efforts that fail. Yet, concluding that discovery is by nature "mysterious" or "magical" is unsatisfying, and leaves much out of the story. More importantly, when the yield of new products drops – even though the environment and its

resources remain the same or even increase, as has happened with pharmaceuticals of late – the "mysterious" theory has nothing useful to offer. One could conclude that some discovery model (of Big Pharma, for example) is "broken," but one cannot so easily pinpoint why.

While some academics and writers have chosen to look at the environment around discovery and innovation, others have sought to examine the discovery process itself. This literature often takes a psychological viewpoint. These thinkers see discovery as a curious phenomenon to be explained, and for the most part are not interested in exploring ways to alter the pace or form of new ideas. Similarly, the public discourse does not often call for creative ideas in music, art, or literature to be more rapid, richer, or trend in a different direction. And there is no formal policy to channel artistic creativity for social or political purposes (at least not in the United States). With artistic endeavors, we accept that they are what they are, and we should enjoy them, not think about changing them. But that blasé disinterest does not hold for discoveries in health or agriculture that can affect our material, as opposed to aesthetic, progress.

So in this book, we want to consider what we, as stewards of our own and society's resources, can do to affect the flow and cost of life sciences innovation. We need to begin with theories about when and why people get creative ideas in this arena. Then we want to go beyond the external environment settings (things like intellectual freedom, the availability of inventor time and resources, and the propinquity of other people worrying about the same problem) to explore more deeply the connection between key features of that environment and what prospective inventors actually think and do. Moreover, we want to ask the deeper question of what entities might choose to change the discovery environment, or generally try to influence the process. Inventors supply good new ideas, but some entity – perhaps a profit-seeking firm, a private nonprofit, or a government – has to pay for what they do, and buyers – consumers or insurers – have to want what they have discovered. This market for life sciences discoveries – partially commercial but also seriously influenced by much more than profit and loss – is what we want to understand.

We pick out what we think are two key strands. One is the economic motivation and model, and the other is the organizational form and influence. The economic model attempts to explain the incentives with which inventors are presented, the resources they have at their disposal, and the channels through which their new ideas might be implemented. We undertake this explanation both from the viewpoint of a community of prospective inventors and from the corporations, venture capitalists, foundations, and governments willing

to buy what they are able to sell. The organizational model fundamentally asks how the supply of new ideas, given a level of real resources committed, varies with organizational structure. To make the most of an opportunity, should the organization be atomistic or collective, large or small, for-profit or for something else? Private or public? Open or secret? While we will go into much more detail later, here we offer some hints as to what these two approaches entail.

THE FINANCIAL MOTIVATION: A BALANCING ACT

The fundamental proposition here is that an agent – firm or individual, public or private – that is considering furnishing resources to a prospective inventor decides to what extent to do so by looking at the decision as an investment. Costs are paid out now for anticipated returns – in sales revenues, in profits, in praise, in population health improvements, in bureaucratic advancement, and in political rewards. The "investor" decides whether a given idea is worth it.

One key insight from this approach is that something which increases the value attached to an innovation that saves lives or improves the quality of life – say, an increase in income or taste for health – will make less certain and more costly projects attractive. The upshot is that the cost per discovery will increase. However, the reason for the increase is not a negative one; the reason for the increase in cost is the higher real income, which enhances the value of a discovery.

Another consideration is lag time. New advances in science breathlessly described on morning talk shows almost always end with the caveat that "much more research will be needed" before this breakthrough turns into a cure for cancer or prevention of HIV or therapy for Alzheimer's. And it's usually true: typically between 10 and 20 years must elapse between the initial discovery in biomedical sciences and the final product. Sometimes it's much shorter, as in the case of statins; about par for the course in the case of penicillin; and sometimes much longer: nearly 200 years elapsed between the discovery of bacteria and Pasteur's development of what is now known as pasteurization, the heat processing of liquid or solid foodstuffs to kill pathogenic bacteria.

The economic model nevertheless gives investors a motive to adopt and sustain a long-distance vision. (Whether it works out this way in practice is another matter: the probability that a return will actually materialize is much less than one.) Not only that, investors have to forecast what will happen when the product finally appears. In particular, and most

controversially, they have to forecast what price they will charge and how much they expect to sell at that price. If the anticipated product will make a major contribution to health relative to anything else on the market, and if the product is protected by a patent (or more likely, multiple patents), at least for that period there will be a profit-maximizing price that will be "high" relative to the cost of production (and probably relative to other kinds of consumer spending).

But the larger the profit the firm can expect (either from charging a high price or creating a large market through marketing and sales efforts), the more likely investors will want the firm to pour resources into the project that will lead to discovery. Thus we get the fundamental economic trade-off – high prices (or, more correctly, high revenues) are needed to cover the anticipated costs of R&D, but, once the product is discovered, consumers, insurers, and government buyers will wish the price and total cost were lower. However, lower price, if imposed by price controls or facilitated by weakening patent protection or international competition, means fewer new products.

This observation sets up the most basic debate about the biomedical sciences discovery process: As we move prices or net revenues up and down, *how many and what type of new products do we gain or lose?* If the answer is that few high-value products are lost, we may want to move in the direction of policy that lowers prices to more "reasonable" levels. If the answer is that even the current set of products do not generate enough revenue to fully reflect their value – so that potentially many high-value products would be lost – the answer may be to extend patent protection from competition (as was done for orphan drugs and biologics[1]) and leave profit-maximizing pricing alone. But the embarrassing truth is that we do not know what the trade-off is currently between economic rewards and the supply of innovative biomedical sciences products at today's prices and with today's patent protection. We don't know the result of the experiment: change the average net profit from a new discovery up or down by a dollar, and how many more or fewer new products – of what health and economic value – will appear?

That trade-off depends on something potentially knowable but fairly technical: if we line up all of the promising ideas for innovation and array

[1] "Orphan drugs" are pharmaceuticals specifically developed to treat rare medical conditions. Biologics are biological products such as vaccines, blood products, recombinant therapeutic protein, or gene therapies. They are manufactured using biological processes, such as recombinant DNA technology.

them by their expected net revenues or economic value, what does the shape of that distribution look like? Do opportunities fall off so fast that little would be lost by lowering prices, and little would be gained by raising prices? Or are there many promising opportunities crowding the potential market that just need a dash more economic reward to become profitable?

Although the definitive answer is not known, in this book we will pull together what *is* known so that readers can judge for themselves. In doing this we hope to help people take with a grain of salt the strident and voluminous literature criticizing the biomedical sciences industry – especially the pharmaceutical industry – while at the same time ignoring the puff pieces written by industry praising its own discoveries and warning off those who would dare to tamper with the fountain of lifesaving medicines.

WHAT SHOULD THE ORGANIZATION LOOK LIKE?

Society has taken some significant and often costly steps toward the goal of altering or promoting creativity in the life sciences. One step has been allowing limited liability (so investors can risk only what they invested in the firm, not their entire wealth) for profit-making corporations that undertake research, development, testing, and marketing of new life sciences products. Such firms, whether Big Pharma or Big Ag, are often criticized for a litany of offenses: excessive prices; crowding out competitors offering alternatives; shutting out certain users such as family farms and solo practice doctors; too much influence over the regulatory process; and general failure to maximize the welfare of US citizens and the world because they are too busy chasing profits.

But drug firms like Pfizer or agricultural firms like Monsanto are not – in theory – the only way to organize discovery or translation. The first vaccines were actually produced by state governments, and the US National Institutes of Health (NIH) has most recently made a foray into translational research that some see as equivalent to the activities of drug companies. Although the government-owned firms in most countries have passed away with the death of communism and the transformation of socialism into a more market-oriented form, private nonprofit enterprises periodically emerge with plans to discover and produce drugs. In addition, there has been some experimentation with combining private and public capital as social investment. The possibilities are many.

The interest in alternatives to large private corporations has been stimulated by the perception that such firms have done a dismal job of bringing

out innovative products since about the late 1990s. But while it is commonplace to remark that "the Big Pharma model is broken," it is less common to suggest a replacement, especially one that has been proven to have a high probability of performing better.

While we will review the evidence in detail, it is safe to say that alternative models involving smaller, theoretically more nimble and more strongly motivated, but riskier, start-ups and innovators have *not* been shown to be superior in terms of their batting averages. More discoveries are coming from small firms not necessarily because they can improve the odds of a hit but rather because there are so many more firms that fall into this category. It is true, and instructive, that almost all of the new wave of biotech products were not discovered or developed by traditional pharmaceutical firms, but rather by separate smaller ventures, with high mortality, but with a few survivors that themselves became large firms with all the pros and cons of large size. The jury is still out.

The evidence in life sciences is consistent with the evidence known by every management expert but that is often surprising to actual managers and the public: large firms don't confer advantages on their owners or managers. Mergers still happen in an effort to achieve some kind of "economies of scale" or "size efficiency" – even though they rarely work – because large firms facing dimming prospects have to take some kind of action. But the ideal size and organizational structure for the entity that should manage the discovery process is still unknown.

This scarcity of evidence on size extends as well to ownership. Should the resources be furnished by the limited-liability firm with stockholders and the ability to sell stock? Should they be furnished by nonprofit entities like foundations or universities, or by governments? Or perhaps everyone should join forces in a public-private-nonprofit collaboration? There is interesting experimentation going on with such arrangements. The bulk of evidence that we have is primarily about things that do *not* work well: i.e., do not be big, bureaucratic, hidebound, self-satisfied, or bullying. But knowing what to do remains elusive.

One key question is whether this process needs "more free market" or "more of something else." Traditionally the "something else" will be more government, but the possibilities we face are richer than simply these two extremes. There are potential roles for nonprofit organizations and research universities. And there are potential roles for novel combinations of these influences, ranging from open science to complex partnership arrangements to social investing.

PUTTING THE PIECES TOGETHER: NEW IDEAS AND THE PROBLEMS OF LOW VOLUME AND HIGH COST

As already noted, there is a commonly expressed concern that compared to the past, the rate of introduction of truly useful new life sciences products has fallen off, even as the cost of bringing a new product to market has risen. More inputs, more cost, less output. Which factors are responsible, and what if anything should be done?

This book will suggest that a proper examination of the data reveals that the falloff in new discoveries has not been as steep as commonly believed, but that the increase in cost associated with the fall in R&D productivity does remain stark. Many of the conventional explanations for this problem focus on the process of translating promising ideas into products. Building on anecdotes about good ideas that failed to be carried forward, some thinkers assert that there exists a "valley of death" for such ideas. Explanations run from criticisms of the motivation of researchers (more interested in publishing than in producing), to criticism of the FDA (too slow to make decisions and too much nit-picking) to criticism of drug firms (overly preoccupied with marketing concerns and too willing to imitate instead of innovate). While we note that these accusations do have some truth to them, our main goal will be to discover whether the slowdown and cost increase are also due in large part to changes in the discovery process.

We begin with the facts and work through the causes. One possible issue is that recent discoveries in basic science have, though no one's fault, started out further away from the point of application than was true of discoveries in the past. In the 1800s, Pasteur discovered the nature of bacterial infection while simultaneously making treatments available, and as recently as the 1980s the discovery of statins, blood pressure medications, and other drugs represented a process that moved swiftly from science to clinical use. In fact, in some cases the effective compound has appeared in practice even before scientists understood how it worked in theory. Obviously this has not been true of recent discoveries in science or of the numbers of innovations that have had longer gestation periods.

The slowdown in new biomedical science products is even more surprising when we note that the US government not so long ago took some fairly major steps to promote the translation of basic research discoveries into applications. The biggest change was the 1980 Bayh/Dole Act,[2]

[2] The Patent and Trademark Law Amendments Act, sponsored by Senators Birch Bayh and Bob Dole. Public Law 96–517, 96th Congress, December 12, 1980. 94 Stat. 3015.