# Federal Funding and the Institutional Evolution of Federal Regulation of Biomedical Research

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## Introduction

The biomedical research enterprise that existed into the 1980s was a product and an emblem of the postwar administrative state. During the early part of the twentieth century, the medical profession nurtured its power and legitimacy, and it was poised to take advantage of the burst of interest in the scientific enterprise brought by World War II. Perhaps even more importantly, it was also prepared to take advantage of the evolution of the administrative state. As Brian Balogh has demonstrated, while the Progressives and New Deal reformers envisioned an alliance of professionals and the central state, it took World War II and the Cold War to fuse that alliance.[1] And of all the professions that profited from the new administrative state, medicine may have benefited the most. Throughout the latter part of the twentieth century and into the twenty-first, biomedical research has received a large and fairly constant infusion of federal funds. In addition—although those federal funds eventually provided the moral footing for federal regulation of biomedical research—that regulation never took on the command and control character of other federal regulation of the era.

The federal regulation of biomedical research is limited and is largely accomplished in the form of audited self-regulation. In essence, the federal government, acting through the National Institutes of Health, formed a partnership with the academic medical community that it created. Together, they set research priorities for all types of biomedical research and depended on academic institutional review boards to oversee the protection of participants in clinical research. These institutional review boards (IRBs) are local committees that bear the primary responsibility for direct oversight of biomedical research with humans. The choice to use IRBs as the central focus of oversight allowed the academic medical community to retain considerable autonomy. This system continues even though the structure and character of the biomedical research enterprise has changed dramatically in the last thirty years.

This paper examines the institutional evolution of the federal regulation of biomedical research and the effect that federal funding has had—or has

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[1] Brian Balogh, *Reorganizing the Organizational Synthesis*, 5 Stud. Am. Pol. Dev. 119, 147 (1991).

not had—on that evolution. Biomedical research is a term that includes basic scientific research into human biology as well as its application to medical procedures and clinical treatments. Federal funding created the system of academic medical research that blossomed and enjoyed unrivaled dominance in the second half of the twentieth century. A change in the focus of federal funding, at least in large part, also brought on the eclipse of that academic dominance by industry in the last decades of the twentieth century. The current regulations for biomedical research, however, are largely based on that earlier academic model. Those regulations have not changed even though the academic model has itself changed beyond the recognition of its creators. As a result, the regulatory structure of oversight for biomedical research is based on a model of medical research that still exists in part but has been greatly complicated by industry relationships, new funding sources, and a global character. There are therefore gaps in oversight: the IRB model does not work as effectively with industry sponsored or international research, the current regulations do not deal with many of the new conflicts of interest, there is likely much research that is not subject to any oversight, and the incentives for biomedical research are profit based more than science based.

In Part I, I describe the history and evolution of the biomedical research enterprise in the United States through the 1970s and the consequent development of a research oversight structure for that enterprise. Federal funding was essential for the development of both the enterprise and its regulation. In Part II, I describe the effect of the Bayh-Dole Act on the biomedical research enterprise and how federal funding has been refocused, and to some degree eclipsed, by private industry. While federal funding was virtually the only support for medical research until the 1970s, now industry is more than an equal partner. This means that the interests of industry, and profit motives generally, dominate research. It also means that the existing regulatory structure, never very strict, no longer functions as designed.

In Part III, I describe the functioning and gaps of federal oversight over medical research as it is now structured. The federal regulation of biomedical research depends on both formal regulation and on more subtle regulation based on funding decisions. Formal regulation, which is largely focused on protection of participants in clinical research, requires local review done by IRBs. That system has been successful in that it is certainly more comprehensive and efficient than a top-down system of review could be, but it still suffers from many structural problems and from a narrow focus. In addition, this system, always subject to internal pressures, is now also subject to commercial pressures and increasingly fragmented oversight and scope. Much biomedical research evades oversight. In addition, a great deal of research is now taking place abroad. This internationalization and globalization of oversight has its own implications. There are thousands of such review boards in the United States. We are only just starting to study how well they all work. It is a daunting task, but we need to do it.

Even if IRB regulation and oversight can be modified to better adjust to our current situation, the IRB system is ill-suited to deal with other gaps in the regulatory structure. When the federal government was virtually the sole funder of biomedical research, it partnered with academic medicine; together, the government and the profession controlled both the substance and the design of most biomedical research. Now federal funding is often commingled with industry funding. It is difficult to determine whether funding is fully directed to science in the public interest, or whether some federal funding is being co-opted by industry and academia for their own purposes. Here too, a more comprehensive and systematic review is necessary. We need to acknowledge that our laws, regulations, and funding structures create incentives that have significant consequences for the safety, value, and efficiency of the resulting research.

## I. Federal Funding, the Birth of Academic Medicine, and Moves to Regulate Medical Research

The story of regulation of biomedical research in the United States begins with World War II, which started a new era in medical research. Prior to that time, there was, of course, some medical research, but it was neither systematic nor truly scientific by current standards. Most research was qualitative and really medical practice. To the extent there was systematic scientific research, most of it was funded by the military and related public health requirements or by private foundations.

The war exposed the need for more and better biomedical research. Biomedical research became an increasingly important part of the war effort and later was seen as a crucial part of post-war planning. Moreover, a government role in such research was also deemed essential. President Roosevelt asked Vannevar Bush, head of the Office of Scientific Research and Development, to provide a blueprint for postwar government aid for scientific research. Bush's report, *Science: The Endless Frontier*, included plans for biomedical research that set the stage for much of the institutional structure that followed as well as how that research would ultimately be regulated.[2]

Bush envisioned extensive federal funding for both research and training of researchers. But he also believed that science should largely be free of government meddling. Thus, the government would provide the funding, but the actual projects would be initiated by the researchers themselves. Funding determinations would be made through a process of peer review of fellow scientists. Bush also favored basic research—research that had no obvious commercial or clinical value—because he believed that it laid the foundation for more innovative research in the long run. Similarly, he

[2] Vannevar Bush, Office of Scientific Research and Dev., Science: The Endless Frontier (1945), *available at* http://www.nsf.gov/about/history/nsf50/vbush1945.jsp.

strongly believed that scientists should not be subject to pressure to produce immediate results. Bush's plan included the creation of an independent central agency, the National Research Foundation, whose members would be appointed by the President from nominations made by the National Academies of Science. The National Research Foundation would have control over all federally funded science. Although most of Bush's plan was novel, it was this independent agency that proved most controversial. Liberal members of the Senate resented the lack of government control over spending, while some scientists viewed any government control as socialism.[3] President Truman viewed the agency as undemocratic.[4] Truman's main concern was the degree of autonomy that such an agency would give scientists.[5] As a philosophical point, he did not believe that scientists supported by federal funds should have complete autonomy.[6]

While the wrangling over the National Research Foundation continued, federal involvement in biomedical research was moving forward. Where World War II had provided inspiration, the Cold War provided urgency. Bush's foundation was ultimately established in 1950 as the National Science Foundation (NSF),[7] but it never achieved the stature or funding that Bush envisioned. This may well have been a loss for funding of science generally, but it was a boon for biomedical research because it meant that biomedical research did not have to compete for funding with other scientific initiatives. While the NSF was not finally created until 1950, in the late 1940s, the Public Health Service (PHS),[8] working through its National Institute of Health and its National Cancer Institute, was expanding both intramural and extramural research.[9] The former involved internal research within the organization, and the latter involved extended grant relationships with universities.[10] A reorganization of the National Institute of Health in 1944 combined several disease-oriented specialized institutes.[11] The resulting research center became the National *Institutes* of Health (NIH) and it

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[3] Paul Starr, The Social Transformation of American Medicine 342 (1982).

[4] Robert Cook-Deegan & Michael McGeary, *The Jewel in the Federal Crown?*, *in* History & Health Policy in the United States 176, 189 (Rosemary A. Stevens et al. eds., 2006).

[5] *Id.*

[6] *Id.*

[7] *1950–May 10: NSF is Established*, Nat'l Sci. Found., http://www.nsf.gov/news/special_reports/history-nsf/1950_truman.jsp (on file with the Harvard Law School Library).

[8] The Public Health Service (PHS), the original federal agency for health, was made the primary division of the Department of Health Education & Welfare (DHEW) in 1944. DHEW became a cabinet-level department under Eisenhower in 1953; DHEW was later restructured into the Department of Health and Human Services (HHS). Victoria A. Harden, Inventing the NIH 171–72 (1986).

[9] The National Institute of Health was created by President Hoover in 1930. But it would take twenty years for it to achieve the stature and promise of its founders. First, of course, Depression economics meant that it was woefully under-funded, but it was also stymied by the essentially conservative viewpoint of its PHS directors. *Id.* at 160–75.

[10] *Id.* at 174.

[11] *Id.* at 175.

received both power and significant funding. This assured the NIH of the preeminent position that Bush had originally envisioned for NSF. In addition, through the 1950s, the rich and newly influential disease advocacy groups chose to dedicate their money and legislative influence to NIH funding rather than directly funding research themselves. Moreover, NIH's funding was a bipartisan goal. Starting before the Truman administration, the idea of a nationally financed health system was politically divisive. Both parties could instead assuage the public desire for medical progress through medical research funding. NIH's budget increased from $81.3 million in 1954 to $1.6 billion in 1968.[12]

Through the 1940s, most of NIH's research had been conducted intramurally. But through the 1950s and 1960s, NIH's research focus became increasingly reliant on extramural work carried out by universities. NIH funded not only extensive extramural research but also the research facilities and medical school training necessary to conduct that research.[13] The research it supported concentrated on basic biological science. Much NIH funding focused on the biological processes of diseases and this research was often open-ended. For example, the Framingham Heart Study, which began in 1948 through an NIH partnership with Boston University, was an ambitious (and successful) attempt to determine the root causes of cardiovascular disease and stroke.[14] The study enrolled more than 5000 people and did extensive physical examinations and lifestyle interviews every two years.[15] An extension of that study continues today.[16]

The influx of federal funds into academic medicine affected the entire research enterprise. Instead of developing its own facilities, the pharmaceutical industry also became dependent on academic biomedical research for a large proportion of its research and development. This meant that from the 1960s through the 1970s, the federal government contributed more than twice the funding for health research and development (R&D) than did industry.[17] This did not change until the late 1980s.[18]

While biomedical research boomed, the government and researchers took only very preliminary steps toward government regulation or even self-regulation in the immediate postwar period. Much of this was due to the perception that biomedical research was inextricably linked to medical practice and that any regulation might inappropriately usurp the physician's role.[19] Indeed, the Nuremberg Code, produced in conjunction with the Nazi

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[12] Cook-Deegan & McGeary, *supra* note 4, at 203.

[13] *Id.* at 183–84.

[14] *History of the Framingham Heart Study*, FRAMINGHAM HEART STUDY, http://www.framinghamheartstudy.org/about/history.html (on file with the Harvard Law School Library).

[15] *Id.*

[16] *Id.*

[17] *Id.* at 203.

[18] *Id.*

[19] ADVISORY COMM. ON HUMAN RADIATION EXPERIMENTS, FINAL REPORT OF THE ADVISORY COMMITTEE ON HUMAN RADIATION EXPERIMENTS 65 (1996) [hereinafter ACHRE].

Doctors' Trial after World War II, had little immediate impact on the research community in the United States.[20] The central tenet of the Nuremberg Code is that human research should not be conducted without the informed consent of research subjects.[21] But a considerable amount of research, some of it undeniably risky, was being done in the United States without informed consent. In his world-shattering piece published in 1966, Henry Beecher described more than fifty studies conducted in the United States during the postwar period by leading institutions—all but two of which lacked informed consent—that involved procedures such as withholding known treatments like antibiotics and exposing patients to risky chemicals, biological processes, or procedures for physiologic or technical study.[22] Most were not done for the benefit of the participant.[23] Some were so risky that death rates varied between the arms of the studies.[24] But major journals published these studies, and did not deem consent necessary because of the importance of the science and the reliability and eminence of the researchers. In fact, some researchers believed that in research involving patients rather than healthy volunteers, requiring informed consent would undermine the patient's necessary trust in his or her physician.[25] Others believed that developing a written policy would "focus unnecessary attention on the legal aspects of the subject."[26]

Although some government-funded studies involving healthy volunteers had required some form of informed consent since the 1920s,[27] more systematic regulation of even government-conducted research did not occur until the 1950s. In 1953, NIH adopted a policy for research involving human subjects taking place at NIH's hospital.[28] The policy required review of proposed NIH projects by a committee of other NIH scientists.[29] NIH designed the oversight to provide the most freedom possible for the researcher. In addition, the policy required written informed consent for all healthy volunteers for research and for some patient subjects involved in riskier research.[30]

The first federal regulation of biomedical research conducted outside the government came in the form of new regulations for drug approval. Prior to 1962, drug approval by the Food and Drug Administration (FDA)

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[20] *See* 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW 181–84 (1949), *available at* http://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf.

[21] *Id.*

[22] Henry K. Beecher, *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1355–60 (1966).

[23] *Id.* at 1354.

[24] *Id.* at 1360.

[25] ACHRE, *supra* note 19, at 65.

[26] *Id.* at 57.

[27] *See id.* at 53.

[28] *Id.* at 65.

[29] *Id.*

[30] *Id.*

depended on safety but did not require efficacy.[31] Estes Kefauver, the Tennessee Senator who led the charge for broad new drug oversight, deeply distrusted the pharmaceutical industry.[32] Kefauver originally focused on drug pricing, and for two years he presided over hearings involving more than 150 witnesses seeking to show how pharmaceutical companies abused their market power.[33] By the time Kefauver introduced his legislation, the focus had shifted to how drugs were marketed.[34] That focus brought the American Medical Association into opposition alongside the pharmaceutical industry.[35] The legislation appeared doomed until the drug industry became a focus of panicked public attention because of thalidomide.[36] Using the thalidomide scandal as a springboard for legislation, Kefauver's bill, the Kefauver-Harris Amendment, granted the FDA sweeping new powers. It introduced new requirements for testing and manufacturing drugs and gave the FDA new authority over the conduct of clinical trials.[37] In addition, it required investigators to obtain informed consent from all participants in clinical trials.[38] Other than the requirement of informed consent, the FDA focused immediately on the pharmaceutical companies' activity rather than on the work of physician researchers. Thus, the regulations addressed the scientific structure of the clinical trials rather than the conduct of the researchers.

With its new authority, the FDA introduced a phased approach involving preclinical animal and toxicity trials and three phases of clinical trials.[39]

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[31] DAVID ROTHMAN, STRANGERS AT THE BEDSIDE 64 (2003).

[32] *See* Robert Bud, *Antibiotics, Big Business and Consumers: The Context of Government Investigations into the Postwar American Drug Industry*, 46 TECH. & CULTURE 329, 337–38, 343 (2006) (discussing Kefauver's crusade against the pharmaceutical industry).

[33] *Id.* at 345.

[34] *Id.* at 346.

[35] *Id.* at 346–47.

[36] *Id.* at 347. Thalidomide was a drug that was sold as a sedative and treatment for morning sickness in Europe. Its approval for US marketing was delayed by the FDA based on the inadequacy of safety data and reports of problems caused by the drug abroad. The drug proved to cause gross deformities in infants whose mothers took the drug during pregnancy. *Id*; *see also* PHILIP J. HILTS, PROTECTING AMERICA'S HEALTH 152–53 (2003).

[37] Pub. L. No. 87-781, 76 Stat. 780 (codified as amended at 21 U.S.C § 355 (2006)).

[38] *Id.*; *see also* ROTHMAN, *supra* note 31, at 64–67 (2003) (noting that this was a watered down version of an amendment that had been submitted by Sen. Javits. Javits' amendment would have required DHEW as well as the FDA to issue regulations requiring informed consent for any clinical drug experimentation. But Javits' amendment was considered to be an encroachment on the rights of the medical profession and did not survive).

[39] Phase 1 clinical trials mark the first introduction of the drug into humans and typically involve twenty to eighty healthy volunteers; safety is the scientific endpoint. Phase 2 trials involve a few hundred people, usually the target of the test drug, and are designed to develop preliminary efficacy data. Phase 3 trials are performed only after preliminary trials have shown some efficacy and involve hundreds and possibly thousands of participants. They are designed to determine the overall risk-benefit profile of the drug and are also designed to provide data that can be extrapolated over the general population. *See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD AND DRUG ADMIN. (Feb. 22, 2010), http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm (on file with the Harvard Law School Library).

This phased system limited general risks for research participants. Large numbers of people would not be exposed to a chemical agent until it had been proved reasonably safe and effective in small numbers of patients. But the FDA, especially in early phase studies, did not focus on specific risk and benefit ratios for participants. Nor did it oversee the specific conduct of the researchers with regard to the participants; the researcher had discretion in this matter. The FDA did not focus much on the role of the researcher until the Department of Health Education and Welfare (DHEW) undertook to do so several years later.[40]

By the early 1960s, some members of academic medicine voiced their growing discomfort with research that had been conducted without proper consent and safeguards.[41] But the motivation for broader rules for research funded by—but conducted outside of—government came from fear of liability. Two research studies that came to light in 1963 made then-Director of the NIH James Shannon aware that extramural activities were both insufficiently controlled and both potentially illegal and damaging to NIH's reputation. The first involved the implantation of a chimpanzee kidney into a human being, which was done with patient consent but without scientific review.[42] The second, ultimately more devastating because it involved some of the most prominent academic researchers in the United States, involved injection of live cancer cells into elderly patients without their consent or knowledge.[43] Shannon wanted NIH to take a leadership role in protecting research participants. He proposed a system whereby grantee institutions would have to create a committee to provide impartial peer review of risks and benefits posed by research before that research could begin. That committee would also insure the "appropriateness of the methods used to secure informed consent."[44] This system became PHS policy in 1966. Although PHS did not believe that it had the authority to dictate controls for all research, it encouraged grantee institutions to apply the PHS policy to all of their research.[45]

There was a fair amount of resistance to the new PHS policy. The guidance provided by PHS was ambiguous, the review committees complained of overwork, and a number of researchers refused to cooperate.[46] In 1971, a new guide was issued: *The Institutional Guide to DHEW Policy on Protection of Human Subjects* (the Yellow Book).[47] The Yellow Book provided the structure, but not the complete philosophy, of the regulations that govern

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[40] ACHRE, *supra* note 19, at 103–04.

[41] *Id.* at 92.

[42] *Id.* at 98; *see also* MARK S. FRANKEL, THE PUBLIC HEALTH SERVICE GUIDELINES GOVERNING RESEARCH 10 (1972).

[43] ACHRE, *supra* note 19, at 98.

[44] *Id.* at 100; *see also* Frankel, *supra* note 42, at 33.

[45] FRANKEL, *supra* note 42, at 35.

[46] ACHRE, *supra* note 19, at 100–01.

[47] THE INSTITUTIONAL GUIDE TO DHEW POLICY ON PROTECTION OF HUMAN SUBJECTS, DHEW PUBLICATION NO. NIH 72-102 (Dec. 1, 1971), *reprinted in* SOURCEBOOK IN BIOETHICS

biomedical research today. Like its predecessor PHS rules, the Yellow Book required the use of institutional committees, and it provided a fair amount of direction as to the composition and duties of these institutional committees.[48] It also required that each committee establish a code of principles that would guide its work.[49] But the guide did not provide insight as to what those principles should be. In addition, the system ultimately had no teeth. The document ends with a somewhat deflated suggestion: "Provision should be made for remedial action in the event of disregard of committee recommendations. . . ."[50]

By the late 1960s, however, federal deference to the medical profession was eroding, especially among liberal Democrats. In 1968, Senator Walter Mondale urged the creation of a national commission to study advances in medical and biological sciences.[51] It would be an understatement to say that the medical community was hostile to the idea.[52] In 1973, Senator Edward Kennedy convened hearings to study biomedical research.[53] In early 1973, without any cosponsors, Senator Hubert Humphrey proposed legislation creating a "National Human Experimentation Standards Board Act."[54] Modeled on the Securities and Exchange Commission, the Board envisioned by Humphrey would be housed outside DHEW.[55]

In 1972, two seriously flawed research projects made national headlines: Willowbrook and Tuskegee. The Willowbrook study involved mentally impaired children and adolescents who were institutionalized at the Willowbrook facility in New York.[56] Hepatitis was endemic at Willowbrook State School for the Retarded, and the researchers sought to study the disease by injecting the participants, new residents at the facility, with a mild form of hepatitis.[57] Ten years earlier, the study would hardly have raised eyebrows. The 1972 study had been reviewed by a research review committee and parents had signed an informed consent.[58] But the ethics climate had changed radically by 1972. Now, instead of seeing researchers curing disease, the media and public saw scientists callously taking advantage of a vulnerable population by using coercive informed consents and engaging in questionable science.

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52 (Albert R. Jonsen et al. eds., 1998). It was called "the Yellow Book" because its cover was yellow.

[48] *Id.* at 16–21.

[49] *See id.*

[50] *Id.* at 21.

[51] ROTHMAN, *supra* note 31, at 168–89.

[52] *Id.* at 169.

[53] *Id.* at 184.

[54] ACHRE, *supra* note 19, at 110, n.53.

[55] *Id.* Neither bill moved out of committee.

[56] Walter M. Robinson & Brandon T. Unruh, *The Hepatitis Experiments at the Willowbrook State School*, *in* THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 80, 80–85 (Ezekiel Emanuel et al. eds., 2008).

[57] *Id.* at 80–82.

[58] *Id.* at 82.

On the heels of media scrutiny of Willowbrook, the media revelation of the Tuskegee study was even more devastating. Tuskegee, unlike most of the questionable research revealed in the 1960s, was a PHS study.[59] Begun in 1932, the Tuskegee study was an investigation of the natural history of syphilis.[60] The study involved poor African-American men in rural Alabama.[61] At the time researchers initiated the study, conventional wisdom held that the disease manifested differently with black men than with white men.[62] The original researchers sought to disprove that theory. They also wanted to know more about how the disease naturally progressed over many years. They cared deeply about the public health issue, but members of the study team never really considered the individual welfare of the actual participants. When the study began, there was no cure for syphilis, but by the mid-1940s penicillin was widely available.[63] The study participants were never offered full treatment and, moreover, were induced to believe that they were receiving treatment.[64] The study continued until 1972.[65]

The public attention given these two scandals, and the adroit political maneuvering of Senator Kennedy, secured legislative action where it had failed before. The National Research Act of 1974 created the first national bioethics commission: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[66] As originally envisioned by the Senate Report, the National Commission would have been a permanent regulatory body, independent of NIH, whose members were to be appointed by the President and whose chairs would be subject to Senate confirmation.[67] The NIH, with strong backing by many scientists, loudly attacked the idea of a permanent bioethics commission with regulatory authority. The scientific community was wary of regulation that it believed would hamstring research.[68] In the end, the House bill's version made the Commission advisory, and it was also thereby made impermanent.[69] Nonetheless, the Commission received, by today's standards, extraordinary regu-

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[59] James H. Jones, Bad Blood: The Tuskegee Syphilis Experiment 1 (1993).
[60] *Id.* at 2, 4, 125.
[61] *Id.* at 1, 4, 13.
[62] *Id.* at 92.
[63] *Id.* at 7–9.
[64] *Id.* 5–6, 125–129.
[65] James H. Jones, *The Tuskegee Syphillis Experiment*, *in* The Oxford Textbook of Clinical Research Ethics 86, 86 (Ezekiel Emanuel et al. eds., 2008).
[66] National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974).
[67] S. Rep. No. 93-381, at 21–23 (1973).
[68] Robert Cook-Deegan, The Gene Wars: Science, Politics, and the Human Genome 257 (1993).
[69] The Federal Advisory Committee Act (FACA), passed by Congress in 1972, requires all advisory committees to be terminated no later than two years after they are established. 5 U.S.C. app. 2 §§ 1–16 (2006). They may continue past the two years if specifically exempted by the entity creating the committee. *Id.* at § 14. The National Commission was extended past the two years, but FACA removes the presumption that a committee will operate continuously.

latory authority. It could recommend that DHEW implement the Commission's proposals or instead make its reasons for rejection public.[70]

The crown jewel of the National Commission's accomplishments is the Belmont Report.[71] The Belmont Report provides the legislatively-mandated philosophical underpinning of the structure for regulation of biomedical research as required by the National Research Act.[72] The report sets out the three ethical principles that the commissioners agreed lie at the center of all ethical research: "respect for persons," "beneficence," and "justice."[73] Those principles have an almost talismanic place in ethical review of biomedical research. The commissioners at the time, however, were not entirely clear about their meaning and that uncertainty remains today.[74] In addition, while the Belmont Report mentions these three principles, the focus both then and since then in the application of the subsequent federal regulations has largely been on patient/subject autonomy and thus on informed consent.

The focus on informed consent was a direct product of the bioethical concerns of the day. Most of the research scandals that provided the impetus for the National Commission involved failure of informed consent. Moreover, the central problem that the National Commission sought to address was the conflict of interest created by the researcher wearing "two hats"—that of the researcher seeking to help future patients (or himself or his institution) and that of the clinician seeking to help the patient before him. In this concern, the commissioners were strongly influenced by Professors John Robertson and Jay Katz. Robertson argued forcefully for a limited purview for regulation, confined to situations where this conflict was likely to arise.[75] Katz argued that the solution to the conflict was better information and understanding on the part of the patient.[76] Their influence meant that the regulations finally recommended by the National Commission were deliberately designed to have a limited impact on the medical profession and that the solutions were also largely left to the profession to implement.

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[70] National Research Act § 202(3)(b). *See also* Tom Beauchamp, *The Origins, Goals, and Core Commitments of* The Belmont Report *and* Principles of Biomedical Ethics, *in* THE STORY OF BIOETHICS 39 n.7 (Jennifer K. Walter & Eran P. Klein eds., 2003).

[71] NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAV. RES., THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH (1979), *available at* http://ohsr.od.nih.gov/guidelines/belmont.html.

[72] *Id.*

[73] *Id.*

[74] Margaret F. Riley & Richard A. Merrill, *Regulating Reproductive Genetics: A Review of American Bioethics Commissions and Comparison to the British Human Fertilisation and Embryology Authority*, 6 COLUM. SCI. & TECH. L. REV. 1, 10–11 (2005).

[75] *See* JOHN ROBERTSON, THE BELMONT REPORT, APP. B, DHEW PUB. OS78-0012, LEGAL IMPLICATIONS OF THE BOUNDARIES BETWEEN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS AND THE ACCEPTED OR ROUTINE PRACTICE OF MEDICINE (1979).

[76] *See generally* JAY KATZ, EXPERIMENTATION WITH HUMAN BEINGS (1972).

The National Commission also studied the institutional committee review system already in place for PHS research through the Yellow Book. This was essentially a system of audited self-regulation[77] using local review boards applying general rules and subject to federal oversight.[78] The Commission generally favored that approach but sought clearer rules for the local review boards and tighter federal oversight.[79] The Commission assumed that most research would be funded by federal grants or contracts.[80] Continuing review back and forth between the local board and federal oversight would therefore take place.[81] The Commission favored local institutional review over regional or national review because the local board would be more familiar with the actual conditions under which the research was taking place.[82] They also believed that a local board would be better able to balance the protection of human subjects with the rights of the investigators to conduct research.[83] In addition, local review provided opportunities for education and resources for the researchers onsite.[84]

Regulations reflecting the National Commission's work were first proposed in 1978 by DHEW.[85] The final rules were put into place in 1981 by DHEW's successor agency, the Department of Health and Human Services (HHS), during the last days of the Carter Administration. With minor tweaking, they have remained largely the same since.[86]

The cornerstone of human subjects regulation is the IRB. The regulations set out the structure of review, and federal agencies can periodically audit IRBs to make sure the rules are being followed, but the lion's share of oversight occurs at the local level. Each institution conducting such research must either establish a local IRB or contract with an outside IRB to review its research.[87] IRBs must be composed of at least five members who have

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[77] Douglas Michael defines audited self-regulation as "the delegation by . . . a federal agency to a nongovernmental entity the power to implement laws or agency regulations, with powers of review and independent action retained by a federal agency." Douglas Michael, *Federal Agency Use of Audited Self-Regulation as a Regulatory Technique*, 47 ADMIN. L. REV. 171, 176–77 (1995). For Michael, an example of this mode of regulation is the regulation of securities exchanges using the exchanges and NASD with oversight of the Securities and Exchange Commission. *See id.* at 203–08. Medical research is far more fragmented, as there are hundreds, if not thousands, of IRBs.

[78] THE INSTITUTIONAL GUIDE TO DHEW POLICY ON PROTECTION OF HUMAN SUBJECTS, *supra* note 47, at 18–21.

[79] NAT'L COMM'N FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAV. RES.,REPORT AND RECOMMENDATIONS: INSTITUTIONAL REVIEW BOARDS, DHEW PUBLICATION NO. (OS) 78-0008, at 1–2 (1978).

[80] *See generally id.* at 55–56.

[81] *Id.* at 2.

[82] *Id.* at 1–2.

[83] *Id.*

[84] *Id.* at 2.

[85] *See* ACHRE, *supra* note 19, at 425–46.

[86] In 1991, most federal agencies involved in supporting biomedical research adopted the HHS regulations, thus establishing a "Common Rule" that applies to all of those agencies. FDA "concurs" with the Common Rule, but has not adopted it entirely. *Id.*

[87] *See* 45 C.F.R. § 46.103 (2010).

sufficient experience, expertise, and diversity. The diversity requirement "include[s] consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel."[88] Because of the requirements of expertise, as well as the burden of heavy loads, many institutions have multiple IRBs, some of which may be focused on specific types of research. In reviewing proposed research involving human subjects, the IRB is to generally determine:

> (1) that risks to subjects are minimized through procedures consistent with the use of a sound research design;
> (2) that risks are reasonable in relation to anticipated benefits to the subjects and the importance of the knowledge expected to result from the research;
> (3) that the selection of subjects is equitable;
> (4) that appropriate informed consent will be sought from each prospective subject;
> (5) that the informed consent will be appropriately documented;
> (6) that if appropriate, the research plan provides for monitoring of data; and
> (7) that when appropriate, there are adequate provisions to protect subjects' privacy and to maintain confidentiality of data.[89]

There are separate specific regulations providing additional protections with respect to research activities involving so-called vulnerable populations. These include fetuses,[90] pregnant women and neonates,[91] prisoners,[92] and children.[93]

## II. The Restructuring of Biomedical Research: The Effect of Bayh-Dole and the New Global Enterprise

The ink was dry on the federal regulations for biomedical research for barely a year when legislative action caused a fundamental change in the structure of such research. The Bayh-Dole Act[94] was enacted in 1980 for the stated reason that the basic research conducted in academic settings did not lead to enough commercial applications.[95] The government was getting exactly what it was paying for: fundamental science. But because the government funded the research, it also owned any patents and other intellectual property associated with that research. There was little incentive for aca-

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[88] 45 C.F.R. § 46.107 (2010).
[89] 45 C.F.R. § 46.111 (2010).
[90] 45 C.F.R. §§ 46.201–46.207 (2010).
[91] *Id.*
[92] 45 C.F.R. §§ 46.301–46.306 (2010).
[93] 45 C.F.R. §§ 46.401–46.409 (2010).
[94] Bayh-Dole Act, Pub. L. No. 96-517, 94 Stat. 3015 (codified as amended at 35 U.S.C. §§ 200–12 (2006)); 37 C.F.R. pt. 401 (2010).
[95] *See* 35 U.S.C. § 200 (2006).

demic researchers to seek commercial applications for their research because those commercial applications did not reap financial benefits for them or their universities.

Bayh-Dole gave academic centers the opportunity to take title to the intellectual property created using extramural federal funds and to share royalties with the researchers. It took some time for Bayh-Dole to penetrate the culture of academic medicine. The cultural divide between industry and academia was wide, and even into the 1980s industry connections tarnished rather than burnished prestige. But a new system has gradually evolved and the twenty-first century financial relationships and intellectual networks are vastly different than those envisioned by Vannevar Bush in 1944. Bayh-Dole has been extremely successful on its own terms: far more academic inventions have been translated into commercial applications than would have been without it. But that success has introduced institutional relationships and conflicts of interest whose implications are just now being examined and are not yet understood.

The context of direct federal funding has also been changed by the objectives underlying Bayh-Dole. Soon after the passage of that legislation, two new federal programs were established by Congress to further develop commercial applications for academic funding. The Small Business Innovation Research (SBIR) Program was established to further develop private-sector commercialization of federally funded R&D.[96] The Small Business Technology Transfer (STTR) Program was established to encourage technology transfer between research institutions and small business.[97] Both programs require active partnerships and sharing of intellectual property between industry and research institutions.[98] The federal government provides seed funding to get the partnerships going and provides early support as the projects are developing.[99] While there is a competitive process for obtaining funding through the SBIR and STTR programs, so long as the requirements of the programs are met, funding opportunities are, at least so far, somewhat easier to attain than traditional NIH extramural grants.

But even the context of more traditional NIH funding has changed. Vannevar Bush's original vision for federal funding of biomedical research was that scientists should not be pressured by a desire for immediate results.[100] This often meant a series of renewable grants funding basic research of unknown utility. Increasingly, NIH views its mission as providing seed

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[96] *See Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs*, OFF. EXTRAMURAL RES., NAT'L INSTS. HEALTH (Feb. 8, 2011), http://grants.nih.gov/grants/funding/sbirsttr_programs.htm (on file with the Harvard Law School Library).

[97] *Id.*

[98] *Id.*

[99] *See id.*

[100] *See* discussion, *supra* Part I.

money rather than continuing support.[101] Programs are provided initial funding but are required to seek and attract other funding and support as they mature. While funding determinations are still made through a peer review process, commercial applications as well as scientific merit are inevitably part of the deliberation.

At least partly due to this shift in incentives, the entire research industry has changed significantly. The emergence of the biotechnology industry was both a cause and effect of the Bayh-Dole legislation. The Bayh-Dole Act has in turn fueled changes within the pharmaceutical industry, which has undergone additional fundamental changes of its own. Whereas through the 1970s, federal funding supported more than twice the health R&D provided by industry, industry expenditures outstripped federal support in 1992 and have been increasing dramatically since then.[102] Academic centers are no longer the sole venues for clinical research. Contract-research organizations (CROs) and site-management organizations (SMOs) now manage clinical research for industry across many settings including private research centers and private physicians. In 1991, academic medical centers received 80% of industry R&D funding; in 1998, that amount had dropped to 40%.[103] This decrease in academic capture of industry R&D funding has also changed the nature of the biomedical research profession. Prior to the 1980s, the best and the brightest scientists sought careers in academic institutions.[104] Now industry is often at least as an attractive option, and, frequently, no choice needs to be made. There is active movement between careers in academia, industry, and government. Increasingly, it is possible to maintain academic and industry affiliations simultaneously.

A prodigious amount of clinical research takes place overseas. Of the 100,000 clinical trials listed on NIH's ClinicalTrials.gov, only about half are conducted in the United States.[105] It is far cheaper to do research outside the United States, but much of that research is funded by U.S. dollars, both private and public.[106] In addition, the impact of China and India's nascent but burgeoning biomedical research facilities has barely been measured.

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[101] *See* Elias Zerhouni, *The NIH Roadmap*, 302 SCIENCE 63, 64 (2003) (describing NIH's intent to "encourage investigators to take on creative, unexplored avenues of research that carry a relatively high potential for failure, but also possess a greater chance for ground-breaking discoveries.").

[102] *See* PAMELA W. SMITH, CONG. RESEARCH SERV., RL 33695, THE NATIONAL INSTITUTES OF HEALTH (NIH): ORGANIZATION, FUNDING, AND CONGRESSIONAL ISSUES 12 (2006), *available at* http://www.nih.gov/about/director/crsrept.pdf.

[103] Thomas Bodenheimer, *Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG J. MED. 1539, 1540 (2000).

[104] *See, e.g.*, P. ROY VAGELOS & LOUIS GALAMBOS, MEDICINE, SCIENCE, AND MERCK 121–22 (2003).

[105] CLINICALTRIALS.GOV, http://clinicaltrials.gov/ (on file with the Harvard Law School Library); Search results for United States, CLINICALTRIALS.GOV, http://clinicaltrials.gov/ (follow "Search for Clinical Trials" hyperlink; then search for "United States") (on file with the Harvard Law School Library).

[106] *See* Seth W. Glickman et al., *Ethical and Scientific Implications of the Globalization of Clinical Research*, 360 NEW ENG. J. MED. 816 (2009).

The movement of clinical research outside of academic medical centers does not mean that there is no oversight. Partly because much of this research is subject to FDA drug approval regulation, and perhaps even more so because industry recognizes the reputational need for regulation, industry-conducted clinical research is subject to IRB oversight and federal auditing. But the system of federal oversight that the National Commission assumed would be combined with the IRB system is lacking. The IRBs used by industry are quite different from those used by academia and quite different from what was envisioned by the original DHEW regulations. Any IRB can be used, and the majority of those used by industry are either their own or private stand-alone IRBs.[107] For industry, one important factor governing selection criteria is the speed with which the IRB can turn around a review.[108] That is not to say that those IRBs are necessarily inferior in scientific or ethical review. But they certainly lack the local situational knowledge that the National Commission envisioned when it formulated the regulations. It is an open question whether they are more or less subject to capture than an academic review board. They are not affiliated with the institution for which they are conducting the review. On the other hand, they are beholden to the commercial market for clients, and an IRB that frequently raises objections to protocols or delays the review process is unlikely to stay in business for long.

There have been numerous critiques of this change in the system of biomedical research. Many of these critiques have an air of nostalgia for the simpler times when academic medicine ruled without rivals.[109] But even discounting this criticism, there is no question that this new structure creates complicated financial incentives, new conflicts of interest, and hidden agendas. These agendas influence research choices and research design. When federal funding was virtually the only funding option, NIH influenced those research choices and design issues and supplied additional oversight. Now, not only are those issues not dealt with, they may be completely obscured. The existing regulatory structure was designed to address these issues, but for the most part, it does not.

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[107] *See* Karine Morin et al., *Managing Conflicts of Interest in the Conduct of Clinical Trials*, 287 JAMA 78, 79 (2002).

[108] *See, e.g.*, Suz Redfearn, *IRB Selection Tips*, CLINPAGE.COM (Feb. 4, 2009), http://www.clinpage.com/article/irb_selection_tips/C9 (on file with the Harvard Law School Library). In 2009 the GAO created a fictitious protocol and submitted it to three IRBs. While two of the three IRBs refused to approve the protocol without additional information and clarifications, a commercial IRB did approve the protocol despite major gaps that should have been easily evident. That IRB advertised the speed of its reviews on its website. Gregory D. Kutz, Statement before the U.S. House of Representatives Committee on Energy and Commerce, Subcommittee on Oversight and Investigations 5 (Mar. 26, 2009) *available at* http://www.gao.gov/new.items/d09448t.pdf.

[109] *See*, *e.g.*, Trudo Lemmens, *Leopards In The Temple: Restoring Scientific Integrity To The Commercialized Research Scene*, 32 J.L. MED. & ETHICS 641 (2004).

## III. The Existing Institutional Structure of Federal Oversight of Biomedical Research

Not surprisingly, the current institutional structure of federal oversight of biomedical research has been profoundly affected by the history of federal funding of that research. Perhaps more surprising is that the institutional oversight structure is still designed more for a full academic model of research than for the complicated relationships that exist today. Oversight of biomedical research is mainly housed within the Department of Health and Human Services (HHS). While there are multiple divisions within HHS that have some jurisdiction over aspects of that oversight, the three administrative agencies that currently have the major roles are the NIH, the Office for Human Research Protections (OHRP), and the FDA.

The NIH's role is both regulatory and quasi-regulatory. It does have rules for grantees, but its most profound influence is through funding decisions. Through these funding decisions, the NIH is able to control research priorities and the design of research studies. OHRP and the FDA have more formal regulatory authority, and much of their oversight is conducted through IRBs. OHRP and the FDA's authorities are concentrated in the protection of participants in research and data integrity. The FDA also has the authority to require specific studies in order to approve or continue marketing a given product, but it has no authority to require that any product be considered for approval.[110] The FDA has jurisdiction over research related to products that it has authority to regulate under the Food Drug and Cosmetics Act regardless of funding source. In the context of biomedical research, these products include devices, biologics, and drugs. OHRP has jurisdiction over most federally funded human subjects research.[111] There is therefore significant overlapping jurisdiction, and, at times, substantial agency competition for authority within those overlapping jurisdictions.

Given that there has been significant evolution in the institutional structure of the biomedical research enterprise, we must ask whether the regulatory structure that was developed earlier still makes sense. This question, in turn, inspires a number of related questions. How well does the system of audited self-regulation through IRBs work in this new reality? Where are the gaps? What happens when NIH no longer has full control of national research priorities? What happens when federal goals, industry goals, and academic goals are both intertwined and competing?

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[110] *See* Susan Bartlett Foote & Robert J. Berlin, *Can Regulation Be As Innovative As Science And Technology? The FDA's Regulation of Combination Products*, 6 Minn. J. L. Sci. & Tech. 619, 623–33 (2005) (explaining the FDA's regulatory authority over drugs, devices, and biologics).

[111] *See* 45 C.F.R. § 46.101 (2010).

### *A. The Scope of Federal Regulatory Oversight of Biomedical Research*

Since the first discussions of potential federal oversight of biomedical research, some have sought to extend the scope of federal oversight to all research, regardless of funding. But none of these proposals have gained much traction, probably more because of professional resistance than because of questionable constitutional authority. Nonetheless, creative use of its spending power has allowed HHS to expand its jurisdiction over a considerable amount of research that is not federally funded. OHRP now requires that any entity receiving federal funding execute a "federal wide assurance" (FWA) whereby the institution agrees to apply federal rules to all research it conducts regardless of funding and to use an IRB registered with OHRP.[112] In theory, there are two carrots given here in return for the assurance: not just funding, but the efficiency of not having to make an additional assurance for each project. But in 2005, in revising the assurance requirements and instituting the FWA, OHRP also phased out the ability to obtain a single project assurance.[113] So, in effect, all institutions receiving federal funds for research must agree to conduct all research according to federal rules. In so doing, OHRP quietly realized a long-standing goal of bringing more research under the federal umbrella. But it did so at a time when more research than ever is conducted by institutions that receive *no* federal funding. It is therefore unknown how much research may be taking place without any federal oversight.

A fair amount of what might ordinarily be considered biomedical research is also outside regulatory oversight. To be covered under the FDA regulations, research must be part of the drug and device product approval process.[114] Thus, research with products outside its purview, such as dietary supplements, are not subject to much FDA oversight. There is also evidence that companies seek to avoid that oversight by invoking exceptions such as claims that their products are not "drugs" or are not "new."[115] To be covered under the Common Rule, research must involve "research," and the use of "human subjects."[116] Under the Common Rule, to be "research," conduct must be both systematic and contribute to "generalizable knowledge."[117] Thus, for example, "research" does not include: medical practice that is primarily directed at care of an individual, even if it is experimental; many surgical innovations; many innovative reproductive treatments; some clinical

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[112] *See* 45 C.F.R. §§ 46.101–46.103 (2010); Office for Human Research Protections, *IRBs and Assurances*, U.S. DEP'T OF HEALTH AND HUMAN SERVS., http://www.hhs.gov/ohrp/assurances/index.html(on file with the Harvard Law School library).

[113] Office for Human Research Protections, *Federalwide Assurance for the Protection of Human Subjects*, U.S. DEP'T OF HEALTH AND HUMAN SERVS., http://www.hhs.gov/ohrp/assurances/assurances/filasurt.html (on file with the Harvard Law School Library)

[114] 21 C.F.R. § 50.1 (2010)

[115] *See* 21 U.S.C. § 355 (2006) (requiring approval of an application for a new drug before it can be introduced into interstate commerce).

[116] 45 C.F.R. § 46.102(d), (f) (2010).

[117] 45 C.F.R. § 46.102(d) (2010).

applications of stem cells; quality improvement activities even if they are systematic; and many public health initiatives. Moreover, to be a human subject, one must be alive and identifiable.[118] Thus, research involving data or tissue that has been permanently stripped of all identifiers is not considered human subjects research. There is no way to quantify how much activity this all represents, but it is clear that there is a considerable amount of activity that most people would define as research that is now unregulated.

### *B. Gaps in IRB Oversight*

The focus of IRBs is narrow. An IRB reviews research by study and assesses the risks and benefits within the context of a single study IRBs lack the means, authority, and time to consider how individual research studies figure in the larger biomedical research enterprise. In addition, the last fifteen years have seen the growth of unaffiliated IRBs.[119] These are usually for-profit IRBs that operate as a review board for any client seeking such review. This fragments review further because it lacks the context of the overall research being conducted by specific researchers within a single institution. The growing globalization of research and consequent internationalization of regulation further fragments and dilutes the process.

IRBs are both too protective and not protective enough. Regulations make paperwork their focus. Where an issue is within their authority and easy to measure, such as informed consent language or privacy issues, IRBs may overplay their hand. Problems such as IRBs' heavy workload, failure of IRBs to understand their role and responsibilities, lack of sufficient scientific expertise required for scientific review, and IRBs' over-concern with informed consent documents means that IRB review may not expose defects and risks.[120] There are institutional conflicts of interest inherent in the process since researchers submitting protocols for review may be IRB members or are certainly colleagues—and sometimes supervisors—of IRB members. In addition, IRBs are often underfunded, and membership is largely uncompensated—both financially and in terms of academic advancement. The relatively weak institutional power of IRBs limits both their authority and their consequence.[121] IRBs also force redundant review since numerous IRBs may review a multi-center protocol. Neither the FDA nor the OHRP have

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[118] 45 C.F.R. § 46.102(f) (2010).

[119] Janet M. Lis & Melinda G. Murray, *The Ins and Outs of Independent IRBs*, J. HEALTH & LIFE SCI. L. 73, 75–122 (2008).

[120] *See* President's Comm'n for the Study of Ethical Problems in Med. & Biomedical & Behavioral Research, *Implementing Human Research Regulations* 105–14 (1983); Ezekiel J. Emanuel et al., *Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals*, 141 ANNALS INTERNAL MED. 282 (2004).

[121] IRBs have a bit more institutional bite now than they did previously. In 1999, federally-funded research at Duke University, one of the most prestigious academic research institutions, was temporarily shut down due to lax documentation and recordkeeping. Rick Weiss, *U.S. Halts Human Research at Duke; University Can't Ensure Safety, Probers Find,* WASH. POST, May 12, 1999, at A1. It is fair to say that the scientific community noticed.

sufficient capacity to audit even the deficiencies that are within their authority. In fact, no one even knows how many IRBs there are; there is no master list. Numerous reviewers including the United States Government Accountability Office (GAO), HHS's Office of Inspector General, and the Institute of Medicine have recommended changes to address these problems, most of which have been disregarded.[122]

One recommendation that has been heeded is the creation of a voluntary accreditation process for IRBs. The Association for the Accreditation of Human Research Protection Programs (AAHRPP) has recently been formed to address some of these problems.[123] This adds another layer of audit beyond what OHRP and the FDA are capable of providing with their limited funds for enforcement. The accreditation process provides education capabilities and higher standards of expertise and management. It has the capability to address some of the concerns about commercial IRBs. But it is not clear that AAHRPP will have standards that actually make a difference, and, moreover, as of now, only a tiny fraction of the more than 3000 IRBs have been accredited.[124]

Yet despite these continuing systemic problems, at least for the academic research model for which they were designed, IRBs likely accomplish what they were designed to do. There are very limited reports of research participants suffering major injury. IRBs have all of the advantages that its model of regulation brings: collected technical expertise, flexibility, incentives for compliance, and vast cost savings to the federal government.[125] Without the IRB system, attention to individual studies and local monitoring of pre-and post-approval processes is impossible. It is also likely that local participation has enhanced acceptance by the profession.[126] The problem is that we don't actually know if all of these advantages are realized, and neither the OHRP nor the FDA has the means to find out.

But a bigger problem is that there are gaps inherent in the current system that cannot be filled by fixing IRBs. While research participants may generally be protected from injury, the research that they are participating in may not be the research that is best designed to help them or society. Because IRBs regulate by reviewing individual studies, they are poorly placed to deal with systemic conflicts of interest. IRBs are also not designed to replace the function that NIH funding brings to research choices and re-

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[122] *See* Kutz, *supra* note 108, at 2; OFC. OF INSPECTOR GENERAL, DEP'T OF HEALTH AND HUMAN SERVS, INSTITUTIONAL REVIEW BOARDS: A TIME FOR REFORM ii–iv (1998); INSTITUTE OF MED., RESPONSIBLE RESEARCH: A SYSTEMS APPROACH TO PROTECTING RESEARCH PARTICIPANTS 37–38 (2003).

[123] *See Our Mission, Vision, and Values*, ASS'N FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS, http://www.aahrpp.org/www.aspx?PageID=5 (last visited June 1, 2011).

[124] See *Accredited Organizations*, ASS'N FOR THE ACCREDITATION OF HUMAN RESEARCH PROTECTION PROGRAMS http://www.aahrpp.org/www.aspx?PageID=11 (last visited June 1, 2011).

[125] Michael, *supra* note 77, at 181–86.

[126] Barbara Mishkin, *Factors Enhancing Acceptance of Federal Regulation of Research*, *in* 2 RESPONSIBLE SCIENCE: ENSURING THE INTEGRITY OF THE RESEARCH PROCESS 79 (1993).

search design. In an era where the majority of research is no longer funded by NIH, but is instead funded by industry, those choices and decisions are largely driven by industry needs. It means that the prime motivator for biomedical research is not scientific discovery but profit.

### *C. NIH's Shifting Role and Diminishing Control*

NIH's role, or, perhaps more accurately, the effect of NIH's role, has changed significantly in the last twenty-five years. Part of that is the shift in NIH's focus from basic science to translational science. But, as described earlier, that has in turn shifted the balance of power in controlling the national research agenda. Whereas NIH, in partnership with the academic research community, controlled most of the entire research agenda through the 1980s, it now shares that control with industry and a more independent academic profession. Thus, while NIH remains the most public face for the research enterprise, its actual control over that enterprise has diminished.

NIH controls research priorities through a peer review structure, so NIH's control of the research agenda has always been in partnership with academic researchers. NIH peer review for extramural research relies on a two-tier system of review.[127] The first is more of a traditional scientific peer review, the second more of an administrative peer review.[128] First, applications are reviewed within the relevant institutes or centers by scientific review groups for scientific and technical merit. They are then assigned a priority score relative to other applications.[129] In addition, the scientific review committees suggest potential improvements for the applications[130] Applications are then funded according to their priority score until the relevant institute or center has used all of its funding.[131] However, these funding decisions are subject to a second level of review by the advisory councils of the relevant centers, and they make funding decisions based on programmatic or policy goals.[132] Those councils are made up not just of scientists but lay members and their decisions are publicly available.[133]

NIH peer review means that participants in research are theoretically participating only in research that is of significant societal benefit and that the study is designed to maximize scientific returns. This peer review is not perfect. Like any peer review system, it tends to favor conventional views and the professionally well-connected. Because it is dominated by the profession, it is also not fully democratic.[134] Finally, it too can be penetrated and influenced by other interests. In 2004, NIH was rocked by reports of

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[127] SMITH, *supra* note 102, at 6.
[128] *Id.* at 6–7.
[129] *Id.*
[130] *Id.* at 7.
[131] *Id.*
[132] *Id.*
[133] *Id.* at 6–7.
[134] SHEILA JASANOFF, THE FIFTH BRANCH 61–83 (1990).

rampant industry conflicts of interest in its intramural program.[135] The extramural program has not been immune from similar allegations.[136] But this fragmented review is better than no review at all.

### *D. Funding Choices Create Gaps in Scientific Discovery in Biomedicine*

Now that industry funds more than half of biomedical research, those funds serve industry research priorities and design. Industry's main goal is to turn a profit. Academic institutions are also engaged in research for institutional profit. Federal funds, academic resources, and industry funds are increasingly commingled. In addition, it is difficult to distinguish between industry interests, academic interests, and federal interests. The implications are discouraging. Basic research, by definition research that is unlikely to lead to demonstrable products within a defined period, is shortchanged. Some discoveries necessary to ready the foundation for future discovery are not being made. More and more dollars are diverted to research that is focused on developing products that are costlier and therefore more profitable. Research may also be redundant. Researchers are forced to hype their research so that they can attract private venture capital. This all leads to the question of whether all federal funds used for biomedical research are truly serving the public interest.

This question can probably only be answered through empirical research of actual institutional behavior. Too often now we draw the conclusion that these are conflict of interest situations that can be addressed through the existing IRB system. The IRB system is not designed to address those conflicts. Moreover, the problems are bigger than conflicts of interest. They have to do with fundamental choices that we make as a society about how we will participate in biomedical discovery. These issues call for new answers. Before we can find those answers, we need to study the questions. We need much more systematic empirical review of the actual consequences of the incentives created by a shifting funding structure. New regulatory solutions and institutions may be required.

## Conclusion

Our biomedical research enterprise is a creature wrought through federal funding. Overall, it has been remarkably successful, and the envy of the entire world. Federal funding also served as the rationale and basis of authority for the regulation of biomedical research. Deliberate changes in the focus and use of federal funding have also had profound effects on the insti-

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[135] More than 100 NIH scientists were found to have undisclosed industry relationships, many of which were prohibited by NIH conflict of interest rules. Editorial, *Taking a Hard Line on Conflicts*, Nature, Feb. 10, 2005, at 557.

[136] *See*, *e.g.*, Office of Inspector General, U.S. Dep't of Health & Human Servs., National Institutes of Health: Conflicts of Interest in Extramural Research (2008), *available at* http://www.oig.hhs.gov/oei/reports/oei-03-06-00460.pdf.

tutional nature of the enterprise. We have a regulatory structure that was created for a different institutional reality. We need more and better empirical research to determine where it works and where it does not. We need to address the changed world created by new partnerships and funding sources. While we are at it, we need to acknowledge that even more change is likely with the growing internationalization of biomedical research and the drugs and other products it creates. Our existing regulatory structure was not designed for the current system of diverse funding sources. We need to bring it up to date.