Research for health: Improving the US system of health research

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The H in NIH is Health. Its function is to support research. It generally does not deliver health, but rather lays the groundwork for improving health over time by adding to the stock of knowledge and by taking the initial steps towards new technologies. Its core constituencies are academic health centers, companies that develop drugs, devices, biologics, and people who do biomedical research. NIH is supported by a very broad, bipartisan, diverse, and passionate legion of advocates whose hopes rest on NIH's future success in addressing conditions that shorten and sully human lives. Everyone is against disease and for health.

NIH is embedded in the Department of Health and Human Services as its largest research unit. It is not an arm of a National Research Foundation that Vannevar Bush envisioned in Science—The Endless Frontier, or even of the National Science Foundation (NSF) that finally emerged in 1950, by which time NIH's budget was in the early stages of explosive growth that continued into the mid-1960s (before it stalled and then resumed growth for another two decades). By the time NSF was established in 1950, the armed forces had spawned their own research units, the Atomic Energy Commission was funding high-energy physics, and NIH was larger than NSF and would remain so. Research was mainly funded as a small part of many mission agencies, with NSF as the flywheel for science and science education. NIH was the research unit for health. The pluralism and lack of a central research ministry allowed NIH to grow spectacularly without having to take money from nuclear physics or militarily relevant research. Several of the appropriation subcommittees became patrons of particular kinds of science, but NIH, Department of Defense, NSF, and what became the Department of Energy were funded from different subcommittees, avoiding direct research budget tradeoffs. Thus, was set in place the highly pluralistic, decentralized U.S. R&D system.

NIH grew faster than other research units (partially rivaled by NASA during the Mercury/Apollo era), in part because both parties in both houses of Congress are united in opposing

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disease. NIH also had a very active group of advocates that high energy physics, mathematics and engineering do not have; advocates who cared passionately about conquering cancer, heart disease, diabetes, Alzheimer's Disease, and other scourges that plague our species and that we need to understand in order to mitigate or avoid.

NIH has always been faced with twin goals: to do great science and add to the stock of knowledge and technology, responding to scientific opportunity, while also focusing on research that responds to the most significant health needs. But how to balance the two? Congress has created institutes and devoted funding mainly according to health needs through categorical institutes that correspond to disease domains (with some exceptions: nursing, biomedical engineering, the Library of Medicine, General Medical Sciences, translational research, and genomics); NIH makes funding decisions project-by-project using criteria of innovation and scientific opportunity. Health need is mainly judged by Congress institute-by-institute through appropriations; project selection is based mainly on scientific opportunity assessed by peer review. So how are we doing?

The honest truth is we have no way to tell for sure. Some heuristics can, however, guide decisions about funding and institutional design. C. Jackson Grayson's Decisions Under Uncertainty (Grayson, 1960) examines resource allocation in the face of unknowns; an apt metaphor for the tasks that NIH confronts. Grayson concluded that a strategy embracing a portfolio of wild-catting (or low probability of success but high reward), drilling at the margin of known oil fields (to extend the margin of known reserves), and drilling in known reserves (more straws in the drink) is more successful than any of its components pursued exclusively, or than careening from one tactic to another. Sticking to a portfolio strategy was more successful in the long run than any one of the elements.

Peer review as practiced at NIH and NSF is the mainstay that fosters the second two approaches—building on what's known and probing the margins—but not terribly adept at supporting wild-catting. This is exemplified by the struggles for funding of CRISPR before it caught fire in 2012 (Ishino et al., 2018), the Karikó and Weissman work on pseudouridine substitution in mRNA constructs (Gibney, 2022), and the early travails of polymerase chain reaction (Rabinow, 1996). Hence the optimism of establishing ARPA-H. Can it supplement the steady but somewhat conservative propensities of NIH peer review?

One reason for optimism is the distinctive pluralism of U.S. biomedical research funding; that is, having multiple competing agencies that fund biomedical research. This is illustrated by the discovery and development of monoclonal antibody drugs to combat breast cancer. Dennis Slamon at UCLA got his initial funding from the newly formed Department of Defense (DoD) biomedical research units, not NIH. The National Academies lauded innovations in the DoD programs: including disease advocates at all levels of review for funding, and promoting a can-do culture intended to contrast with the process-oriented, inertial NIH (Institute of Medicine, 2004). Clinical trials were dramatically accelerated by direct engagement of the National Breast Cancer Coalition and Breast Cancer Action (Bazell, 1998).

Some have emphasized the need to address the coordination problems and quest for cultural independence of ARPA-H. It might be useful, however, to attend to other features of NIH that might benefit from reform. And here I will emphasize the H in NIH.

NIH is not the National Foundation for Biomedical Research, although that is close to what it actually does. I don't mean this as a tired critique, but rather as an observation, which draws us into politically perilous territory.

NIH is largely devoted to supporting research to understand what goes wrong in the human body that leads to disease or disorder, in hopes we can do something about it. It also supports clinical research, and some institutes also study determinants of health beyond biology, including features of health care delivery (health services research) and financing (economics) that limit health benefits, or that document social determinants of health. But those are relatively small by comparison to mainstream wet-lab and clinical research (Cook-Deegan, 2011). The default pathway at NIH is a technical fix: research to understand molecular and cellular mechanisms that cause disease leading to drugs, biologics, devices to treat medical conditions or preventive measures such as vaccines to avoid ill health.

This logic is tried and true. Do we understand this biological system? Once we understand enough, can we do something to fix it or avoid it? The role of research here is clear, studying a biological problem and the various means to address it.

It works, but it is incomplete. The causes of ill health are more than just biology, because human beings live as organisms in complex ecosystems and social environments that also deeply affect health. This is obvious and well understood, including by (almost) everyone I know at NIH.

If this is true, then why does NIH devote relatively few resources to understanding the factors beyond the organismal level that affect health? The NIH role in hypertension and tobacco control may help illustrate the issues that arise. The first example is the National High Blood Pressure Education Program initiated in the 1970s, which was a massive communications effort that had real effects on raising awareness of how and why hypertension mattered (Jones & Hall, 2002). It involved 15 agencies and many private and state and local institutions as well as private philanthropy (Roccella & Ward, 1984), but it was led by the National Heart, Lung and Blood Institute. It entailed extensive research, but not just research on hypertension. The challenges and need for understanding concerned how to get the word out and change behavior. It persevered for decades and showed what NIH could do. Would it emerge from NIH culture today?

The federal role in tobacco control research is a decidedly spotty story. It has been clear since the 1950s, and widely known since the Surgeon General's Report of 1964, that smoking and tobacco use account for more preventable death than any other cause (Institute of Medicine, 2013). Indeed, the health toll of tobacco use is as significant for heart and lung disease as it is for cancer (Institute of Medicine & National Research Council, 1998). When the National Cancer Policy Board sampled NIH funding on tobacco-related disease in 1998, however, the NIH funding streams on tobacco control were paltry relative to the disease burden (Institute of Medicine & National Research Council, 1998). The federal government was spending less than California's Tobacco-Related Diseases Program, which was funded by a state referendum that set aside 5% of an excise tax to fund research. When the National Cancer Institute (NCI) funded a grant to study the underlying vector transmitting the disease—political networks influencing governments to hamper tobacco control and protect tobacco firms' marketing efforts—Representative John Porter (R-IL) wrote language into House appropriations to defund the grant, responding to a systematic lobbying campaign funded by tobacco firms (Landman and Glantz, 2009). The head of the American Cancer Society and former Surgeon General C. Everett Koop took out a New York Times advertisement defending the grant and chastising Porter as the new chair of the NIH appropriations subcommittee. Porter was a champion for NIH funding, but on this issue, he deemed research on political activity to be out of bounds for NIH.

What was NIH's role in tobacco control research? One cannot call it leadership, although the NCI programs COMMIT and ASSIST lay groundwork for interventions to reduce tobacco

use. But who could blame NIH for being gun-shy when the appropriations subcommittee chair had his hand on the spigot for all NIH funding? The issue in this case was resolved by the private American Cancer Society picking up the funding for the parts of the grant to University of California, San Francisco researcher Stan Glantz to which Porter most objected. That let NCI off the hook, but it was a strong signal about the political risks in tobacco control research.

Both hypertension and tobacco control are examples of research that bears on public health, where NIH and the Centers for Disease Control and Prevention (CDC) share responsibility. NIH's role in such cases is complicated because its research budgets are much larger, yet CDC also has a research budget and its mission is public health. Both agencies are funded by Congress and subject to the perils of conducting research that might offend powerful constituencies. Yet such research is essential to understanding the factors that affect health.

Health services research is another domain that faces vexing problems of political economy. The Agency for Health Care Policy and Research (AHCPR) had a near-death experience when its funding was zeroed out by the House and Senate Budget Committees, and a floor amendment offered to kill its appropriations (Cook-Deegan, 2011, Supporting Online Material). Here the issue was not a particular grant, but a body of work yielding clinical practice guidelines that were opposed by health professionals whose livelihood was threatened (Gray et al., 2003). The agency survived as the Agency for Healthcare Research and Quality (AHRQ), and continued to gather evidence about health care practices, but backed away from making practice guidelines. Despite these changes, AHRQ has faced several proposals to reduce or eliminate its budget. This illustrates a fundamental problem. Some of the most valuable information that comes from studying the delivery of health care is about what is not worth paying for, but the people and institutions who deliver the goods and services deemed inefficient, ineffective, or not cost-effective will oppose such research and fight against policies to reduce use of their services. Health would be improved if the health care system were more efficient and effective. Indeed, the U.S. system of health care is the most expensive in the world by far, with only middling health outcomes to show for all the money spent. The main impediments are not biological problems, but financing, institutional complexity, and political forces.

This is a deep conundrum. NIH is all about research to foster understanding. But such understanding of "health and human services," as opposed to molecular and cellular biology, can lead to controversy and conflict. Understanding how the systems work that support health is necessary but far from sufficient. Even NIH's $47.5 billion annual budget is dwarfed by the $4.3 trillion national health expenditures. (Consolidated Appropriations Act of 2023; NHE Fact Sheet, 2022) NIH may be the largest research enterprise on the planet, but even if all its resources were devoted to increasing the efficiency and effectiveness of health services, it would still be only one percent of U.S. health expenditures.

Understanding the systems that deliver health care and promote public health must be part of any solution. But such understanding does not necessarily lead to solutions when those solutions entail complex social systems, politics, and economics. Moreover, doing the research to make the system work better can be dangerous to the institutions carrying it out. It is no small wonder that NIH has been cautious in venturing into research that could risk a backlash to its valuable molecular, cellular and clinical research. But to actually achieve health outcomes, biology is not enough; social sciences and health services research are also essential as part of the research portfolio.

I wish I could say I have a solution for the gaps in knowledge needed to improve public health and health services. Reverting back to the metaphor of oil-drilling. Some parts of NIH, including NCI and the National Heart, Lung, and Blood Institute (NHLBI) and the institutes of the former Alcohol, Drug Abuse and Mental Health Administration (The National Institute on Drug Abuse, National Institute of Mental Health, and National Institute on Alcohol Abuse and Alcoholism) do support some health services research that explores the margins of what NIH can safely support. Other agencies also support social science and health services research: CDC, AHRQ, the Veterans Administration, the Patient-Centered Outcomes Research Institute, the Food and Drug Administration and private philanthropies. That research can build a policy agenda that is "poised to pounce" when and if the political window of opportunity for change opens, as norms change or crisis draws attention to problems in the U.S. health care system.

To an optimist, the hundreds of thousands of deaths that could have been avoided if U.S. residents had adopted vaccines and control measures to prevent the spread of Covid-19 might be such an opening. Or the death toll from use of opiates. Or the continued incidence of Hepatitis C prevalence despite discovery of highly effective antiviral drugs. NIH has been an essential element in research that has created technical fixes—immensely important accomplishments. Yet Egypt has been far more effective fighting Hepatitis C (Haseltine, 2020) opiate use and vaping have spread through our culture in distinctively American fashion, and most other countries suffered far lower morbidity and mortality from Covid. The United States utterly botched the roll-out of testing and early surveillance despite U.S. technical prowess and witnessed obvious inequities in disease impact. The reasons for relatively poor health outcomes are not technical and understanding how to improve outcomes will surely include research, even if research is only a starting point. Understanding our national health system is a weak point in U.S. health research.

NIH was a major source of the technical fixes, not only in background research on coronaviridae and vaccine technology, but also in clinical testing. DARPA also played a role in early use of mRNA vaccines, providing early support for Moderna's vaccine technology, a foundation on which Covid vaccines built. The Biomedical Advanced Research and Development Authority paid for manufacturing capacity and stockpiling of goods. These agencies supplied an estimated $337 million before the pandemic, and the U.S. Government spent another $31.9 billion through March 2022, once the pandemic hit (Lalani et al., 2023). Yet the communications strategies, understanding of behavior, and appreciation of political factors affecting health fell far short of what was needed, and some of that is a relative dearth of understanding of the communication strategies, economics, politics, and social factors affecting health (Collins et al., 2023). Can NIH, coordinating with CDC, FDA, VA, AHRQ, PCORI, BARDA, Department of Defense, and now ARPA-H do a better job of building capacity to understand the factors that affect health beyond the molecular and cellular level?

It is tempting to call for a new institute or center on health communication and behavior change to pursue such research, analogous to the Center for Advancing Translational Sciences created a decade ago, but that would compound the already considerable problem of institute proliferation and decentralization that plague NIH as an institution. Several NIH reports over the years, and articles by NIH directors and former directors have urged consolidation and simplification of how NIH Is organized (see Appendix I).

NIH's coordination problem of decentralization, redundancy, and institutional inertia are certainly issues that need to be addressed. Perhaps the rechartered Social and Behavioral Sciences unit in the Office of Science and Technology Policy can help think through the policy options. But many of the biggest gaps in knowledge that research can fill concern dysfunction of public

health and medical institutions, not just the biology of disease. If a major reform of NIH moves from the policy discussion agenda onto the action agenda, then the role of public health and health services research at NIH needs to be addressed, if NIH really wants to promote the Health in its name.

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Appendix I: A sample of National Academies' reports on the structure and function of NIH

A 1984 Institute of Medicine report that directly addressed NIH structure, and the tension between scientific opportunity and meeting health needs: https://nap.nationalacademies.org/catalog/762/responding-to-health-needs-and-scientific-opportunity-the-organizational-structure

A 1988 report on NIH's intramural research program: https://nap.nationalacademies.org/download/9929

A 1990 NIH-wide analysis, with a title that implied something is "out of balance:" https://nap.nationalacademies.org/catalog/1625/funding-health-sciences-research-a-strategy-to-restore-balance

A 1998 review, with another title reflecting the tension between scientific excellence and health needs: https://nap.nationalacademies.org/catalog/6225/scientific-opportunities-and-public-needs-improving-priority-setting-and-public

And five years later (2003), another take: this one included a recommendation for an ARPA-like capacity: https://nap.nationalacademies.org/catalog/10779/enhancing-the-vitality-of-the-national-institutes-of-health-organizational