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The revolution that never arrived: Clinical and genetic paradigms in bio-medical research and the R&D productivity paradox

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Abstract

The purpose of this paper is to describe two major paradigms that have shaped biomedical research paradigms in the United States, and to link those research paradigms to the productivity of discovery in medicine. The timespan described in this paper consists of an early period (1940s-1970s) in which the dominant research paradigm was patient oriented clinical research: experiential, ?bedside to bench? learning, followed by a period (1980s-present) when the dominant paradigm was driven by basic research centered on genetics and ?bench to bedside? learning. This shift in the epistemic basis of research entailed a major re-orientation of the locus of discovery: from physician-researchers working at the bedside in teaching hospitals, to geneticists working in laboratories in pre-clinical departments of medical schools, university basic science departments, or entrepreneurial science-based firms. These institutional differences stem from an epistemic divide concerning the utility of causal models in drug discovery, and beliefs about the best research strategies to find new medical treatments. Contrasting the two paradigms of genomics and patient-oriented clinical research (POR) shows that medical research transitioned from experiential learning based on intact organisms, to a reductionist, theory-driven approach centered on basic research in laboratories. While the historical and case data do not allow for controlled experimental design, a review of the history is nonetheless instructive, and may contribute to an understanding of how new drugs are discovered.

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The revolution that never arrived: Clinical and genetic paradigms in bio-medical research and the R&D productivity paradox

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ABSTRACT

The purpose of this paper is to describe two major paradigms that have shaped biomedical research paradigms in the United States, and to link those research paradigms to the productivity of discovery in medicine. The timespan described in this paper consists of an early period (1940s-1970s) in which the dominant research paradigm was patient oriented clinical research: experiential, "bedside to bench" learning, followed by a period (1980s-present) when the dominant paradigm was driven by basic research centered on genetics and "bench to bedside" learning. This shift in the epistemic basis of research entailed a major re-orientation of the locus of discovery: from physician-researchers working at the bedside in teaching hospitals, to geneticists working in laboratories in pre-clinical departments of medical schools, university basic science departments, or entrepreneurial science-based firms. These institutional differences stem from an epistemic divide concerning the utility of causal models in drug discovery, and beliefs about the best research strategies to find new medical treatments. Contrasting the two paradigms of genomics and patient-oriented clinical research (POR) shows that medical research transitioned from experiential learning based on intact organisms, to a reductionist, theory-driven approach centered on basic research in laboratories. While the historical and case data do not allow for controlled experimental design, a review of the history is nonetheless instructive, and may contribute to an understanding of how new drugs are discovered.

Scholars and practitioners have long endeavored to identify the best research paradigm to advance human knowledge. The question harkens back to ancient philosophical debates, when Plato and Aristotle – both believers in the existence of universal laws of nature – differed over whether pure inquiry was sufficient to uncover those laws, or whether empiricism and observation of the natural world were a necessary component of discovery. In the 17th century, the rationalist position that knowledge advances from pure reason was challenged by philosophers Francis Bacon and John Locke who maintained that all knowledge derives from sensory experience. Victorian-era historians resisted the role played by accidental discovery in scientific progress, arguing that scientific principles provided for a rational and planned method for advancing knowledge (Merton and Barber, 2004). In the modern period, postwar science policy was framed around the idea that government-funded basic science – knowledge for knowledge sake - would serve as a boon to industrial R&D (Stokes, 1997). Similarly, the emphasis on "translational research" in current science policy is based on the idea that stronger linkages between the "bench" (basic research) and the "bedside" (the practice of medicine) will advance knowledge in human health care and raise the productivity of drug discovery.

These debates are reflected in current research on the question of how firms should manage R&D in complex, uncertain fields (Arora and Gambardella, 1994; Fleming and Sorenson, 2004; Gavetti and Levinthal, 2000, Nelson, 2003). Nelson (2003) makes the claim that technologies advance more rapidly when they can draw upon an institutionalized body of applied sciences and engineering knowledge. This position is countered by research that argues that abstract representations and basic science provide a useful map of technological space

that can yield rapid and efficient solutions to complex technological problems. (Arora and Gambardella, 1994, Fleming and Sorenson, 2004; Gavetti and Levinthal, 2000).

It is instructive that much of this research references the fields of medicine and drug discovery. This is not surprising, since drug discovery is a highly complex technological problem that builds directly on scientific knowledge. The question of which type of search strategy yields better R&D outcomes is particularly salient, given a productivity crisis in pharmaceutical R&D. As blockbusters are coming off patent, new drugs are not being discovered at a rate that will keep revenues from declining rapidly (Kola and Landis, 2004). In the face of the R&D productivity crisis, many large pharmaceutical firms are reducing R&D and shuttering entire branches of research (Jack, 2001). In 2007, the CEO of Eli Lilly stated that "[t]he industry is doomed if we don't change" (Wall Street Journal, 2007).

The productivity crisis is puzzling, a paradox even, given both quantitative and qualitative shifts in R&D: in the past 25 years, pharmaceutical R&D expenditures have risen markedly, and have been accompanied by the adoption of new discovery tools that are rooted in basic science and advances in molecular biology and genetics. The adoption of genetics-based research in the pharmaceutical industry represented a major shift in research paradigms, involving not only a new set of tools and techniques but a wholly new cognitive and scientific approach to managing research. This change in the orientation of research towards basic science promised rapid advances in the rate new drug discovery and increasing number of clinical successes; indeed, the adoption of biotechnology was considered a "radical" technology that would revolutionize medicine. To spur this wave of innovation, the government (and private sector firms) invested billions of dollars to sequence the human

genome and advance the science of genetics and molecular biology. The application of new and powerful bio-informatics techniques vastly increased informational throughput and promised to improve the success rate in identifying new drugs based on the flood of genomics information that became available. An entire industry of small, research specialized firms emerged in the 1980s and 1990s to capitalize on the new technologies; spun off from university research, these firms brokered between basic research and the industry, forming dense networks of partnerships to trade technology and knowledge. The deepening of the innovative division of labor and major investment in commercial biotechnology were expected to increase the innovation performance of the bio-pharmaceutical industry overall(Arora and Gambardella, 1994). .

The purpose of this paper is to describe the history of biomedical research paradigms in the United States during the postwar period. Though biotechnology is frequently referred to as a "radical", "breakthrough" and "revolutionary" technology, scant attention is generally given to the discovery paradigms that preceded it. The history is instructive. The timespan described in this paper is characterized by an early period (1940s-1970s) in which the dominant research paradigm was patient oriented clinical research: experiential, "bedside to bench" learning, followed by a period (1980s-present) when the dominant paradigm was driven by basic research into genetics and "bench to bedside" learning. This shift in the epistemic basis of research entailed a major re-orientation of the locus of discovery: from physician-researchers working at the bedside in teaching hospitals, to geneticists working in laboratories in pre-clinical departments of medical schools, university basic science departments, or entrepreneurial science-based firms. These institutional differences stem from an epistemic

divide concerning the utility of causal models in drug discovery, and beliefs about the best research strategies to find new medical treatments.

Contrasting the two paradigms of genomics and patient-oriented clinical research (POR) thus provides something of a natural experiment in which medical research transitioned from experiential learning based on intact organisms, to a reductionist, theory-driven approach centered on basic research in laboratories. While the historical and case data do not allow for controlled experimental design, a review of the history is nonetheless instructive. Much empirical research into private-sector R&D productivity assumes as a given the dominant research paradigm conducted in academia, and does not account for differences in the scientific fields upon which firms draw for their own R&D. A notable exception is Nelson (2003) who asks the important question of why some fields of technology advance more rapidly than others. In a sense this paper is an extended case analysis of the ideas seeded by Nelson; the intention is to develop a deeper and more nuanced historical understanding of research paradigms in medical discovery.

Following on that work, I suggest the following claim: that in a complex, highly uncertain field of technology, experiential learning based on feedback from real-world experiments can be more conducive to rapid discovery than theory-driven search using abstract models of reality. The claim is based on the simple observation that when complexity and uncertainty are high, robust causal explanations are lacking and those that do exist are likely to be at the frontier of scientific discovery and hence fragile and incomplete. The paper does not focus on the drug industry itself, although firms are central actors in drug discovery. Instead, I focus on the larger system of biomedical research from which firms can draw knowledge. By

drawing attention to changes in the paradigms of scientific research in the post-War period, I try to show that the menu of research options available to firms has changed in ways that might impact their own productivity.

Science and industrial R&D as search logics

While there is a natural inclination to view "science" and "industrial R&D" as distinct practices, it is useful to note that they share many common features. Both involve formalized processes of search and learning: manipulating and combining elements, tangible and abstract, with the goal of generating new information about a problem or question. Both occur in organized settings that are specially designed and equipped to carry out research, e.g. labs and testing facilities. Both unfold in conditions of uncertainty, involving selection across a range of alternative and pathways of search. Both are cumulative, in that the choice to proceed along a given pathway involves investment in learning specific language and codes, routines, skills, methods of testing and instrumentation that make it difficult to switch to alternative research streams, even if the latter appear more productive of useful outcomes. In this sense, both scientific and industrial research may be characterized as "paradigmatic", consisting of search and learning routines that are learned over time and difficult to change; at a broad level, scientific specialties and fields (e.g. molecular biology or cardiac surgery) are research paradigms. Paradigms set in motion distinctive logics of search, comprising empirical methods, objects of study, learning routines, skills, and instrumentation.

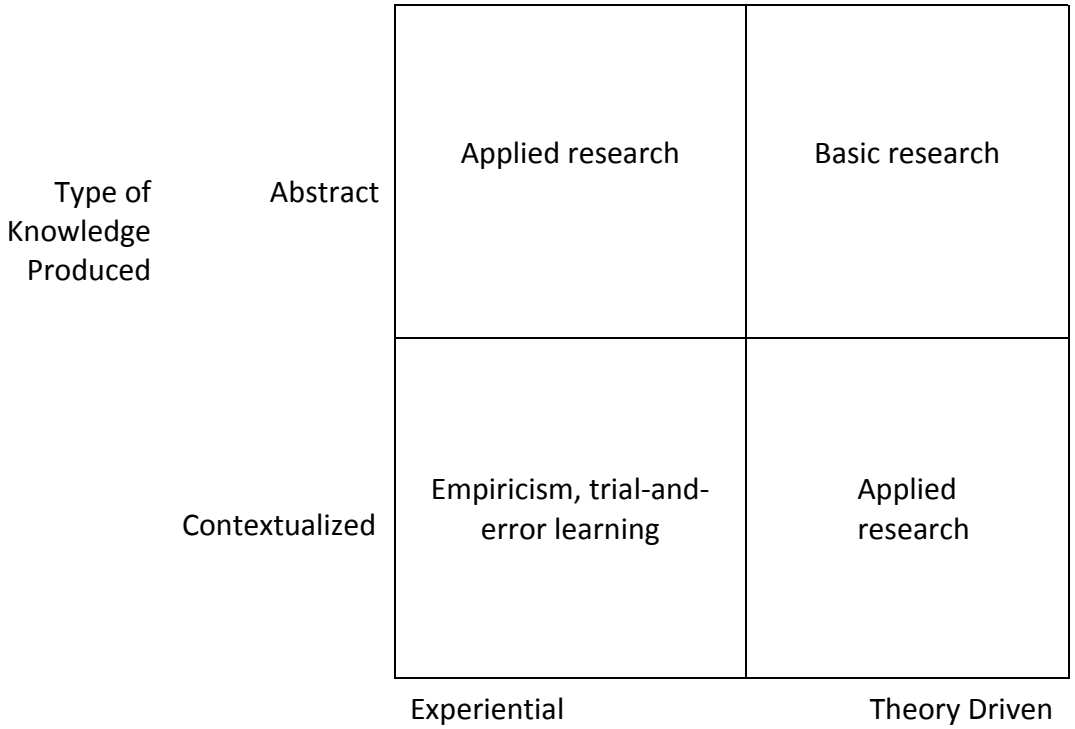
Figure 1 provides a representation of two important dimensions along which search logics may vary[1]. Along the vertical axis is the type of knowledge that is produced by search, whether intentionally or as a byproduct. These correspond broadly to knowledge that is useful in practice - *contextualized knowledge* - and knowledge that is useful for generalized analysis - *abstract knowledge*. Abstract knowledge relates to principles, laws, frameworks and understandings that are stripped of the details describing the operation of real objects in specific contexts. Mathematical axioms and laws of physics constitute abstract knowledge. Abstract knowledge is general, dis-embedded from any particular context or locus of action (Nelson, 2003). The more abstract it is, the greater the potential scope of the knowledge or, as Fleming and Sorenson put it, the greater the ability to recombine it with other knowledge from a wide variety of sources. Knowledge of how variables interact in general sheds light on the likely outcomes of a menu of research choices, and thus may be particularly useful in narrowing the range of options for testing (Nelson, 1982). For instance, a general theory of the causes of high blood pressure may be useful in narrowing down predictions about the classes of drugs most likely to be effective in treating the disease.

Contextualized knowledge relates to understandings of how real objects function in the real world. Unlike abstract knowledge, contextual knowledge is wedded to the myriad unexplained details that attend to the functioning of objects in action. Contextualized knowledge may not provide an understanding of why things work as they do, and without such an understanding may not be readily applied to new and different situations. It is therefore of

[1] The categories used to develop Figure 1 were drawn from multiple sources: Arora and Gambardella, 1994; Fleming and Sorenson, 2004; Gavetti and Levinthal, 2000; Nelson, 2003; Thomke, von Hippel, and Franke, 1998.

practical use but not of predictive use. For instance, a clinical trial may yield knowledge that a drug works to lower blood pressure. That is useful knowledge for future action, but may not

Figure 1. Search Logics



shed light on the causes of high blood pressure, nor provide information about whether alternative drugs are likely to be more effective, or how well the drug will work on people outside of the trial setting. Contextualized knowledge is embedded in specific and localized contexts and concerns objects whose functions and actions may not be fully characterized nor well understood.

The horizontal axis represents to the types of learning processes actors engage in the practice of research. Of particular importance along this dimension are the techniques by which researchers design experiments, the objects and tools used in study, and the learning

and feedback mechanisms that advance research forward. In the experiential learning paradigm, experimentation is "online", in that it simulates real-world conditions and utilizes objects that are approximations of objects as they exist in the real world. Learning is "backward looking" in that it advances based on feedback generated in real-world situations or experiments that mimic the actual objects and phenomenon being studied (Gavetti and Levinthal, 2000). For instance, administering an experimental blood pressure drug to rats in a controlled setting uses real-world objects – animals and drugs - that simulate the actual objects of study, humans and drugs. Administering the drug to humans in a clinical trial provides even clearer feedback about how the drug will function in the real world. Experiential search is sequential: the outcome of a test must be observed before the researcher can move on to the next test. It is therefore slow and inefficient insofar as multiple trials cannot be run simultaneously. At its extreme, experiential learning may take the form of random trial-and-error experimentation, without any a priori expectations about the possible outcomes of experiments (Thomke et al, 1998).

Towards the right end of the axis is theory-driven search. Whereas experiential search is based on ex post learning from feedback, theory-driven search follows a predictive, forward-looking logic (Gavetti and Levinthal, 2000). Research is guided by beliefs about cause-effect relationships that help plan search and testing of alternatives. Theory-driven knowledge does not rely on observation of whole objects to develop predictions; it is reductionist, focusing on essential properties of objects to develop fundamental understandings of causal relationships. Validation and testing occurs "offline", utilizing simulations, models and instruments that abstract, to varying degrees, from real-world settings (Arora and Gambardella, 1994).

Predictions can be derived for untried experiments, thereby expanding the scope of search options as compared to experiential learning (Fleming and Sorenson, 2004). For instance, the theory that a certain gene is associated with high blood pressure can be used to generate predictions about the properties of drugs that will be effective in lowering blood pressure.

Complexity, search logics and the rate of discovery

These search logics can be directly applied to the question of how scientific methods can influence the rate of technological progress. Richard Nelson (2003) makes the argument that experiential, "online" search is not only essential in technological innovation but for advancing scientific knowledge itself. He de-constructs technologies as consisting of both "techo" and "logy": techno relates to the practical knowledge of how real objects function in real-world settings, and "logy" is the broader understanding of why objects behave as they do. He claims that these two bodies of understanding co-evolve, and that technologies that advance most rapidly are distinguished by their connection to a well-developed body of institutionalized applied, experimental science, not basic research. He also suggests that science itself advances through experiential knowledge:

> "[M]ost of the strong fields of empirical science that have been developed have involved experimentation in an essential way. And I believe that this is especially the case with sciences that illuminate technologies. *Those sciences cannot progress effectively, at least not in a way that is useful to advancing the technology, unless the technology itself is suitable for experimentation*." (italics added)

Nelson suggests that the principles of basic science – fundamental cause effect relationships – are *already embedded in* applied sciences and engineering knowledge, and that

applied sciences, because they are so tightly connected to real-world problems, are the most useful scientific fields for technological innovation.

In contrast, Arora and Gambardella (1994) describe how increased computational power coupled with scientific advances allow for knowledge to be cast in universal frameworks and categories, and these cognitive framings can be usefully applied to solve complex technological problems. Scientific methods allow for parallel rather than sequential testing, a more efficient way to sift through the multiple solutions to complex problems (Fleming and Sorenson, 2004, Thomke et al, 1998).

Gavetti and Levinthal (2000) introduce the construct of a fitness landscape to compare the effectiveness of experiential and abstract search logics. While their concern is managerial strategic choices, their approach is directly applicable to the issue of science-technology linkages, e.g. Fleming and Sorenson (2004). Complexity is a measure of the number of realized correlations between the possible combinations of elements in a search space. When complexity is high, finding the highest payoff (peak) is a challenge, given the high number of trials that the researcher must iteratively test to move towards it. Moreover, feedback-based, experiential learning can lead researchers into exploratory loops that fix them in local positions on the search space but do not lead them towards the highest peak.

Faced with complex landscapes, forward-looking theoretical search logics trump experiential search by providing an unbiased (albeit highly simplified) representation of the terrain, pointing searchers towards globally-maximal solutions. It is only in environments characterized by low complexity that "online" experiments and experiential learning provide accurate feedback that leads to the best solutions. Fleming and Sorenson (2004) apply a

similar logic to argue that scientific knowledge provides a "map" of a technological search space, and that fundamental cause-effect understandings are most valuable when applied to technological problems characterized by a high degree of complexity and interdependence. Science provides a ready-made rationality and abstract cause-effect logic to help solve complex problems.

A problem with this logic is that the complexity of the problem is itself a statement about the extant state of scientific knowledge at a given point in time. In other words, complexity is a *symptom* of an underdeveloped body of fundamental understandings, and persistent complexity points to an absence of "true" and unbiased statements about the variables and the outcomes of a given set of combinations. The notion that theoretical knowledge is useful in complex search spaces is a tautology: problems appear complex when researchers don't understand them, not the other way around (Rees, 2002).

The problem thus arises that faced with complexity, researchers lack robust and abstract knowledge about cause-effect relationships. In such situations, the adoption of a representational, abstract mapping of a problem space may confound the search process if the maps are inaccurate or incomplete representations of the full set of variables and their (unknown) relationships. For instance, in the 1990s Amgen seized upon leptin as a solution to the complex problem of developing an obesity drug, once it was shown in scientific research that leptin was implicated in appetite regulation. Amgen paid $25 million to license the hormone; however, leptin proved to be useless as a drug for obesity, and further research revealed that a host of other complex factors besides leptin were important in appetite regulation. Belief in the validity of the simple causal model created a false sense of

fundamental understanding, and caused Amgen to overspend resources on what they believed was a solution; in fact, the full complexity of the problem defied the utility and validity of the early model.

Therefore, the conditions of complexity and uncertainty define situations in which researchers lack robust knowledge about the variables and correlations between them that influence outcomes. In such situations, trial-and-error experiments, using study objects that approximate those in real-world settings, can help generate clues about underlying causal relationships. At a very early stage, where there is no ex ante knowledge of the problem space, exploration may be a messy, trial-and-error, random and atheoretical endeavor. Insights from such experiments can reveal information about cause-effect relationships that cannot be predicted ex ante. The process of serendipity is likely to be salient in early exploration. Since researchers do not yet have abstract representations of the problem, learning advances by manipulating objects that bear a strong resemblance to those in the real world. In the process, researchers are likely to hit upon correlations that they could not predicted ex ante. If they are suitably trained, researchers will seize upon these events as valuable insights into new causal mechanisms that they had not anticipated. Over time, as more knowledge accumulates from these experiments, hypothesis-driven search becomes possible, eventually allowing for "offline", predictive search. An example of this type of experiential search is brain imaging: it is an empirical technique without much theory to guide its progress; instead, the empirical data from the images are helping to trace out understandings of the physical manifestations of brain functions.

Several propositions flow from this discussion. The first is that that for complex problems where key variables and their relationships are not well understood, robust causal explanations are lacking, and experiential, feedback-based search logics can uncover underlying cause-effect relationships. A second implication is that basic science, which generates abstract knowledge, may not be the most useful knowledge for solving complex technological problems. Instead, science that directly engages with real-world objects, experiential learning, and solving practical problems – the applied sciences – are more likely to speed discovery.

Research paradigms in bio-medicine: Genetics and clinical search logics

The case of drug discovery provides a useful context for studying problem-solving in complex search spaces. Diseases are complex because multiple variables and systems of variables interact to produce disease states: environmental stressors, genetics, behaviors, related medical conditions, all interact in numerous ways to produce disease in one individual but not another. Indeed, it is the persistent variability across individuals in the incidence of disease that has thwarted efforts to pin down causal triggers, and the complex causes of many important diseases such as diabetes, cancer, and depression are still not well understood.

Drugs are technologies in the sense that they are real objects that need to function safely and effectively in a complex, variable real-world context: the human body. Theoretical predictions of how drugs ought to function is irrelevant if a drug fails to operate safely and effectively in the unpredictable context of a living organism. Since it is so difficult to forecast all of the possible ways in which a drug will behave within the body, abstract models are limited in their predictive power, and "online" testing in animals and humans is necessary before drugs can be marketed. Indeed, even after they reach the market, drugs can produce unanticipated

effects. Therefore, drug discovery is a process of innovation that unfolds under conditions of high uncertainty and extremely high level of complexity.

Genomics is a reductionist technique that begins with the most basic elements of human life, DNA, to predict disease processes in cells and, ultimately, the whole organism. In this paradigm, intact humans do not formally enter the discovery process, entering only in the final phase of clinical testing. In the POR paradigm, discovery *commences* from observations of intact organisms (usually humans) to deduce of micro-level processes within the body. Compared to the reductionist model, the sequencing of objects in the discovery and development process – genes, cells, animals, and organisms – is reversed.

At the core of these differences is an epistemic conflict over the concept of disease causality and the appropriate research strategy to discover new medicines. Genomics is predicated on the belief that genetic information yields understanding about the causes of disease, and that this knowledge creates a forward-looking path to finding drugs. In contrast, the clinical paradigm holds that causality and the operation of effective therapies are disconnected, at least at the current state of knowledge about pathology. These fundamentally different belief systems are expressed in an entirely distinct set of institutional arrangements that form the locus of discovery and the ways in which scientists conduct their work: the key investigators, methods and materials, instrumentation and disciplines are specialized and distinct. Figure 2 lays out these differences, which I discuss below.

The clinical research paradigm: bodies as the locus of discovery

Throughout the history of medicine, major discoveries have been made through clinical observation and experimentation well before scientists explained causality. These discoveries

were frequently haphazard and ad hoc, and serendipity played an important role. For example, the initial chemical agent (dicoumerol) that led to the blood thinner coumadin was discovered when farmers observed that cattle were dying of internal hemorrhaging after feeding on rotting sweet clover (Campbell, 2005). The link between cholesterol and heart disease originated in experiments conducted in 1913, when the Russian scientist Nikolai Anichkov discovered that rabbits fed high-fat diets developed atherosclerosis. This knowledge was important for a stream of research that ultimately led to the development of statins, some 70 years later.

In many cases, the discovery of new treatments has paved the way for subsequent models of pathology. In psychiatry, observations of surgical patients receiving a new, safe pre-operative sedative (chlorpromazine) in a trial using hospitalized psychotic patients led to the unexpected finding of marked decreases in hallucinations and delusions. The discovery of an effective treatment for psychosis subsequently facilitated new theories of brain activity associated with schizophrenia. Similarly, unexpected patient responses to new medications led to the discovery of major treatments for depression and anti-psychotics; these treatments in turn facilitated unique findings concerning the importance of neurotransmitters in mental disorders.

More recently, important discoveries made from clinical observations paved the way for subsequent discoveries of disease mechanisms at the genetic level. Williams (2004) documents how the fundamental discoveries leading to effective treatments for sickle-cell anemia were triggered by the bedside observations of clinical researchers, who noticed that some populations (infants and certain ethnic groups) showed irregularities in disease rates and

pathologies. Later discoveries of the underlying genetic manifestations of the disease were motivated by models developed through earlier clinical research.

Figure 2. Genomics and Clinical research paradigms

	Epistemology	Discovery tools and methods	Locus of discovery	Disciplinary base	Key investigator
Genomics	"Bench to bedside" Genes cause disease. Unlocking fundamental (genetic) cause-effect relationships yields important clues to disease mechanisms and therapies.	Cells Genetic information Analytical equipment In vitro studies Human gene expression	Laboratory Firm	Molecular biology Genetics	PhD/Specialists
Basic clinical research	"Bedside to bench" Causation is complex. Experiments on humans both in normal and "perturbed" states lead to insights into mechanisms and potential treatments.	Human Beings Drugs Pathology Pharmacology	Clinical setting (hospital, academic medical center) Large-scale population studies	Physiology Pharmacology Epidemiology Behavioral sciences	Physician scientist MD-PhD Cross-disciplinary training

An important reason why medical discovery has been driven by clinical observation is that biology, unlike physics, is not a paradigmatic science: it lacks fundamental unifying laws and over-arching theories that link micro- and macro-level processes. Whereas physics seeks to uncover universal laws and cause-effect relationships, biology has been primarily concerned with establishing facts, as illustrated in the following quote:

> The great physicist-turned biologist Leo Szilard said that once he changed fields (no pun intended) he couldn't enjoy a long bath as he could when he could dream abstract physics in the bath. . .As a biologist he was always having to get out to check on some annoying little fact. It is the problem of predicting across several levels of biologic explanation, and the absence of the all encompassing general laws in biology, that accounts for the fact that most clinically relevant discoveries come from the clinic rather than the laboratory and not, contrary to what many believe, vice versa. (Rees, 2002)

With only a handful of robust biological theories of disease, medical research is not a paradigmatic science in the sense described by Kuhn: it has historically been a recombination of other, mostly applied disciplines (chemistry, pathology, physiology), and is driven by an external social need. Indeed, many fields of medical research can be described pre-paradigmatic, characterized by numerous competing concepts, claims, methods, interpretations of data and theories that are only weakly linked to one another.

In the clinical paradigm, the concept of *disease causality* does not have immediate practical consequences for the discovery of treatments. This is based on the observation that factors that trigger disease processes are usually not the same factors that reverse those processes: knowledge of causes does not point to knowledge of solutions, and understanding the causes of disease may have little actual bearing on the discovery of treatments.

Physician Jonathan Rees, underscores the distinction between biology and medicine and argues that causal understandings are difficult to apply to drug discovery (Rees, 2002, 2004)

Whereas biology uncovers fundamental processes – the pathways inside a cell that are implicated in diabetes, for instance, he proposes that medicine is more akin to engineering, designing a system or object of intervention that may not be based on causality. Complex diseases may have simple solutions, and mechanistic insights, as opposed fundamental understandings, frequently lead to the most successful interventions. Multiple pathways may be implicated in causing disease, but the task of curing that disease may hinge on only one. He cites as an example pernicious anemia, a complex, inheritable autoimmune disease that is usually fatal. In that case, understanding causality was not the key to finding a treatment; it hinged on experiments in which patients were fed different foods, until one – liver - caused the symptoms to subside. This mechanistic insight, made in the 1920s, was key to developing a treatment; it took decades before the active ingredient, vitamin B12, was isolated. While addressing this deficit cured the disease, the vitamin deficiency was not the main cause of the disease, but was merely one of many complex symptoms and causal factors.

Treatments, according to Rees, should not be understood as emerging from an understanding of pathology, but as operationalized statements about where the "Achilles heel" of a disease lies. In this paradigm, basic knowledge is not fundamental understanding of causes, but any theory that provides a workable solution. The research strategy therefore needs to be defined by the actual problem and the context in which it is embedded. Rejecting the link between causality and solution, the clinical paradigm explicitly embraces experiential, context-embedded research as the driving principle of drug discovery.

Clinical research may encompass a wide range of medical specialties (biochemistry, pathology, pharmacology, epidemiology), but the unifying theme, as defined by leading NIH

researchers, is “research performed by a scientist and a human subject working together, both being warm and alive” (Schechter, 1998). Patient-oriented clinical research (POR) is characterized by close contact between the investigator and human subjects (Ahrens, 1992). The clinical research paradigm is thus intimately connected to the *practice* of medicine and the delivery of healthcare.

The locus of discovery in the clinic or hospital does not necessarily imply an applied, end-stage approach -- sometimes referred to as “translational research” -- in which ideas developed in a laboratory are tested in a clinical setting. The distinguishing features of basic patient-oriented research are empirical induction based on observation of human subjects, interaction between theory and practice, and an experimental, hypothesis-driven approach geared towards developing and testing theories of human pathology and treatment (Ahrens, 1992; Rees, 2004). Investigators are typically cross-disciplinary, trained as both doctors and researchers.

Close observation of patients is an essential aspect of the POR discovery paradigm, as investigators look for unexpected changes that provide important clues to pathology. Ahrens (1992) describes the fundamental importance of close interactions with patients in a POR discovery paradigm:

> Scientifically, the most important asset of a POR facility is the golden opportunity it provides for medical investigators and their staffs to watch carefully and to think deeply about the medical challenges posed by their patients; this forces them to formulate new hypotheses and to devise new stratagems for attacking unsolved problems. There is time to ponder an unexpected event – an unexplained turn in the course of the disease or a puzzling response to a medication – and thus to obtain fresh insights into a disease or a manipulation under study.

From insights gained about cause-effect reactions in the human body, clinicians build theoretical models about pathological states and potential interventions. These theories of disease mechanisms are translated to lab research and further experimentation to identify the micro-level pathways and the search for lead molecules. It is at this point that pharmaceutical firms become involved in the search for lead compounds.

The Genomics paradigm: Causality and drug discovery

Over the last thirty years there has been a profound shift in the landscape of drug discovery and a new paradigm – genomics – has emerged as dominant. Based on molecular biology, genomics studies the most fundamental elements of living organisms – genetic information – to deduce macro-scale disease processes in intact organisms. As such, it is a reductionist technique, focused on breaking down objects of study into micro-level components. Reductionist techniques became prevalent in biomedicine in the 1970s, when in-vitro cell cultures and animal models grew in importance in research (IOM, 1994). Genomics became important in the 1980s, when scientists discovered tools to manipulate DNA and study cellular processes at the molecular level. It was distinguished by its roots in basic science of genetics, which had previously had no linkage to any clinical applications.

In the genomics paradigm, researchers working with DNA uncover genetic mutations that are believed to be associated with disease states; this in turn allows for the identification of the targets expressed by those genes. Targets are molecules (mostly proteins and enzymes) that exist in the body, are produced by DNA, and are active in metabolic processes and pathways. Drugs work by interacting with targets in the cells of living organisms. The ability of targets to bind with drug molecules make them critical mechanisms by which medicines work in

the human body. Once identified, targets become the basis for drug design projects. In this paradigm, drugs can be designed and tested "offline" – using knowledge of the molecular structure of the target to draft designs of a potential drug. Indeed, the phrases "rational discovery" and "designer drugs" were used to describe new paradigm.

The genomics paradigm offered the promise of a technologically-driven, rational and scientifically planned approach to the stubborn problem of discovering new drugs. The ability to sequence and study DNA therefore represented a powerful cognitive framing device in which drug development took on a forward-looking, predictive, and *predictable* logic. The promise was enormous; as expressed by William Haseltine, the Nobel-prize winning founder of an early genomics firm Human Genome Science: "Death is a series of preventable diseases" (Fisher, 1999). The genomics paradigm thus represented a revolutionary shift in medicine, a "silver bullet" approach to drug discovery that promised to vastly improve the productivity of pharmaceutical R&D.

The promise of genomics was thus to shift medical research from an uncertain, experimental process that relied heavily on serendipity, to a rational, theory-driven approach that would allow for a *planned* discovery process. This was naturally appealing to industry and private investors. In the early 1990s, the Human Genome Project was funded for $3 billion with the promise to revolutionize medicine. Private investors invested far greater sums: in the mid-2000s, cumulative private investment in biotechnology was estimated at $100 billion (Hamilton, 2004).

The institutional features of the new genomics paradigm have been well documented (e.g., Kenney 1986, Kaplan and Murray, 2010, Nightingale et al, Gittelman, 2006), however the

work practices of these scientists in the discovery process have been less studied. Dougherty and Dunne's (2011) ethnographic research uncovers a sharp contrast between two groups of scientists, whom they refer to as "digital" and "therapy" scientists. Digital scientists frame problems and products using abstract, systematic maps of the search space, e.g. , gene maps to identify well-specified targets. Therapy scientists focus on studying reality-based, concrete, emergent processes. They are more involved in physical interaction with tangible materials and study the body's functioning as it actually operates. From their fieldwork it is apparent that the search logics and knowledge production of digital and therapy scientists correspond to the upper right hand quadrant and upper left quadrants of Figure 1, respectively.

The clinical research institutional infrastructure: The "Golden Years" of patient-oriented research

The different belief systems embodied in the genomics and clinical paradigms are expressed in different loci of discovery. In the former, the discovery process is centered in the laboratory, performed by PhD scientists working with machines to decode and analyse genetic data. In the clinical paradigm, the locus of discovery is the hospital bed, involving close interaction between physician and patient.

The central role of hospitals in medical discovery emerged in the Paris hospitals of the 19th century, and French physician Claude Bernard was instrumental in establishing experimental methods in medical research (Bynum, 1994). However it was not until the early 20th century that scientific principles were applied to the field of medicine in the United States, spurred by reformers – many of whom had trained in the more scientifically-oriented European system -seeking to raise standards and quality of medical research (Rasmussen, 2005). In the

1940s, a major effort was initiated to institutionalize the field of patient-oriented clinical research (POR). This period, called the "Golden Years" of POR, witnessed the emergence of an institutional infrastructure designed to create the optimal conditions for the clinical research paradigm, centered around the close interaction between a doctor and patients at the hospital bedside.

The development of clinical research in universities and medical schools

The development of a field of POR in the United States can be traced to the late 1880s. Medical training occurred outside the university system; doctors studied in small, privately-run, for-profit schools that were practitioner-oriented and did not adhere to rigorous standards of scientific training. That changed at the beginning of the 20th century, when reformers undertook to introduce rigorous scientific principles and quality control in medicine and medical education. Three models of medical education were debated: apprenticeship training in hospitals; research-oriented medical schools attached to universities; and private, for-profit schools of medicine. The Flexner report, published in 1910, set the agenda for the establishment of university-based medical schools employing full-time university faculty. The "full time plan" established first at Johns Hopkins in 1913 put clinical departments on the same footing as other university departments, enabling medical school faculty to earn a fixed salary similar to other university faculty and freeing them of the need to earn income from private practice (Bryan and Stinson, 2002). This became the dominant model of medical education in the United States, and by 1925 80 medical schools had been founded; by 1940 there were 2800 fully time medical school faculty. A rapid period of growth followed the Second World War, and by 1960 there were 11,300 medical school faculty (IOM, 2004).

The Rockefeller Institute was an important early paradigm of an institution dedicated to the principles of patient-oriented basic research. Founded in 1901, it supported transdisciplinary research that integrated clinical and laboratory-based research with the aim of finding solutions to major infectious diseases of the day. In 1910, the Rockefeller Hospital was created to give researchers the opportunity to work directly at the bedside. Rockefeller encouraged a cosmopolitan, open culture, and fostered a unique research climate, without departmental divisions, minimal hierarchy and few administrative controls. Because teaching was not part of the Institute's mission, Rockefeller was able to attract many eminent researchers from Europe, a particularly important source of talent when World War II forced many Jewish scientists to leave Europe. Creativity flourished among the mix of cultures and scientific orientations, and major medical breakthroughs were made by Rockefeller researchers. The role of clinical observation and interactions between basic and clinical scientist were at the center of the discovery paradigm institutionalized at Rockefeller. Indeed, the foundational discovery in the science of genetics – Oswald Avery's discovery of DNA – was made when he was working with a team to discover a cure for pneumonia.

The period after World War II has been referred to as the "Golden Age" of clinical research, during which patient-oriented research became a central research paradigm in biomedicine. Major advances in quelling human disease were being made at the time through breakthroughs in physiology, biochemistry, and pharmacology, and a host of new drugs were being developed to treat infectious disease, particularly antibiotics. Clinical science was growing as a scholarly discipline: the first randomized clinical trials were conducted in the UK in 1948, and statistical methods were developed for large-scale clinical studies that could validate

small differences between treatment regimens. Advances in medical technologies opened up new avenues of investigation. Medicine was a high-status career and full-time faculty at medical schools grew from 2800 in 1940 to 11,300 in 1960.

The period witnessed growing investment in building Academic Medical Centers attached to universities (IOM 2004). These institutions were characterized by a close interaction between scientists of different disciplines and an integration of experimental work with clinical activity, a novel combination that set the US medical research system apart from the more discipline-based European system. The small size of research staff and their close physical proximity to both the bedside and the lab were hallmarks of the clinical research paradigm evolving at leading AMCs, fostering a camaraderie among researchers and students as well as close interactions between doctors and patients (Swazey and Fox, 2004). Trainees described a "milieu of inquiry and freedom" that encouraged risk-taking and curiousity-driven science. The Harvard Medical School proudly adopted the principle of serendipity as a hallmark of their scientific culture (Merton and Barber, 2004). The opportunities to mix bedside work with laboratory research attracted many European scientists to top institutions in the US after World War II.

The central role of the clinic in POR reflected the evolving system of healthcare after the war. Teaching hospitals were sites for advanced medical technology and long-term hospitalization was common, reimbursed by third-party insurance and, after the mid-1960s, by Federally-funded programs Medicare and Medicaid. This meant that indigent patients could be hospitalized in research hospitals, at no cost to the hospitals, and revenues from patient case were available to fund research. Long-term hospitalization was an invaluable resource for both

medical training and for clinical research, affording clinical investigator access to patients on a long-term basis (Bloom, 2003).

Clinical research and the NIH

An important event in the institutionalization of clinical research was the creation of the NIH in 1930, founded to administer a grant-system on a wide range of health-related fields. The National Cancer Institute was founded in 1937, and over the next 30 years thirteen additional Institutes were founded (Luft, 1997). The Cold War spurred rapid growth in Congressional funding for medical research: funding for the NIH grew from $700,000 in 1940 to $28.5 million in 1950, to $292 million in 1959 (NIH Office of the Budget). NIH grants for disease-specific research in the 1950s and 1960s spurred the growth of clinical programs at such institutions as the Brigham, Johns Hopkins, Yale, and Duke (Swazey and Fox, 2004).

During this time important initiatives were taken within the NIH to create a federally-funded institutional infrastructure to support patient-oriented research. The intention was to emulate the institutional model set by the Rockefeller Institute, but on a much larger scale. The plan was not uncontroversial. It was opposed by science policy architect Vannevar Bush who promoted government funding of basic, not applied, research, and the NIH was focused on biology and chemistry without direct clinical relevance (Chung, 2007). Despite Bush's opposition, those who favored a strong medical and disease-management orientation at the NIH prevailed (Nathan and Schechter, 2006, Schecter, 1998). A clinical research leg at the NIH was established, and the Clinical Center was founded in 1955. Based in Bethesda, the Clinical Center was a hospital with 500 beds to serve as a model of patient-oriented research, and was the largest hospital devoted to patient-oriented clinical research (Luft, 1997, Nathan, 2002).

Following on its success, in 1959 Congress authorized the formation of a network of clinical centers based in academic medical centers around the country. These centers, called GCRC (General Clinical Research Centers), coordinated their work with the NIH but were funded through the extramural grant system funding (Luft, 1997). Research at GCRCs center was supervised by a program director, but funding was granted to a university administrator, to ensure commitment of the host university to the center. By 1960 there were 8 centers and 133 beds; at its peak the GCRC comprised 93 centers and over a thousand beds in 1969 (IOM, 1994).

The operation of the clinical centers reflected the orientation of healthcare delivery towards long-term hospitalization, small size, and close doctor-patient interactions (Robertson and Tung, 2001). Each center resembled a mini-hospital that was equipped with ample resources for patient care and research. The goal was to provide an optimal setting for scientifically controlled clinical research. The centers were fully staffed with dedicated, full-time personnel, including specially trained nurses, medical fellows and students. Resources also included laboratory facilities and biostatistical support. They were intentionally small, with no more than about 30 beds, in order to foster close interaction between doctors and patients and allow for ongoing observation of patients over a long stretch of time, an important element in a clinically-motivated discovery paradigm (Luft, 1997). Major clinical initiatives involving multiple sites and population-level data were launched, including the Framingham Heart Study as well as collaborative clinical trials program, notably in oncology (Schechter, 1998).

The NIH clinical research network played an important role in fostering careers in patient-oriented clinical research . The clinical center itself trained some 300 investigators between 1960 and 1980, most continuing on to research careers at AMCs (Nathan, 2002). To

expand the ranks of researchers trained in patient-oriented research an NIH training program was initiated in 1974. The CAP, Clinical Associate Physician program, provided up to three years of salary support to junior faculty taking clinical research jobs. In addition to financial support, the program provided an opportunity for young investigators to advance her research to point where she could independently apply for NIH grant funding (Luft, 1997).

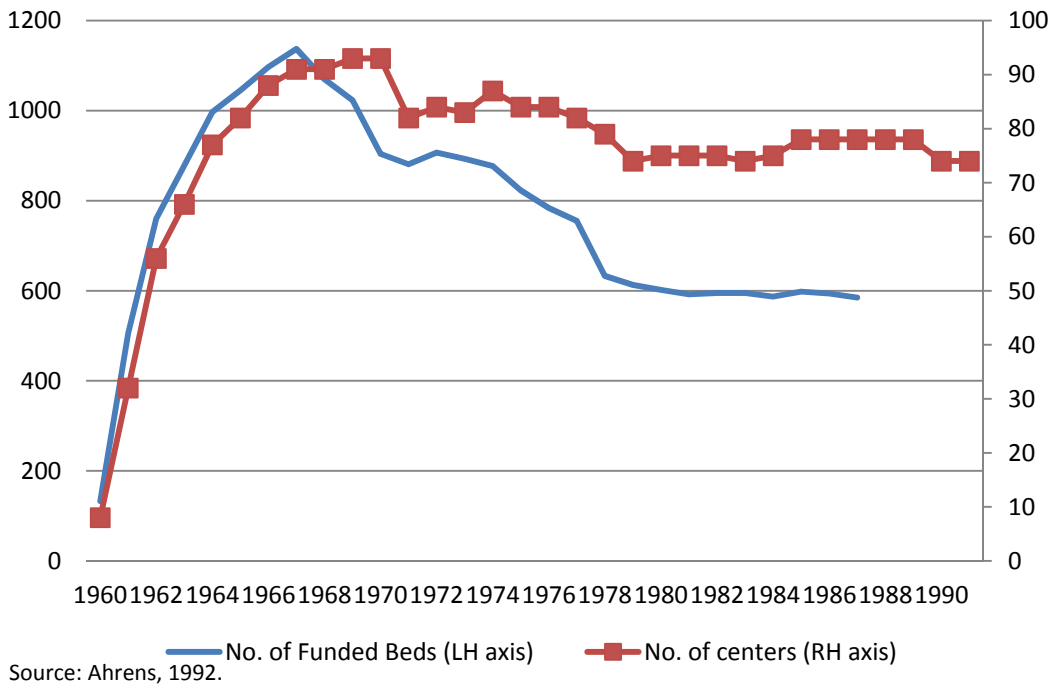
The decline of the clinical research paradigm

By the 1980s, the institutional infrastructure supporting POR was in severe decline, and the population of investigators trained in POR was stagnating. Figure 3 shows the decline in the GCRC system both in terms of number of centers as well as the number of funded patient beds, and Figure 4 shows the stagnating number of NIH research grants going to MD-Phds while the share to PhDs has grown. An analysis of R01 (primary research) grants in 1991 showed that only 30 per cent of grants involved the use of humans or human materials, and of those only one third (a tenth of the total) actually involved human subjects (IOM, 1994).

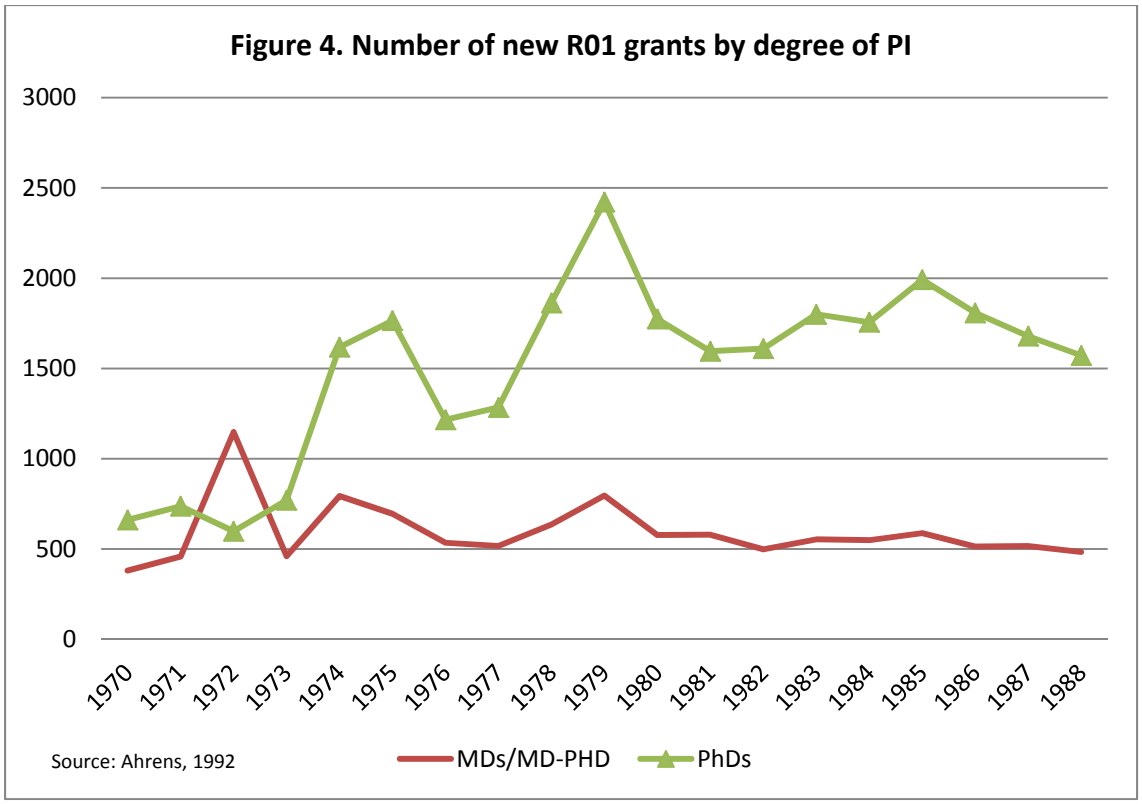
Several factors have been identified as contributing to the decline in patient oriented research: eroding institutional and financial support for patient-oriented research; declining number of young investigators choosing a clinical research career; and the rise of genomics and other reductionist methods as a dominant model of disease research (Ahrens, 1992). Since the practice of clinical research is intimately tied to medical care, changes in the overall healthcare system had direct consequences for patient-oriented clinical research. The rise of managed care in reimbursements had a major impact on the sources of funding and opportunities for patient-oriented clinical research. Managed care meant that long-term hospitalization – a cornerstone of the clinical paradigm – was no longer reimbursed, giving way to shorter stays

and outpatient care. Increasing revenue pressures also encouraged the growth of Academic Medical Centers into larger, more bureaucratic organizations, controlled by administrative guidelines and managerial professionals; the proliferation of hierarchy and administrative controls has been associated with a dampening of the curiousity-driven research culture that characterized AMCs in the post-war period. At the same time, clinical research was also made more difficult by increasing regulation of research involving human subjects, reflecting ethical concerns.

Figure 3. Number of GCRCs and funded beds, 1960-1990



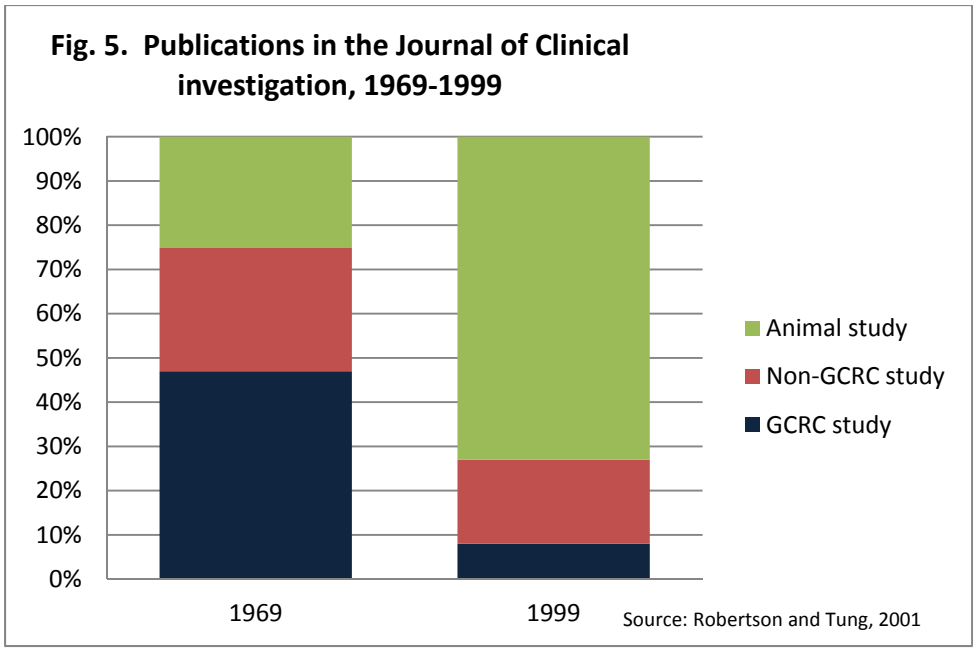
Source: Ahrens, 1992.



As a result of these changes, the optimal conditions for clinical research that had been created in the postwar period deteriorated. In the late 1960s, all GCRC studies were conducted on an in-patient basis, but by 1999 only 18 per cent of studies were conducted on an in-patient basis, with the remainder consisting of outpatient studies. Within the GCRC system, average hospital stays in GCRCs decreased from 16 days in the 1970s to 4-6 days in 1990 (Robertson and Tung, 2001). With the growth in size and complexity of AMCs, the physical distance between investigator and the clinical centers also grew. Robertson and Tung (2001) document how investigators had been physically located adjacent to the clinic in the late 1960s, effectively making the clinical unit a "personal research laboratory"; as AMCs have grown and new buildings are constructed, that distance has increased markedly, to roughly a long city block, making close and frequent bedside interaction and close observation more difficult.

Career pressures also contributed to the decline in clinical research, as fewer talented young scientists were attracted to the clinical investigator career path. Faced with revenue pressures from managed care as well as mounting student debt (from an average of $81,000/student in 1981 to $150,000 in 2010), fewer medical students chose to pursue research careers that would prolong their training and lower wages. In the 1960s, most medical schools revenues came from government research funds; by the 1990s, medical care and private medical funds provided the lions' share, lowering incentives to train researchers (IOM, 1994).

An important deterrent to patient-oriented research is the difficulty in establishing a strong publication record early in a young investigators' career, as compared to lab-based research and research using animal models or other reductionist methods. Patient-oriented research is slow, and it is among the most costly types of medical research (Luft, 1997). Moreover, the demands of patient care and teaching take time away from research as compared to those pursuing pure research (PhD) tracks. As a career path, POR grew less attractive in the 1970s when reductionist techniques – which allow for shorter, cheaper studies and higher number of publications - were becoming more important. Figure 5 shows the decline in GCRC publications in a leading clinical research journal, and the marked rise in studies using animal models.



Biomedical research paradigms and drug discovery outcomes

It is now acknowledged that the belief that genetic information would yield rapid discovery of new medicines is deeply flawed and that while the science of genetics has flourished, the application to drug discovery has been limited. This limitation was underscored by a recent study at Brigham and Women's Hospital, in which 101 genetic markers that have been statistically linked to heart disease were shown to have no value in forecasting disease among 19,000 subjects followed for 12 years; a more valid predictor was the old-fashioned method of a family history (Wade, 2010).

The hope that genetic variations would yield single targets as sites for drug discovery was not realized. It is now acknowledged that most diseases are triggered by multiple targets (receptors) operating in unknown sequences, and that the identification of a single target through a genetic assay does not capture these complex intra-cellular events.

It is beyond the scope of this paper to collect primary data that would allow a comparison of the genomics and POR paradigms on the rate of discovery of new drugs. That is a complex task that has not been attempted, and it is a notable gap that the discovery outcomes of the GCRC system has not been systematically studied. However, some important exceptions have tackled the question of the contribution of clinical research to major medical discoveries and innovation. A recent study examined the sources of discovery of new off-label uses for drugs, and found that 59% of innovations came from clinicians practicing in the field rather than from universities or drug companies (De Monaco, Ali, and Von Hippel, 2006). This finding lends significant weight to the idea that clinical insights are important for medical discovery. A handful of earlier studies have also addressed this question. The Comroe and Dripps report (1976) studied the sources of major discoveries in pulmonary and cardiac medicine. Through exhaustive review of the medical literature, they identified a set of critical research papers that contributed to the advancement of each of a list of subfields. Overall, they found that in 4 out of 10 subfields, over 75% of articles were clinically oriented. They also found that 62% of articles involved "basic" research, defined as research that was directly concerned with identifying a causal mechanism. A follow-on study of major advances in neo-natal care (Grant et al, 2003) used a revised literature review method. The researchers identified the most highly cited papers contributing to the field over 17 years, and found that in all subfields over 80 per cent were clinically oriented; interestingly, between 26 and 55 per cent of the research was conducted in hospitals.

The evidence from the biotechnology industry is itself also instructive. The fact that the industry has never been profitable is suggestive that biotechnologies, while useful as research

tools, have failed to provide a solid platform for rapid drug discovery (Hamilton, 2004). Few of the promised drugs have emerged from the biotechnology revolution, with the exception of several successful monoclonal antibodies. The MaB discovery process does not reflect the central genomics paradigm: instead of starting from genetic data and working forward to discover a drug, development of MaBs involves identification of known antigens and designing molecules to bind to them to neutralize their activity.

Adding to the lack of solid clinical outcomes for genomics-based drugs is the failure of the early genomics firms such as Incyte, Human Genome Sciences, Myriad, and DeCode. These firms were founded precisely to exploit the core principle that genetic variations would yield valuable and near-certain clues to the origins of disease – and from that information, the drugs that would cure them. The firms were issued a slew of patents on genetic information that, if they have ultimately proved productive of validated targets and drugs, would have been worth vast sums in downstream development rights. As practiced by these firms the model was, despite claims to theory-driven search, driven by raw computing power and, in the extreme, raw empiricism: using high throughput screening technologies, DNA from healthy and diseased tissue could be compared and the variations isolated and studied. The vast stores of information produced by these firms proved to be insufficient as a basis for a drug discovery platform, and with few exceptions the major genomics firms exited or relied on revenues from diagnostic tests and kits. The case of DeCode was notable, as it possessed one of the richest resources of genetic information in the industry: the genome data drawn from the entire population of genetically homogenous Iceland. The firms' initial claims that its data that would yield treatments for a host of major diseases- schizophrenia, Alzheimers, arthritis – did not

materialize and the company now sells diagnostic kits and home-based genomics tests. Indeed, much of the industry has shrunk to the specialized (and scientifically unsubstantiated) niche of personalized genetic test kits.

Concluding discussion

The question of whether abstract or experiential learning is conducive to rapid discovery is at the core of current debates in medical research policy and the design of institutional supports for translational research (Ahrens, 1992; Nathan and Schecter, 2006). The phrase "translational research" has become a catchword in medical policy that reflects the need to cope with the massive amount of new information and scientific understanding of genetics, and to close the gap between basic science and clinical practice. The call to integrate basic and applied medicine, and a return to "systems biology" is essentially a policy response to a new technological paradigm that has provoked a fundamental shift in the landscape of biomedical research in the United States.

A panel commissioned by NIH Director Harold Varmus was formed in 1995 to investigate obstacles to clinical research and provided recommendations for strengthening financial support and training to clinical researchers (Nathan, 2998). In 2004, the NIH Roadmap launched by NIH Director Elias Zerhouni emphasizes the "reengineering of the national clinical research enterprise" with greater integration of basic and clinical research (Zerhouni, 2005). The Roadmap not only sought to promote more effective clinical research, it also attempted to foster closer working relationships between basic, translational, and clinical scientists (Zerhouni, 2005). Parallel to these efforts at the Federal level are important reorganizing initiatives at major universities who are in the process of engaging in significant reorganizations

of their biomedical research infrastructures in order to break down disciplinary silos and encourage cross-disciplinary collaboration with the aim of promoting the productivity of research.

It is remarkable that these initiatives have been carried out in the absence of good statistical evidence linking research strategies to drug discovery outcomes. Many of the accounts of important medical discoveries are anecdotal, and a review of medical policy literature on the topic (e.g., JAMA 2005, special issue on Medical Research: State of the Science; Nathan and Schecter, 2006), reveals substantial data on changing funding patterns but little in the way of statistical analysis tying basic and clinical research to discovery outcomes.

This paper describes the epistemic divide between major medical paradigms, and the ensuing shifts in the institutional landscape supporting biomedical research in the United States. The empirical question of whether these shifts have influenced the productivity of discovery in both public institutions and private-sector firms remains to be answered. It is hoped that the discussion of the recent history of these divergent paradigms will help stimulate such important research.

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