Critical Review

A Journal of Politics and Society

ISSN: 0891-3811 (Print) 1933-8007 (Online) Journal homepage: http://www.tandfonline.com/loi/rcri20

Constraining Knowledge: Traditions and Rules that Limit Medical Innovation

Amar Bhidé

To cite this article: Amar Bhidé (2017): Constraining Knowledge: Traditions and Rules that Limit Medical Innovation, Critical Review

To link to this article: http://dx.doi.org/10.1080/08913811.2017.1288464

Amar Bhidé

CONSTRAINING KNOWLEDGE: TRADITIONS AND RULES THAT LIMIT MEDICAL INNOVATION

ABSTRACT: *Non-medical innovation has become progressively more open, harnessing the enterprise and creativity of a variety of players (including venturesome consumers) and relying on diverse structured and unstructured methods to generate and select advances. Medical innovation, however, remains more closed and regimented because of age-old traditions, reinforced by modern funding and regulatory practices that require the costly ex-ante demonstration of efficacy. These practices, which seek to replicate those of the natural sciences, militate against the pluralistic creation and use of medical innovations and suppress ad-hoc, accretive—and potentially life-saving—advances.*

Keywords: *discovery; Food and Drug Administration; innovation; scientific knowledge; venturesome consumption.*

The relentless development of new products, practices, and ideas has transformed everyday life to a degree we scarcely could have imagined a decade ago. This transformation has created new artifacts, such as

Amar Bhidé, amar@bhide.net, Fletcher School of Law and Diplomacy, 160 Packard Ave., Medford MA 02155, is the author, *inter alia*, of *The Venturesome Economy* (Princeton, 2008). A key section in this paper, about AIDS, relies heavily on an ongoing project to compile a collection of case histories about medical innovation. The author is very grateful to David Roux, whose generous gift made the project possible; Katherine Stebbins McCaffrey, a research associate at Harvard Business School who is diligently and thoughtfully writing up the case histories; and Srikant Datar, his valued collaborator and partner on the project, who also provided valuable comments on this draft.

Critical Review ISSN 0891-3811 print, 1933-8007 online
 http://dx.doi.org/10.1080/08913811.2017.1288464

scarily smart mobile phones; changed how we perform old tasks, such as booking flights and paying tolls and taxes; and even revived defunct practices, such as pedaling around cities on bicycles.

Some recent medical advances have been equally dramatic. Cholera, leprosy, the plague, tuberculosis, and polio took millennia to cure or control; AIDS was tamed in a matter of decades after its sudden outbreak in the 1980s. Gleevec and related drugs have nearly doubled the five-year survival rate for people with chronic myeloid leukemia. Harvoni, a recently approved drug, offers a cure for most hepatitis-C patients. Minimally invasive surgery has revolutionized knee replacements, and cataracts are removed and lenses replaced without hospital stays.

Overall, however, advances in health care have not had the same transformative impact on most people's lives as has, for example, information technology. Total deaths from cancer have increased even as age-adjusted deaths from cancer have declined. Life expectancy is increasing at a snail's pace. AIDS and hepatitis C apart, many new drugs target diseases that afflict relatively few patients. Obvious applications of information technology have not been used to improve the delivery of health care: We can renew driver's licenses online, but most of us can't make medical appointments in the same way. And while technology drives down the cost of clothes, computers, and other goods, health-care costs continue to rise.

Inadequate research funding cannot easily account for the apparently sluggish rate of health-care advances over past few decades. Public and private investments in medical research and development have been significant. Worldwide spending on pharmaceutical R&D in 2015 (approximately $335 billion) was about six times the R&D spending on semiconductors, for example (Mardin 2017). Other explanations of slow progress are more plausible: The low-hanging fruit of diseases caused by a single bacterium or virus may already have been plucked. The great afflictions of our time—such as cancer and aging disorders, whose causes are murky—are more intractable. Great advances in basic scientific knowledge that have been made by mapping the human genome, for instance, cannot be expected to produce immediate therapeutic breakthroughs. Social norms about safety and privacy impede medical innovation to an unprecedented degree.

This essay focuses on how limits on pluralism have slowed medical innovation. In other fields, I argue, innovation has been progressively democratized and decentralized, and this multiplayer system has fostered

a high degree of dynamism. In contrast, Western medicine has long relied on elite researchers with extensive, standardized training. Modern approaches to funding and regulating medical research have reinforced this age-old tradition of exclusivity. AIDS stands out as an exception, I argue, in the speed and manner in which the disease was contained. Special circumstances spurred an unusually multifaceted, multiplayer effort. The outbreak of the disease was scary and sudden, so the impetus for a quick response was strong, with no entrenched paradigm blocking a try-anything approach. Perhaps more important, patients included many well-educated and well-placed individuals who forced regulators and other procedure-bound organizations to deviate from their routines. Such potent patient coalitions are unlikely to be established in many other cases.

Yet exceptions also can serve as beacons, potentially making the success against AIDS more than just a one-off. Some of the practices and attitudes it catalyzed—such as the greater openness of the Food and Drug Administration (FDA) towards drug "cocktails," and the skeptical assertiveness of patients—might persist. These and other trends could make medical innovation more pluralistic and fast-paced.

The next section discusses the nature and role of multiplayer innovation. Section 2 examines the degree to which advances against AIDS fit the multiplayer pattern. Sections 3 and 4 analyze the age-old and contemporary barriers to multiplayer medical innovation that make AIDS an outlier. The concluding section covers the trends that could make innovation in medicine and health care more inclusive.

I. MULTIPLAYER INNOVATION

Before the Industrial Revolution, highly talented, ambitious individuals of undistinguished lineage could shine by serving God or their sovereigns as priests, soldiers, or colonizers of distant lands. By contrast, the Industrial Revolution allowed creative and enterprising individuals without pedigree or formal qualifications to accumulate wealth and power by developing revolutionary inventions, such as the following products of the nineteenth century: the telephone, microphone, cash register, phonograph, incandescent lamp, electric train, steam turbine, gasoline engine, streetcar, dynamite, movies, motorcycles, linotype printing, automobiles, refrigerators, pneumatic tires, aspirin, and X-rays. These may well overshadow inventions credited to the entire twentieth century. While the

industrial revolution was meritocratic, however, it took mass production to make such products widely affordable. And mass production, ironically, was elitist. Pioneers such Henry Ford espoused theories of Scientific Management and Taylorism that sought to reduce rank-and-file employees to automatons. At the Ford Motor Company, assembly-line workers were well paid, but they also were worked hard and told what to do by a small cadre of industrial engineers and time-and-motion experts.

Over the course of the twentieth century, however, innovation progressively became an inclusive multiplayer game (Bhidé 2008).[1] Big business learned to use the division and specialization of labor in the development of new products and services. Pioneers such as DuPont established large-scale laboratories to harness the efforts of many scientists and engineers rather than rely on the serendipitous inventions of a few individuals. Large firms also employed marketing experts to assess consumer wants, financial staff to evaluate proposals, and middle managers to plan and monitor complex development projects. "Empowering" all employees, including factory workers, to exercise their creativity and initiative eventually became the mantra of forward-looking managers.

Innovations systematically undertaken by large corporations have not replaced ad-hoc entrepreneurial enterprise. Scrutiny by bosses and committees and careful planning of new initiatives helps reassure the diffuse shareholders of large firms that their funds will be judiciously used, giving such firms an advantage in undertaking large projects whose execution cannot be improvised. But small startups have an edge in initiatives whose prospects cannot be objectively verified (i.e. the "Knightian" uncertainty is high) and which do not require much capital or planning. More generally, multi-player innovation proceeds through the cumulative contributions of diverse individuals and organizations. Thus, the development of personal computing or the Internet cannot be credited to a solitary Alexander Graham Bell. Innumerable entrepreneurs, executives of large companies, standard-setting institutions, scientists, programmers, designers, investment bankers, lawyers, and politicians transformed personal and networked computing. Cryptographic techniques to protect computers are developed both by researchers working at behemoths such as Google and by offbeat individual programmers such as Moxie Marlinspike, whose simple encryption programs are used by the likes of Facebook (Yadron, 2005). The "slow and often invisible accretion of individually small improvements in innovations" are crucial although

often ignored because of "a preoccupation with what is technologically spectacular," as Nathan Rosenberg (1982, 62), puts it.

International interactions have an important but subtle influence on the realization of the benefits of multi-player innovation. While entirely indigenous innovation was never common, collaboration and rivalry across national borders now play an unprecedented role in developing the science, technologies, design principles, and business concepts undergirding new products and processes. Because ideas now travel so quickly and easily—and because intense competition forces producers to cede more than ninety percent of the value of innovations to their consumers (Nordhaus 2005)—it matters more where innovations are widely and effectively used than where the underlying ideas originate.

Widespread, effective use is not automatic, however—the democratization of "venturesome consumption" also now plays a critical role (Bhidé 2008). Unlike rich hobbyists who bought early automobiles, millions of the not-so-well-to-do scoop up products, such as the Apple iPad, from the get-go. But buying a new product involves a leap of faith: We cannot know in advance whether it will be worth the price. Similarly, using new products effectively often requires resourceful effort. Modern artifacts are rich in features and are complex. Few products, iPads and iPhones included, "just work" out of the box; we have to learn about their quirks and nonobvious attributes. Affordable products also are standardized for mass production, and have to be hacked and tweaked by consumers to suit their individual needs. The risk-taking and resourcefulness of consumers is essential to stimulating innovations and in realizing their economic value.

II. ROLLING BACK AIDS: A MULTIPLAYER SUCCESS

AIDS is thought to have jumped from apes to humans in the 1920s. After the first recorded fatalities in the early 1980s in North America and Europe, infections and deaths grew at fearsome rates. The virus was not airborne, waterborne, or vector borne. Rather, it spread through bodily fluids transferred in distinctively twentieth-century ways. The retreat of colonialism brought Haitian doctors to Central Africa, who then carried the infection west. Artifacts from the twentieth century—notably syringes, blood banks, and blood products—and growing drug use, anonymous sex, and international travel after the 1970s helped infect diverse groups, including heroin addicts, gays, bisexuals, and hemophiliacs.

But in contrast to older epidemics, the AIDS epidemic was contained, at least in the West, in just a few decades. In the mid-1990s, the number-one cause of death for individuals ages 25–44 in the U.S. was AIDS-related illnesses. (AIDS does not kill directly; instead, it renders its host vulnerable to a variety of other illnesses.) Then, in a stunning turnaround, mortality dropped by 85 percent.[2] At present, the life expectancy for North Americans and Europeans infected with the virus is about the same as for those who are uninfected. Treatment has become so effective that GlaxoSmithKline foresees that, in about a decade, its AIDS unit, now the company's most profitable business unit, may no longer have a purpose. According to Glaxo's chief strategy officer, "The industry has done a fantastic job of taking the fear of the late '80s, and the death sentence, to one tablet a day" (Staley 2015).

This progress has been accomplished through accretive advances in the absence of a vaccine, an unambiguous test, or a complete cure. Therefore, the process of taming AIDS had a lot in common with the multiplayer industrial processes whose features I have summarized. The fight against AIDS drew—to a nearly unprecedented degree in medicine—on the contributions of a diverse cast, including researchers in government-funded and pharmaceutical-company laboratories, hospital-based physicians, public-health officials, providers of private capital and research grants, and community organizations. The venturesome role of at-risk individuals and patients in mobilizing a multifaceted, multiplayer rollback of AIDS was also pivotal and unprecedented. They were determined, articulate, resourceful, well-educated, and affluent. They formed advocacy groups and recruited Hollywood stars to lobby for funding research and treatment and persuaded the FDA to make significant changes in the design of drug trials.

The multiplayer character of the effort against AIDS was evident from the outset when astute clinical observation, prior advances in immunology, and technologies that enabled rapid sharing of information alerted public-health officials to a pattern across a relatively small number of disparate and geographically dispersed cases. The pattern provided the basis for naming and categorizing the disease before much had been learned about its underlying causes. Similarly, even as a consensus about its name emerged, many actors undertook multifaceted efforts that drew on different knowledge and capabilities to control transmission, test for infections, and treat patients.

Initiatives to control transmission focused on modifying behavior and practices, rather than on scientific breakthroughs or technological innovations. Transmission through unprotected sex was controlled by education about the risks, by new rules (such as the closing of bath houses), and by condom-distribution programs. Infection through contaminated syringes was attacked by instituting procedures to protect doctors and nurses from accidental needle sticks; and by distributing clean needles to heroin addicts. Transmission through transfusions of contaminated blood was controlled first by screening donors and later by treating the blood.

Researchers developed tests for detecting HIV infections by building on the paradigms, knowledge, and techniques of virology. Testing was crucial because of the long lag between infection and the appearance of clinical symptoms. Early detection facilitated the control of transmission (since extra precautions could be taken with individuals who tested positive) and increased the effectiveness of treatments (since treatment could be administered before the virus had seriously compromised the patient's immune system). Researchers who developed treatments followed a different approach than researchers who developed tests. They did not rely on a scientific paradigm, but simply tried drugs that had shown efficacy in treating other viral infections and boosting immune systems in an ad hoc, "see what helps" way. Treatments were subject to more stringent regulation than tests, but patient groups pressured regulators to modify existing rules and standards.

Progress on all three fronts was accretive, proceeding through many incremental advances informed by novel discoveries and concepts, as well as by large and small disappointments. The first efforts to control transmission through contaminated blood, for instance, were crude: Blood from anyone in a group considered to be at risk was simply rejected. Similarly, early tests could not detect early-stage infections or show how far the infection had progressed. And AZT, the first effective drug to treat AIDS, had serious side effects, often damaging the liver and causing anemia; patients also quickly stopped responding to AZT treatments.

As is common in contemporary multiplayer innovation, participants were interconnected but not tightly coupled within and across their specializations. Sometimes, they consciously agreed to collaborate; in other instances, they drew on ideas and artifacts developed by strangers; and in yet other cases, they engaged in head-on competition.

International collaboration and rivalry were likewise salient. French scientists first identified the AIDS-inducing virus—debunking a prior hypothesis advanced by an American, Robert Gallo—while using a chemical agent developed by Gallo. Test kits for the virus were produced and marketed by competing multinationals. AZT was first developed in Detroit to treat leukemia, shelved after it failed to deliver hoped-for results, shown to have antiviral properties by German scientists, and ultimately turned into an anti-AIDS drug by a UK-headquartered pharmaceutical company.

The campaign against AIDS deviated from the typical multiplayer pattern in one important respect: The participation of private businesses was almost entirely through large, public companies, along with a few new and growing businesses that could raise significant amounts of funding from professional venture capitalists or public markets. Informally financed and self-financed ventures did not play the role they often play in nonmedical innovation, where they frequently conduct pioneering experiments and diffuse new technologies (Bhidé 2000, 363–64).

III. TRADITIONAL BARRIERS TO MULTI-PLAYER MEDICAL INNOVATION

How and why might AIDS be an outlier? In this and the following sections I will first suggest that traditions going back to antiquity discourage inclusive innovation in medicine. Then I will show how contemporary rules for the public of funding of medical research and regulatory efforts to ensure safety and efficacy (administered by the FDA) reinforce these traditions.

The practice of medicine has long been controlled by physicians who undergo lengthy and arduous training. Qualifying to practice medicine in the United States, for instance, requires a four-year baccalaureate college degree, usually with a curriculum that emphasizes biology, chemistry, and physics; four years of medical school; between three and five years of a residency program, depending on the specialty; and one to three years of additional training in a fellowship program for those who want to become highly specialized in a particular field, such as gastroenterology or pediatrics.[3] The pedagogy includes textbooks, lectures, demonstrations, "grand rounds," and learning by doing, especially in residency and fellowship programs.

The extended training period and the range of methods used reflect both the large and expanding corpus of codified knowledge (e.g., of

anatomy, physiology, pathology, and now genetics) and the difficult-to-codify skills (e.g., palpating organs and eliciting patient histories) that physicians are expected to master. The necessary instructional capacities, equipment, and infrastructure (such as wards in teaching hospitals) in turn limits the number of students trained, and, in the absence of a state subsidy, requires medical schools to charge high fees. Tuition and fees at private U.S. medical schools can amount to well over $50,000 per year. Entry into the profession is thus restricted to individuals with unusual stamina, innate skills, and the capacity and willingness to pay high fees.

This situation originates in the effort launched by Hippocrates and his followers to transform medicine nearly 2,500 years ago. Before Hippocrates, illness was attributed to supernatural causes and healing was thought to require magical spells or sacrifices to gods. Hippocrates's revolutionary effort to secularize medicine included the extensive codification and training of elite practitioners. The codification spanned some 60 works, such as *Epidemics*, *On Regimen*, and *On The Sacred Disease* (as epilepsy was then called) (Straus and Strauss 2006, 28). In spite of the extensive codification, however, Hippocratic physicians regarded healing as an art transmitted by skilled healers to selected acolytes. The Hippocratic Oath required every initiate to swear that he would "impart a knowledge of the Art to my own sons, and those of my teachers, and to disciples bound by stipulation and oath according to the law of medicine, *but to none others*" (emphasis added). Thus, Hippocratic healers sought an elite professional status even though their treatments were not in fact much more effective than spells and sacrifices.

Galen, the second-century Greek who became the "medical Colossus of the Roman era" (Porter 1999, 71) some five centuries after Hippocrates, used his "prolific pen" and his influence with Emperor Marcus Aurelius to establish "dominion over medicine for more than a millennium" (ibid., 73). Galen's 350 authenticated titles equaled those of all other prior Greek medical writers together. They provided a foundation for the university-based education of physicians that started in the ninth century with a school in Salerno, the first university of any sort in Europe (Nuland 2008, 70). Several new universities that opened in the High Middle Ages—Paris (1110), Bologna (1158), Oxford (1167), Montpellier (1181), Cambridge (1209), Padua (1222), and Naples (1224)—followed Salerno's lead in educating physicians.

Training was lengthy. A bachelor of medicine degree took about seven years—inter alia, students had to acquire fluency in Latin and Greek—and a medical doctorate took ten. Training based on set texts was expounded in lectures delivered by professors who "tried to prove that the discipline formed a noble chapel of the temple of science and philosophy; the learned physician who knew the reasons for things would not be mistaken for the hireling with a knack for healing" (Porter 1999, 124).

Medical faculties were minuscule. In 1436, Oxford had only one doctor of medicine. The number of degrees granted was likewise tiny. Bologna granted just 65 medical degrees between 1419 and 1434 and Turin thirteen between 1426 and 1462. Only Padua, with an unusually large faculty of sixteen professors, had a sizable enrollment; medical students accounted for about a tenth of Padua's total student population (Porter 1999, 114).

Not surprisingly, then, university-trained physicians had their pick of patients. Princes and patricians welcomed cultivated doctors who could explain the whys and wherefores of the drugs and diets they prescribed. The rest of the population, especially in the larger towns, was served by "a diversity of healers" (Porter 1999, 118). For instance, fifteenth-century Florence had, besides medical-school graduates from Padua and Bologna, bone setters from Rome; families specializing in eye diseases, hernias, and kidney stones; midwives; herbalists and peddlers of folk remedies; and parish priests offering "pious cures" (Porter 1999, 118).

A loose medical hierarchy, defined by the restricted number of learned physicians at its apex, would gradually give way in the West to one in which medical practice was restricted to licensed, university-trained doctors. In the United States, for instance, medical practitioners in the mid-nineteenth century did not have to be licensed. They could train, if they chose to, in a "variety of competing medical schools, attached to different brands," including herbal medicine and homeopathy (Pickstone 1996, 305). But even when a few learned physicians served a small number of patients, medical schools and their graduates had an outsize influence on the selection and propagation of medical knowledge. University-based professors screened new ideas and helped shape accepted ones into a canon that would be passed on to succeeding generations. Medical schools that drew students from afar also helped disseminate standardized knowledge across Europe. (William Harvey, who discovered the circulation of blood, studied medicine in Padua after receiving his bachelor of arts in Cambridge.)

As Thomas Kuhn famously argued, once a scientific community accepts a paradigm, its foundational ideas and assumptions are not open to question. The medical paradigm that had been founded by Galen in the second century was as resilient as it was flawed. For example, Galen provided an "elaborate pulse lore" (expounded in sixteen books on the pulse) to justify bloodletting, and these remained influential until the 19th century (Bynum 2008, 13). "Whatever the disorder—even blood loss—Galen judged bleeding proper" (Porter 1999, 76). In severe cases, the treatment was to be administered twice a day: the first to be stopped before the point of fainting, while the second continued until unconsciousness (Porter 1979, 75–76). Bloodletting remained a "mainstay of therapeutics until the mid-19th century, and physicians abandoned it only gradually and reluctantly" (Bynum 2008, 13).

Stringent qualification requirements also restricted who could innovate —or at least whose innovations would be included in the canon. The official history of medicine is almost entirely a record of new ideas and techniques developed and advanced by credentialed physicians. Leonardo da Vinci's anatomical drawings are famous now, but they had virtually no influence on physicians in his time. They struck to Galen's false anatomical accounts, in which they had been trained. Ambrose Paré, the son of a cabinetmaker who could not afford a proper university education, instead apprenticed as a barber/surgeon and served in French military campaigns. Paré's military service secured him an outstanding reputation, and his books eventually transformed surgery. Yet they were disdained by University of Paris professors because Paré wrote in French, not Latin. Louis Pasteur risked prosecution for conducting the first human trial of the rabies vaccine on a nine-year-old boy who had been mauled by a rabid dog. Pasteur did not hold the syringe, and the head of the pediatric clinic at Paris Children's Hospital was present. But because Pasteur was not a licensed physician, his supervision of the vaccination was illegal. As it happens, because the boy was cured, Pasteur was spared prosecution and hailed as a hero.

In contrast, builders of complicated artifacts such as bridges, cathedrals, and aqueducts were not required to have a formal university education. They acquired the necessary knowledge and skills through observation, autodidactic study, and formal or informal apprenticeships. Their ability to undertake technically challenging tasks was assessed not by their diplomas, but by their record of past projects, the quality of their mentors and patrons, and, in some cases, by their membership in a guild. Complete

outsiders with spotty educations could innovate. George Stephenson, considered the "father of railways" in Britain, was illiterate until age 18. He became an engine wright in a coal mine after repairing a pumping engine. In 1815, he invented a mining safety lamp. Then, after studying the workings of a locomotive used to haul coal, he constructed his own locomotive in a workshop behind his home. Thomas Edison, who had just three months of formal schooling, provides another example. His first inventions derived from a brief stint as a telegraph operator, but he proceeded to rack up more than a thousand patents for a wide range of inventions ranging from electric lighting to power generation to sound recording and motion pictures. Certainly, autodidacts did invent some medical artifacts (such as Benjamin Franklin's bifocals) but, as a rule, virtually all medical pioneers were trained, practicing physicians steeped in the prevailing medical paradigm.

IV. FUNDING AND REGULATION

In medicine, as in many other fields, the increasing resources disbursed by the state in the twentieth century, and the broadening of its regulatory reach, significantly expanded the influence of government in shaping innovation.

Government Funding and Innovation

The National Institutes of Health (NIH), the biggest source of federal funding for medical research, originated in the Marine Hospital Service (MHS), which was charged with providing medical care to active and retired Navy personnel. When Congress asked the MHS to investigate epidemics, such as cholera and yellow fever, it established a lab to study bacteria. In 1930, that lab was designated as the NIH. In 1967, the NIH created a division to fund research on noninfectious diseases, notably cancer, strokes, and heart disease, which had historically been of lesser interest to governments than infectious diseases. The NIH already had started supporting cancer research in the 1920s through a partnership with Harvard Medical School and, in 1937, had taken over the previously independent National Cancer Institute (NCI). After President Nixon declared "war on cancer," Congress passed the National Cancer Act of 1971, greatly increasing the NCI's (and thus the NIH's) budget and

responsibilities. In the 1980s, the resources of the NCI were used in the campaign against AIDS. In the 1990s, the NIH increased its emphasis on basic genetic research not tied to a specific disease, joining with international partners to launch the Human Genome Project. Overall, the budgets of the NIH increased more than 500-fold[4] in the latter half of the twentieth century. The NIH now undertakes research in twenty-seven of its own institutes and centers (such as the NCI) that employ more than 1,000 principal investigators and more than 4,000 postdoctoral fellows, making it the largest biomedical entity in the world. The NIH also disburses four-fifths of its total budget to researchers at universities, medical schools, and research institutions such as the Mayo Clinic.[5]

Federal funding has helped reinforce the traditional aversion to heterodox innovation. Unlike private philanthropists, taxpayer-funded agencies have to avoid the perception of caprice or bias. A structured process by means of which well-established researchers peer review thoroughly documented grant applications has therefore become the norm for the NIH and other federal agencies that fund research. The process favors projects that address problems derived from the prevailing paradigm ("normal science," in Kuhn's terms). Projects based on inchoate or outside-the-box hunches, and projects whose steps cannot be specified in advance, are rarely funded.

Similarly, despite blind peer review, credentialed insiders with impressive curriculum vitae and training in preparing proposals have advantages. Many universities now even have professional staff who help their faculty with their grant proposals. And because universities receive a share of grant funds as overhead, they bestow promotion and honors on faculty who undertake larger, more expensive projects. For instance, prestigious U.S. universities were at the forefront of securing large research grants to develop the radiological knowledge necessary for Computed Tomography (CT) and Magnetic Resonance Imaging (MRI). But they lagged in the development—and many even resisted the use—of laparoscopic surgery, where the equipment costs were much lower.

There is dispute about whether the NIH unduly favors prestigious researchers and organizations. The NIH, which likely is sensitive to the need to maintain support in Congress, points out on its website that it funds research at more than 2,500 institutions spread across every state in the union. But however broadly the funds might be disbursed, it is a virtual certainty that nearly all of its grantees have doctoral degrees and institutional affiliations. In medical research, freelance innovators do not

apply for or receive government funds. Even researchers from prestigious institutions can be shut out if they challenge the prevailing paradigm.

The history of immunological cancer research illustrates the difficulty of going against the prevailing paradigm. The idea of stoking the body's immune system to fight cancer goes back to the early 1890s, when Dr. William Coley, a prominent New York surgeon, noticed that some cancer patients who contracted acute bacterial infections experienced spontaneous remissions. Acting on a hunch, he audaciously injected bacteria into a patient with an inoperable tumor to induce a "virulent infection." When the patient recovered completely, Dr. Coley developed a bacterial mixture, known as "Coley's mixed bacterial toxins," for treating cancer patients. But the idea of stimulating the body's immunological response was overshadowed by radiology and chemotherapy, and Coley's work was forgotten. After his death, his daughter, Helen Coley Nauts, found records of her father's "toxin treatment" as she was going through his papers. For the next twelve years, Mrs. Nauts, a housewife with no medical training, "taught herself oncology, immunology, and record keeping," tracked down 896 patients who had been treated with Coley toxins, and published findings showing the beneficial effects. Nauts also secured a $2,000 grant from Nelson Rockefeller to start the Cancer Research Institute (CRI) in 1953.

In 1971, the CRI recruited Dr. Lloyd Old, a physician/researcher, as its medical director, and started a fellowship program to "attract outstanding young scientists to immunology."[6] According to Don Gogel,[7] who has served on CRI's board since 1981, the fellowships stimulated

> basic research that provides the foundation of today's immunotherapies. The researchers we funded now form the core of the new wave of cancer immunology leaders. But for my first 20 years on the CRI board, I saw a sustained lockout of immunotherapies from the mainstream of funding and research blessed by NIH. The prevailing paradigm of chemotherapy and radiation treatment was favored. We stayed the course largely because of the conviction of Dr. Lloyd Old, who also served as chair of the Department of Immunology at Memorial Sloan Kettering.

Lone-wolf innovators acting on hunches or challenging prevailing orthodoxies are not altogether absent in the medical sphere. Dr. Charles Kelman, an ophthalmologist in private practice in New York, invented the cyroprobe, an instrument to freeze and extract cataracts, in 1962. The following year, he developed freezing techniques to repair

retinal detachments.[8] Most of Robin Warren's and Barry Marshall's early paradigm-defying work on how bacterial infections cause duodenal ulcers was done by the two Australian physicians—"after hours or at home," according to Warren (2006)—without a research grant. The "standard teaching," according to Warren (2006), was that "nothing grows in the stomach." After Marshall was denied renewal of his hospital contract in Perth, he resumed research at a hospital in Fremantle in the face of continuing skepticism. He writes that

> most of my work was rejected for publication, and even accepted papers were significantly delayed. I was met with constant criticism that my conclusions were premature and not well supported. When the work was presented, my results were disputed and disbelieved, not on the basis of science, but because they simply could not be true. I was told that the bacteria were either contaminants or harmless commensals. (Marshall 2006)

Where these exceptions occur is noteworthy. They usually take place in areas that are not of primary interest to the NIH or to grant applicants from mainstream research establishments. Thus, while developers of new surgical techniques or inexpensive diagnostic equipment face greater difficulty in securing grants than researchers doing cutting-edge genetic research, they also are less handicapped by their unorthodoxy. Similarly, development of treatments for conditions such as cataracts and ulcers—which people have learned to live with—offer more opportunities to unfunded innovators than diseases such as cancer, which the NIH prioritizes.

The research and development projects of large, professionally managed corporations, which also became a major feature of innovation in the twentieth century, have a similar bias. The dominance of a few firms in industries such as nuclear energy and aircraft manufacture limits innovation to carefully planned, inside-the-box development, especially if the firms also receive government research support. But outside of medicine, instances of industries where oligopolists have a lock on the market are exceptional, and therefore innovation is generally more open and multi-player.

Safety and Efficacy Regulation

Ample opportunities to innovate outside the areas that interest the NIH and the mainstream research community should, in principle, produce

considerable freelance innovation by outsiders. But they face disadvantages beyond the need for research grants. One disadvantage, as previously discussed, is the restriction of medical practice to trained physicians. Like René Laennec (who invented the stethoscope) and other Pre-Industrial Revolution medical innovators, Drs. Charles Kelman, Robin Warren, and Barry Marshall developed their novel ideas in the course of caring for patients. Another important disadvantage is the Food and Drug Administration.

The FDA became a formidable force in the twentieth century;[9] before that, there were few federal laws regulating the production and sale of food or pharmaceuticals. The agency's foundational legislation was the Pure Food and Drug Act of 1906. As suggested by the out-of-alphabetical order, the legislation was promoted primarily by "pure food" advocates—as well as by dairy producers wanting margarine labeled "imitation," and by "straight" whiskey producers who wanted to deny their "blended" competitors the label of "whiskey." The inclusion of drugs in the Act targeted "patent" remedies. This dimension of the Act was backed by the American Medical Association. Patent-medicine makers often advertised their products as a way of avoiding visits to doctors (High and Coppin 1988).

After the legislation was passed, the Bureau of Chemistry (which Congress had tasked with enforcing the Act) mounted an aggressive campaign against patent medicines, but it found its authority checked by the courts. In 1911, for instance, the Supreme Court ruled that the 1906 act did not cover false claims of therapeutic efficacy. Congress responded by expanding the definition of "misbranding" to include "false and fraudulent claims," but the courts again limited enforcement by setting high standards of proof for fraudulent intent.

In 1938, Congress passed the Food, Drug, and Cosmetic Act after an elixir formulated with a toxic solvent had claimed more than 100 lives. The 1938 legislation gave the FDA (as the Bureau of Chemistry had by then been renamed) sweeping powers. The law did not just mandate premarket review of the safety of all new drugs, which could have prevented the elixir tragedy; it also allowed the FDA to ban false therapeutic claims without proving fraudulent intent. This brought the FDA close to being able to restrict the marketing of new drugs on the grounds of inefficacy. Practically speaking, moreover, the evaluation of a drug's safety would logically weigh its risks against its potential therapeutic benefits, raising the issue of efficacy. However, the FDA lacked the authority to

prevent the introduction of ineffective drugs where there was no evidence of potential harm; in such cases, it could only force recalls.

A 1962 amendment to the 1938 act authorized the FDA to put the onus of providing "substantial evidence" of efficacy on developers before they could market a new drug.[10] The amendment defined substantial evidence as comprising adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate effectiveness.

As of 1962, the "prevailing efficacy study model" had been "a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses." Over time, however, the FDA required efficacy studies to be "multicentered, with clear, prospectively determined clinical and statistical analytic criteria" (FDA, 1998, 12). In addition, the FDA (1998, 2) took the position that, in passing the 1962 amendment, Congress had "intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."

There was an obvious downside to efficacy requirements that went beyond those that naturally stem from weighing the potential harm of a drug against its benefits. As a 1998 FDA document acknowledges, "the demonstration of effectiveness [now] represents a major component of drug development time and cost. The amount and nature of the evidence needed can, therefore, be an important determinant of when and whether new therapies become available to the public." The high costs of efficacy requirements also limit pharmaceutical innovation to established companies and the relatively few new businesses that can secure multiple rounds of funding from professional venture capitalists. The mean cost, in 2002 dollars, incurred during Phase I trials (which provide the first screen for safety) for drugs approved in the 1990s was $15.2 million; the Phase II cost (in which new drugs are tested for safety and efficacy on as many as a few hundred patients) was $23.5 million; and the Phase III cost (which involves large-scale randomized and blinded testing of thousands of patients) was $86.3 million (DiMasi, Hansen, and Grabowski 2002, 162). These sums are outside the reach of informally financed new businesses. For instance, most founders of companies on *Inc.*'s list of the 500 fastest-growing companies in the United States started with less than $20,000. Unsurprisingly, very few "Inc. 500" companies develop products that require FDA approval.[11]

FDA rules also discourage continuous iterative innovation, which is the hallmark of innovation outside the biomedical sector. As I have previously argued (Bhidé 2008), the FDA has adopted the sensibilities of researchers in the natural sciences, who try to discover universal, parsimonious laws, rather than that of engineers or technologists, who try to develop artifacts that solve specific problems and are often complex.[12] The "science-mindedness" of the FDA has engendered a strong preference for simple, single-molecule drugs whose therapeutic effects on a specific indication can be more easily isolated than with drug cocktails or mixtures.[13] The scientific orientation of the FDA also is reflected in rules requiring well-specified, controlled experiments to test the efficacy and safety of the molecules.

This regulatory posture limits the scope for "try it, fix it" innovation. Once a compound has been submitted for approval, and the FDA has approved a testing protocol, the developer is in the same position as someone conducting a science experiment: Unplanned deviations are not allowed. A skilled chef can make up for a missing ingredient by modifying the recipe, but if a compound is discovered to have an unexpected toxicity, the FDA's single-molecule approach makes it impossible to effect compensatory adjustments by adding something to offset the toxicity. In fact, because FDA-approved trial designs are more or less cast in stone, the developer cannot adjust the dosage or other aspects of how the drug is administered to patients once an efficacy trial is under way.[14]

The rules discourage ongoing development after a new drug has made it to market as well. The costs of establishing safety and efficacy represent an obvious barrier in developing new applications or versions. In addition, according to industry insiders, when pharmaceutical companies discover that an approved drug produces better results in a different dosage, or has utility in treating a different condition, they are reluctant to go through FDA trials for the different dosage or indication because they are afraid the trials might produce data that will lead the FDA to reexamine the drug already being sold. At the same time, strong intellectual property rights limit the competitive pressures that induce non-medical companies like Intel to introduce advances on regular "tick-tock" cycles (improving the manufacturing process on the "ticks" and the architecture of chips on the "tocks").[15] As long as the patent has not expired, pharmaceutical companies typically focus on ways to increase sales (by persuading more doctors to prescribe or insurance companies to reimburse) rather than on making improvements.[16]

Differences between the FDA's regulation of new devices and its regulation of surgical techniques provide a useful contrast. The 1976 Medical Device Regulation Act[17] first brought the efficacy of medical devices under the FDA's purview. (Earlier legislation had covered safety). The 1976 Act required the FDA to classify devices as new products or extensions of existing products. Devices classified as new have to undergo clinical trials before they can be sold. As with new drugs, clinical trials themselves require FDA approval; companies have to submit applications specifying how their trials will be conducted, which the FDA scrutinizes for safety and trial design. If, however, the FDA classifies a device as an extension of an existing device, no trial is necessary; companies merely have to file a "510(k)" notification with the FDA.[18]

The FDA's first classification of a device as "new" (therefore requiring an approved clinical trial) was of MRIs in 1981 (Steinberg and Cohen 1984; Steinberg, 1986; Steinberg, Sisk, and Locke 1985). In response, over a dozen companies that had MRIs under development joined with their trade association to challenge the FDA's classification, claiming (perhaps disingenuously) that MRIs were simply extensions of industrial instruments that had long been used to analyze chemicals. But they also took the precaution of applying to the FDA for permission to run clinical trials in case their challenge failed (Steinberg and Cohen 1984),[19] and by 1988, eleven companies had (after submitting the results of their trials) obtained approval from the FDA to sell MRIs (Mitchell 1983; Mitchell 1988).[20] The FDA then reversed course and redefined MRIs as extensions of existing devices. However, this change (made in 1988), which eliminated the need for clinical trials, mainly helped existing producers expand their product lines.[21] Eight MRI developers that had not secured approval to sell had already given up.

The 510(k) exemption, which does not exist for pharmaceuticals, does reduce barriers to incremental advances. Therefore, ongoing improvements may be a more routine feature in medical devices than in pharmaceuticals (Gelijns, Rosenberg, Nathan, and Dawkins 1995). The true extent of incrementalism is hard to pin down, however, because of the incentive to define a device as an "extension." And although there is no equivalent of the totally unregulated weekly or monthly updates made by companies such as Microsoft in medical devices, less stringent FDA rules (in comparison to pharmaceuticals) may enable faster and more effective innovation (as the Fuchs and Sox (2001) survey suggests).[22]

In sharp contrast to its power over new drugs and medical devices, the FDA has virtually no say in the development of new surgical techniques (except to the extent that the techniques use "new" devices that require regulatory approval). There are, in fact, no explicit federal regulations governing innovative surgery, save general Department of Health and Human Services Institutional Review Board (IRB) guidelines covering research on human subjects; but surgeons experimenting with new techniques rarely seek IRB review (Reitsma and Moreno 2002). The absence of FDA rules has allowed surgical advances to embody much of the multiplayer innovation characteristic of non-medical advances. Laparoscopy, which has revolutionized surgery in the abdominal cavity, provides a striking example, as documented in a case study (Bowler, Bhidé, and Datar 2017) from which the following account is derived.

Raoul Palmer, a French gynecologist, developed the foundational techniques before and after the Second World War. A German gynecologist, Karl Semm, broadened these foundations in the 1960s and 1970s, and a British gynecologist, Patrick Steptoe, refined laparoscopy for female sterilization. Steptoe detailed his techniques in a 1967 textbook that quickly became popular in the United States, as onerous restrictions on female sterilization were eliminated. Laparoscopy then expanded from gynecology to general surgery. Following the first laparoscopic removal of a gall-bladder in the United States in 1988 by surgeons from Georgia, Eddie J. Reddick and Douglas O. Olsen, colleagues at a Tennessee hospital, improved and popularized the procedure. They incorporated several new technologies that were emerging at the time, such as miniaturized TV cameras, surgical laser knives for cutting tissue, and suturing clips to rejoin cut tissue. By 1992, 80 percent of all gall-bladder removals in the United States were performed laparoscopically.

Many mainstream surgeons, especially those in academic medical circles, had resisted the new techniques. But the enthusiasm of patients won out. Burgeoning demand from women for laparoscopic sterilizations, which did not require large incisions and long hospital stays, impelled residency programs in gynecology to teach laparoscopy. Likewise, the first patient for laparoscopic gall-bladder removal was recruited in a barber shop by one of the Georgia surgeons after a conversation with a fellow customer who suffered from gallstones but did not want an operation that would leave a large scar. When the possibility of a new, less invasive operation was described to her, she wanted it immediately.

Developers of complementary devices and technologies also provided crucial support. In Germany, where safety concerns had led to a ban on laparoscopy in most clinics until 1966, two instrument manufacturers had collaborated with laparoscopy pioneers Palmer and Semm to develop safer techniques. Similarly, U.S. Surgical (which anticipated a large market for its suturing clips if laparoscopy took off) helped the Tennessee surgeons improve clip-based suturing—and then deployed its sales force to promote the technique to other surgeons in the United States.

Crucially, the FDA did not prevent patients from volunteering for experimental laparoscopies. It did not require well-designed trials or regulate the development of complementary instruments and devices (since the development was deemed incremental rather than new). Yet rapid development and adoption provided more than cost and cosmetic benefits; laparoscopic surgeries have saved untold lives by reducing deadly post-operative infections.

Laparoscopy plausibly exemplifies the more rapid innovation possible in surgery than in stringently regulated drug development, as the aforementioned Fuchs and Sox (2001) survey suggests. While the regulatory regime in pharmaceuticals may reduce the visible occurrence of bad outcomes (harms to patients because of poorly designed trials and ineffectual drugs), it may also induce the invisible non-occurrence of good outcomes, namely the development of valuable treatments such as laparoscopy.

Alternatives to FDA-Supervised Trials

The absence of FDA-supervised trials of new surgical procedures (or of incremental innovations in devices) does not leave decisions about their use entirely to individual physicians. The NIH and professional associations evaluate outcomes, as best they can, after the fact. In some instances, their evaluations of procedures whose initial adoption did not require FDA approval can include randomized trials. And for procedures the NIH and professional bodies deem worthwhile, they recommend protocols and regimens for appropriate use. Physicians who flout the recommendations (which do not have legal force on their own) face the risk of malpractice lawsuits. Private and public insurers also review the cost effectiveness of new procedures and devices. Their verdicts can make or break innovations: one reason for the rapid proliferation of

laparoscopic gall-bladder removal, for instance, was that insurers quickly appreciated the cost advantages of eliminating the hospitalization necessitated by traditional open surgery.

Outside of medicine, systematic assessments of new products and technologies by regulators have also become common. But as was the case with the FDA's regulation of new drugs before 1962 (and devices before 1976), the primary emphasis has been on safety rather than efficacy. For instance, the National Highway Traffic Safety Administration's New Car Assessment Program encourages manufacturers to build safe vehicles. The Federal Aviation Administration has an elaborate process to oversee the design, manufacture, and maintenance of aircraft to ensure that they meet "the highest safety standards."[23] The EPA seeks to control pollution in the air, land, and sea. The Federal Communications Commission screens new computers and other digital devices for "harmful interference" with "police, ambulance, and fire communications" and "air traffic control operations" (Federal Communications Commission 1996). Safety rules, in turn, do entail implicit consideration of utility and efficacy: the criteria to determine what makes a car "street legal" naturally take into account the benefits of less than perfectly safe automobile transportation. But safety regulators do not require controlled randomized testing of efficacy, however new or radical an innovation might be.

As with surgical innovations, the absence of ex-ante regulation does not require end users of innovations to assess efficacy on their own. New consumer products are routinely and widely evaluated in the mass media, by specialist publications such as Automotive News, and, increasingly, through reviews and rankings on social media and online intermediaries such as Amazon. Similarly, consultants such as the Gartner Group advise large companies on their IT purchases. While these efficacy evaluators seek to back up their judgments with objective facts, facts are collected and assessed in multifarious and seemingly unscientific ways. For instance, in September 2014, Microsoft launched its Windows Insider Program to collect continuous feedback about its operating system during its development. By the end of the year, nearly 1.5 million people had signed up. They did not at all comprise a random sample, nor did Microsoft test features in successive releases in any structured or controlled manner. Developers of non-medical products rely on several other kinds of tests and evidence that also do not include careful randomization and placebo treatments but do facilitate try-it-fix-it

improvements. These include A/B tests of web pages, physical prototyping, customer surveys, focus-group interviews, alpha and beta tests of software, and unpublicized product launches in test markets. It is, apparently, only in medicine (and increasingly in foreign aid to third-world countries) that "evidence-based" assessments of effectiveness appear to have become synonymous with controlled randomized tests.

Restricting Venturesome Consumption

In fields other than medicine, consumers make leaps of faith in deciding whether new, nonmedical products will be worth the price and risk. They often mix and match or tinker with standardized, mass-produced products to suit their idiosyncratic needs. But the FDA has been mandated to make choices about the safety and effectiveness of drugs and new devices on everyone's behalf. Indeed, many opponents of the 1938 Food, Drug, and Cosmetic Act anchored their resistance in the transgression of a centuries-old right to "self-medication" or "autotherapy" that expanding the FDA's powers would entail (Carpenter 2010, 79, 108). The agency deems something to be safe and effective when "used as directed," where the "as directed" matches the precisely specified conditions under which preapproval trials were conducted. As in the traditional physician/patient relationship, the FDA's approach favors patients who comply with injunctions rather than making choices of their own. Additionally, and in contrast to experimental surgeries such as laparoscopy, the FDA does not permit patients who have not enrolled in an FDA approved trial to try experimental drugs.

One manifestation of the tension between venturesome consumption and the FDA's mandate is in the area of at-home and direct-to-consumer testing. The FDA treats all home-use testing equipment—and tests sold directly to the consumer—as medical devices. Therefore, manufacturers of testing equipment (or providers of tests) have to establish that the tests are safe, reliable, and properly labeled (with warnings prescribed by the FDA). In addition, the FDA also "requires the results to be conveyed in a way that consumers can understand and use." In particular, the FDA requires that "user comprehension" studies "must obtain values of ninety percent or greater user comprehension for each comprehension concept." If the agency deems consumers incapable of understanding the results of a test, it requires that the results be channeled through a "licensed practitioner." The cost of satisfying these requirements can make at-home

testing commercially unviable, hindering the ability of venturesome individuals to take charge of tweaking interventions and therapies.[24] In one celebrated instance, the FDA forced 23andMe to stop marketing its $99 Personal Genome Service, which provided more than 200 health reports to consumers who mailed in a saliva sample. The FDA's 2013 warning letter complained that the tests could "produce false positive or false negative assessments for high-risk indications" and that patients who did not adequately understand the test results might use them to "self-manage," possibly even abandoning necessary treatments. (In early 2015, the FDA allowed 23andMe to offer a single test, the Bloom syndrome carrier test, after the company conducted two separate studies: a "usability study" to show that consumers could adequately follow instructions about how to submit saliva samples, and another test to show that consumers could understand the results.[25]) Similarly, in 2013, the FDA declared that apps on mobile devices would be regulated as medical devices if they were "used as an accessory to a regulated medical device," or if they "transform[ed] a mobile platform into a regulated medical device." It encouraged "app developers to contact the FDA—as early as possible—with questions about mobile apps, their level of risk, and whether a premarket application [for FDA approval] is required."[26]

As it happens, consumers are not always mistaken in questioning accepted treatments. Radical mastectomy, introduced in the United States in the 1880s, was the standard treatment for breast cancer until 1975. The few doctors who questioned its effectiveness would have been ignored had it not been for a patient revolt against the drastic surgery. Conversely, as we saw in the case of laparoscopic gall-bladder removals, if the FDA doesn't stop them, venturesome patients can spur the adoption of valuable innovations by mainstream physicians.

Nor has FDA regulation been foolproof in terms either of safety or effectiveness. Recent products that had to be recalled after passing safety tests included the anti-inflammatory drug Vioxx and Guidant's defibrillators and pacemakers. Overestimates of effectiveness may be even more commonplace. The use of antibiotics to treat ulcers displaced treatments of dubious utility that, nonetheless, had received regulatory approval. Though completely useless treatments rarely make it through FDA scrutiny, efficacy in actual use often tends to be much lower than reported in randomized, blind trials. This so-called "decline effect" is "extremely widespread" in medicine, affecting therapies such as cardiac stents, antidepressants, vitamin E, and antipsychotic drugs (Lehrer 2010).

Outside of medicine, competing products or technologies are subjected to a pluralistic, Darwinian sort of selection that isn't blind, standardized, or centralized. Rather, in the multiplayer game, many buyers decide whether to take a chance on new offerings, using their own objective and subjective standards. In some cases, this trial by the many may lock everyone into a poor choice (such as, allegedly, the "Qwerty" keyboard or VHS videotapes). As a rule, however, decentralized consumer choice supports the diversity of innovators and their offerings by protecting innovators against the prejudice or bias of a few expert judges. (Many industry experts, it may be recalled, panned the iPhone when it was first introduced, but the device nonetheless secured a fanatical following). Moreover, unstructured pluralistic testing produces much more data (e.g., by millions of testers in the Windows Insider Program, compared to the thousands enrolled in FDA trials). Potentially, to the extent that a large number of testers represent greater diversity, pluralistic testing better matches products and features with the heterogeneous problems and preferences of users.

V. PROGNOSIS FOR MORE MULTIPLAYER INNOVATION

Concern about the nature and cost of medical innovation in the United States has been long-standing.[27] Critics argue that new therapies now target diseases of the few rather than of the many, provide small incremental benefits (adding only a few weeks to the lives of the terminally ill, for instance), and control rather than cure chronic conditions. Cheap, effective treatments are underutilized because of inadequate incentives for their widespread adoption. Spending on medical research—and on health care overall—continues to rise even as prices in much of the rest of the economy remain steady or even fall.

Typical remedies seem to focus on increasing the effectiveness of specialized researchers. One such approach is to promote "translational" and "interdisciplinary" research. In 2006, for instance, the NIH created the Clinical and Translational Science Award (CTSA) program, which had expanded to about 60 academic medical institutions in the United States by 2015. Similarly, in 2005 the NIH launched an Interdisciplinary Research (IR) program to "change academic research culture such that interdisciplinary approaches and team science spanning various biomedical and behavioral specialties are encouraged and rewarded." The

program's components include interdisciplinary research consortia, training programs, a "Multiple Principal Investigator (Multi-PI) Policy," and the fostering of new "interdisciplinary Technology and Methods."[28]

However, the history of innovation both within and outside of medicine suggests that the relationship between knowledge developed through basic research (typically undertaken without regard to its practical use) and the practical application of such knowledge is difficult to predict and control. In some instances, researchers have been able to apply basic research systematically and successfully; in other cases, applications have been discovered serendipitously (e.g., the use of the transistor principle in transistor radios) or after frustrating lags (as in the effort, started in the 1980s, to apply knowledge of nano-molecules, which is only now bearing fruit). In yet other cases, practical knowledge and inventions have led the development of scientific knowledge. As L. J. Henderson quipped, "Until 1850, the steam engine did more for science than science did for the steam engine" (quoted by Dickenson 1958, 165).

In medicine, too, clinical practice often has preceded scientific understanding (Nelson et al. 2011), and long lags between scientific discovery and treatments have been commonplace. Harvey's revolutionary discovery that blood circulates had virtually no impact on treatments (including the treatment of Harvey's own patients) for nearly a century. The practical consequences of the many disease/pathology correlations discovered in French hospitals in the nineteenth century took just as long to materialize. Linus Pauling and his colleagues demonstrated in 1949 that sickle-cell disease occurs as a result of an abnormality in the hemoglobin molecule. This was a milestone in the history of molecular biology, yet the disease remains incurable.

Similarly, while many important medical and nonmedical innovations have resulted from the cross-pollination or integration of ideas across fields, the process has often been serendipitous. As often as not, innovators have borrowed ideas from other domains without any formal collaboration. For instance, Charles Kelman was inspired to develop photo-emulsification (to remove cataracts after pulverizing them with ultrasound) as he was having his teeth cleaned by a dentist. There are certainly examples of successful, structured collaborations, which are integral to modern design-thinking approaches to organized innovation. Some of the important advances in cataract treatments that followed Kelman's serendipitous insight resulted from purposeful multidisciplinary effort. But where and

how structured multidisciplinary innovation works better than the ad hoc cross-pollination of ideas remain challenging, and very likely unanswerable, questions.

Meanwhile the prognosis for more pluralistic, decentralized, and continuously accretive medical innovation appears mixed. As we have seen, medicine long has favored an epistemological monoculture that induces centralization by standardizing knowledge and training. There are, nonetheless, signs of increased openness.

Outside players have expanded their roles. After the success of Genentech, venture capitalists who previously had specialized in nonmedical technologies, such as computers and software, started investing in biotechnology, medical-device, and medical-services companies. Companies such as IBM and Google are seeking to apply their big-data analytics and cloud-computing capabilities to health care. Many technologies that were not developed for medical purposes have nonetheless been incorporated into medical devices. Lasers, which had "no connection with research aimed to understand disease," became "a central component" of many "effective medical treatments." Similarly, CT scanners "drew heavily on advances in computers and mathematics, ultrasound had its origins in submarine warfare, and magnetic resonance imaging (MRI) had originated in the work of experimental physicists" (Nelson et al. 2011). Large industrial companies and venture capital-backed businesses—not traditional medical researchers—drove much of this cross-fertilization.

Widespread online information-sharing has encouraged venturesome consumers to take many medical matters into their own hands. Online information-sharing started modestly with the formation of Usenet groups at the University of North Carolina and Duke University in 1980. Through the 1980s, Usenet membership was restricted to the few individuals who had access to the Internet and the technical skills necessary to participate. Since then, Internet connectivity has become ubiquitous, and posting or retrieving information has become mundane. In addition, channels for information sharing have multiplied to include online forums and social networks such as Facebook and YouTube. Easy information sharing has, in turn, prompted individuals to investigate and try to solve problems in domains—including medicine—where they have no training or experience. For many, a Web search has become a complement to—and in some cases a substitute for—consulting a physician.[29]

The FDA has apparently not abandoned its foundational opposition to auto-therapy. It continues to resist self-diagnosis and self-testing. As

mentioned, the agency now regulates home-testing devices and tests sold directly to consumers. At the same time, the FDA has accommodated the demands of patients by changing some of its efficacy requirements. In the mid-1980s, AIDS activists pressured the FDA to allow several thousand patients access to AZT before it had been approved. In 1987, the FDA formalized the conditions for granting "treatment INDs" under which patients could get new drugs that were still in trials.[30] By August 1994, 29 drugs had been granted treatment INDs, of which 24 had received normal approval by the end of that year (Flieger 1995). In the 1990s, the FDA began "priority" reviews for applications that might produce major advances. It also began accepting evidence of proxy effectiveness —for instance, approving drugs that reduce cholesterol on the premise that reducing cholesterol reduces the risk of heart disease.

Such changes evoke the specter of a return to the nineteenth-century peddling of snake oil. But the world has changed considerably from the snake-oil era. Most individuals now rely on insurance or public aid to pay for their health care; as mentioned, insurers have a strong incentive to independently evaluate cost-effectiveness. In non-medical areas, many new sources and channels have evolved that assess new products and services. Curtailing the FDA's role in evaluating efficacy could encourage a similar profusion of evaluations in the medical sphere as well. Arguably, the alternative evaluations of efficacy would be less reliable. Evaluators of non-medical products often include less knowledgeable and independent individuals than the experts who serve on the FDA's review panels. Pluralistic evaluations also naturally entail more varied standards and can therefore produce conflicting verdicts, including endorsements of snake oil. But while ineffectual treatments certainly can be risky, risks to the public's health are also posed by the suppression of potentially life-saving and life-enhancing innovations under centrally supervised trials that implicitly start with the presumption of inefficacy. Understandably, regulators favor the visible results of double-blind studies over the invisible results of innovation squelched by the requirements of those studies. The net effect may well be a net loss in health, well being, and life itself, although there is no scientific way to tell with assurance.

NOTES

1. The thesis of pluralistic, multiplayer innovation is not novel and should not be controversial. Richard Nelson has been emphasizing its importance, and its policy implications, for decades. (See, for instance, Merges and Nelson 1994).

Nathan Rosenberg's (1976 and 1982) arguments about accretive incremental advances implicitly attribute a pivotal role to pluralistic innovation. Unfortunately, Schumpeter's stirring rhetoric about great innovators who "found kingdoms" effaced this role. And the "sharp disjunction" Schumpeter posited between "the high level of leadership and creativity involved in the first introduction of a new technique as compared to the mere imitative activity of subsequent adopters" has helped obscure the value of multiplayer innovation.

2. "New Report: Precision Oncology in an Era of Healthcare Reform," *Economics21*, April 27, 2016.
3. "Requirements for Becoming a Physician," American Medical Association post downloaded from http://www.ama-assn.org/ama/pub/education-careers/becoming-physician.page? on October 23, 2016
4. Congress, which appropriated $28 million for the NIH in 1949, increased that amount more than 500-fold in the next 50 years to $15.6 billion in 1999. Appropriations doubled again to $30.5 billion in 2009, but leveled off thereafter. Compiled from NIH: Office of Budget data posted at https://officeofbudget.od.nih.gov/approp_hist.html
5. In 2003, NIH grants paid for 28 percent of $94.3 billion spent on biomedical research in the United States (Osterweil 2005).
6. "About Us," http://www.cancerresearch.org/about/history (downloaded July 26, 2015)
7. Personal email.
8. Kelman did, however, receive a $250,000 grant to develop his breakthrough photoemulsification technology (introduced in 1967), and he secured a clinical appointment at New York University.
9. Carpenter 2010 provides the definitive account of the history of the FDA and its influence on medical innovation and on the structure of the industries it regulates.
10. As with the 1938 legislation, the 1962 amendment is widely thought to have been catalyzed by an outcry about drug safety—namely birth defects induced by thalidomide—rather than by a shortfall in efficacy. The only nexus between the expanded role of the FDA in premarket trials and the thalidomide deaths was that they occurred during safety trials whose design the FDA then lacked the authority to regulate. The FDA's (1998) own account of the 1962 amendment makes no mention of the thalidomide tragedy. Rather, it asserts that "the original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices."
11. The high costs of satisfying regulatory requirements also may encourage developers to piggyback off NIH-funded research. This incentive should, ceteris paribus, narrow the scope of development to areas favored by the NIH, and favor individuals (particularly NIH grantees) and organizations plugged into NIH research.
12. Vincenti 1990 provides an excellent analysis and persuasive examples of the differences.
13. Until 2004, a company seeking FDA approval for a therapy based on an herbal extract, for instance, had to identify the single active ingredient that is doing the job—and prove its safety and efficacy. In June 2004, the FDA did, however, issue guidelines that would make it easier to secure approval for botanical drugs that have not been "purified" to a single molecule.

14. Among those I have interviewed whose companies developed medical devices, I frequently heard that they first sought approval in Europe, where regulators were more tolerant of the need for ongoing adjustments.
15. Quoting Intel's description of its tick-tock process, at http://www.intel.com/content/www/us/en/silicon-innovations/intel-tick-tock-model-general.html
16. According to Nelson et al. (2011), however, "the cumulative result of a series of more incremental advances in medical knowledge often is a major improvement in ways of treating patients." This raises the question of how the incremental advances cited by Nelson et al. (in angioplasty and the treatment of coronary diseases, cataracts, and diabetes) overcame regulatory barriers. Did they pertain to improvements that are not regulated by the FDA? Did they involve use of "clearance" rather than "approval" rules for medical devices?
17. This act is sometimes referred to as the Medical Device Amendments of 1976, because it amended the Food, Drug, and Cosmetic Act of 1938.
18. "What Does It Mean When FDA 'Clears' or 'Approves' a Medical Device?" http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194460.htm (downloaded July 23, 2015).
19. See also "Medical Devices; Procedures for Investigational Device Exemptions–Food and Drug Administration. Final Rule," *Federal Register* 45, no. 13 (January 18, 1980): 3732–59.
20. Two of the companies (Picker and Elscint) were asked to revise and resubmit their applications before the FDA granted approval to sell.
21. 53 Fed. Reg. 7575 1988. According to the FDA 510(k) database, established companies that obtained 510(k) approvals during this period included Instrumentarium, Philips, GE, Siemens, Diasonics, and FONAR. Many developers appear to have waited to apply for FDA approval under the new rules. Entrants at this stage included longtime developers such as Bruker, Toshiba, Resonex, and Hitachi (in a joint venture with startup Summit World Trade Corporation), and only two new developers: Shimadzu Medical Systems; and Health Images Inc., a network of imaging centers, which got approval for its own brand of MRI. The two apparent startups were Stein-Gates Medical Equipment, which obtained approval for a portable ventilator; and MRT Inc., which obtained approval for an MR therapeutic device. Other companies also received approvals for accessories and/or MRI-compatible supplies.
22. Fuchs and Sox 2001 surveyed 225 general internists about the relative importance of thirty medical innovations to their patients. The innovations were chosen by electronically searching the *Journal of the American Medical Association* and the *New England Journal of Medicine* between 1975 and 2000 to identify the innovations that were the principal focus of the published articles. The survey also invited respondents to suggest omitted innovations that the respondents thought were particularly important. Respondents were asked to select the five to seven innovations whose absence would have had the most adverse effect on their patients, as well as the five to seven innovations whose absence would have had the least adverse effects. Each innovation was then "scored" by assigning a value of 1.0 if the innovation was selected as having the most adverse effect if it were unavailable, 0.0 if placed in the least adverse category, and 0.5 if it was neither most nor least. Innovations that took the form of medications had a statistically lower mean score (0.473) than did diagnostic innovations (0.570) and surgical innovations (0.582). Note that about midway between 1975 and 2000, the FDA began to require efficacy trials for "new" diagnostic innovations.

23. See https://www.faa.gov/aircraft/ (downloaded on July 17, 2015).
24. To cite a personal example, my physician told me to take vitamin D supplements to bring my vitamin D levels to normal. Because there is no way to know how much additional vitamin D would do the job, the obvious solution would be to experiment with different amounts and monitor the effects. Unfortunately, there are no home tests that would permit such monitoring, even though vitamin D deficiency is a common condition. Similarly, I have been unable to find cheap and reliable tests to monitor, and thus help control, cholesterol, blood sugar, and sleep apnea. There is no technical reason why, in this day and age, there should not be such tests, much as there are for HIV infections (a test, however, that was allowed only because of political action against the FDA).
25. FDA press release, February 19, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM435003 (downloaded July 16, 2015).
26. See http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ConnectedHealth/MobileMedicalApplications/ucm255978.htm (downloaded July 16, 2015).
27. Bhidé 2008, 434-35, reviews some of the standard criticisms of medical innovation and outcomes.
28. Summarized from http://commonfund.nih.gov/Interdisciplinary (downloaded July 15, 2015).
29. For instance, I had a bout of nausea and giddiness in 2003. An emergency room doctor performed an "Epley maneuver" on me that immediately resolved the problem, which apparently had been caused by benign paroxysmal positional vertigo. Many years later, when the vertigo reappeared, I looked up a video of the maneuver on YouTube, avoiding another visit to a doctor. An online search also allowed me to figure out why I had periodically suffered from cramps and how to solve the problem—something diligent and competent physicians had been unable to do for more than a decade.
30. Under "treatment" Investigational New Drug (IND) rules, doctors can prescribe the drugs to patients who were not enrolled in a clinical trial only if the patients had advanced life-threatening diseases for which no other treatment was available. The rules also required the drugs' developers to "diligently" pursue normal trials, and to refrain from promoting or otherwise commercializing not-yet-approved drugs.

REFERENCES

Bhidé, Amar. 2000. *The Origin and Evolution of New Businesses*. New York: Oxford University Press.

Amar Bhidé. 2008. *The Venturesome Economy: How Innovation Sustains Prosperity in a More Connected World*. Princeton: Princeton University Press.

Bhidé, Amar. 2015. "The Demise of U.S. Dynamism Is Vastly Exaggerated—But Not All Is Well." In *Understanding the Growth Slowdown*, ed. Brink Lindsey. Washington D.C.: Cato Institute.

Bowler, Caitlin, Amar Bhidé, and Srikant M. Datar. 2017. "Innovation in Laparoscopy: A Case Study." Boston: Harvard Business School Publishing.

Bynum, William. 2008. The *History of Medicine: A Very Short Introduction*. Oxford: Oxford University Press.

Carpenter, Daniel. 2010. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*. Princeton: Princeton University Press.

Dickenson, H.J. 1958. "The Steam Engine to 1830." In *A History of Technology, Volume IV: The Industrial Revolution c. 1750 - c. 1850*, ed. Charles Singer, E. J. Holmyard, A. R. Hall, and Trevor I. Williams. Oxford: Clarendon Press.

Federal Communications Commission. 1996. Understanding the FCC Regulations for Computers and Other Digital Devices. OET Bulletin 62. https://transition.fcc.gov/Bureaus/Engineering_Technology/Documents/bulletins/oet62/oet62rev.pdf (downloaded July 17, 2015).

Flieger, Ken. 1995. "FDA Finds New Ways to Speed Treatments to Patients." FDA Consumer Special Report, January.

Food and Drug Administration (FDA). 1998. "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products."

Fuchs, Victor R., and Harold C. Sox. 2001. "Physicians' Views of the Relative Importance of Thirty Medical Innovations." *Health Affairs* 20(5): 30–42.

Gelijns, Annetine, Nathan Rosenberg, and Holly V. Dawkins. 1995. *Sources of Medical Technology: Universities and Industry*, *Medical Innovation at the Crossroads*, vol. 5. Institute of Medicine (U.S.) Committee on Technological Innovation in Medicine. Washington, D.C., National Academy Press.

High, Jack, and Clayton A. Coppin. 1988. "Wiley and the Whiskey Industry: Strategic Behavior in the Passage of the Pure Food Act." *Business History Review* 62(2): 286–309.

Lehrer, Jonah. 2013. "The Truth Wears Off." *The New Yorker*, December 13.

Marshall, Barry J. 2006. Autobiographical Essay (www.nobelprize.org).

Mardin, Osman. 2017. Email to author.

Merges, Robert, and Richard R. Nelson. 1994. "On Limiting or Encouraging Rivalry in Technical Progress: The Effect of Patent Scope Decisions." *Journal of Economic Behavior & Organization* 25(1):1–24.

Mitchell, William G. 1988. "Dynamic Commercialization: An Organizational Economic Analysis of Innovation in the Medical Diagnostic Imaging Industry." Ph.D. dissertation, University of California, Berkeley.

Mitchell, William G. 1983. "The Diagnostic Imaging Industry." Elscint Ltd., Form 10-Q, March 31, 15–16; Elscint Ltd., Annual Report for 1983, 5; Elscint Ltd., 1985, Form 10-Q, 4–6, 14–15, 22.

Nelson, Richard R., Kristin Buterbaugh, Marcel Perl, and Annetine Gelijns. 2011. "How Medical Know-How Progresses." *Research Policy* 40 (10): 1339–44.

Osterweil, Neil. 2005. "Medical Research Spending Doubled Over Past Decade." *MedpageToday*, September 20.

Pickstone, John. 1996. "Medicine, Society and the State." In *Cambridge Illustrated History of Medicine*, ed. Roy Porter. Cambridge: Cambridge University Press.

Rosenberg, Nathan. 1976. *Perspectives on Technology*. New York: Cambridge University Press.

Rosenberg, Nathan. 1982. *Inside the Black Box: Technology and Economics*. New York: Cambridge University Press.

Reitsma, A. M., and J. D. Moreno. 2002. "Ethical Regulations for Innovative Surgery: The Last Frontier?" *Journal of the American College of Surgeons* 194(6): 792–801.

Staley, Oliver. 2015. "Success at Glaxo's HIV Unit May Mean Having to Call It Quits." *BloombergBusiness*, July 9.

Steinberg, Earl P. 1986. "The Status of MRI in 1986: Rates of Adoption in the United States and Worldwide." *American Journal of Roentgenology* 147, no. 3 (September 1): 453–55.

Steinberg, Earl P., and Alan B. Cohen. 1984. *Nuclear Magnetic Resonance Imaging Technology: A Clinical, Industrial, and Policy Analysis*. Health Technology Case Studies, vol. 27. Washington, D.C: Office of Technology Assessment, Congress of the United States.

Steinberg, Earl P., J. E. Sisk, and K. E. Locke. 1985. "X-Ray CT and Magnetic Resonance Imagers. Diffusion Patterns and Policy Issues." *New England Journal of Medicine* 313(14): 859–64.

Nuland, Sherwin. 1988. *Doctors: The Biography of Medicine*. New York: Alfred A. Knopf.

Nuland, Sherwin. 2008. *Doctors: The Illustrated History of Medical Pioneers*. New York: Black Dog and Leventhal.

Straus, Eugene W., and Alex Straus. 2006. *Medical Marvels: The 100 Greatest Advances in Medicine*. New York: Prometheus Books.

Vincenti, Warren G. 1990. *What Engineers Know and How They Know It*. Baltimore: Johns Hopkins University Press.

Warren, Robin J. 2006. Autobiographical Essay (www.nobelprize.org).

Yadron, Dannie. 2015. "Moxie Marlinspike: The Coder Who Encrypted Your Texts." *Wall Street Journal*, July 10: B1.