The Role of Military-Industrial Relations in the History of Vaccine Innovation

Kendall L. Hoyt
BA English and Biological Psychology
Duke University, 1993

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Signature of Author _____ 5/23/02
Program in the History and Social Study of Science and Technology
May 23, 2002

Certified by _____ 5/23/02
David Mindell, Associate Professor in the History of Technology and Manufacturing (STS)

5/23/02
Evelynn Hammonds, Professor of the History of Science and Medicine (STS)

_____
Harvey Sapolsky, Professor of Political Science
Director of the Security Studies Program

Abstract:

This thesis examines the historical conditions that have contributed to high rates of vaccine innovation in the U.S. during the twentieth century. Empirical analysis of vaccine license data demonstrates that the highest rates of innovation were achieved during the 1940's. Historical analysis of this data indicates that a large percentage of these innovations were the product of World War II vaccine development programs. Participation in these programs fostered a uniquely productive culture of collaboration between military and industrial vaccine developers that persisted through the postwar era, maintaining innovation rates through the 1960's and early 1970's. By the mid-1970's, however, the historical circumstances and cultural factors that engendered and sustained military-industrial collaboration began to change, causing rates of vaccine innovation to fall and vaccine stocks to dwindle.

Poor economic incentives for vaccine development are often cited as the reason for falling rates of innovation. This explanation is correct but incomplete, because, for example, economic incentives for vaccine development were poor during the 1940's and 1950's, when innovation rates were high. I demonstrate that vaccine innovation is tied to levels of military-industrial collaboration and that declining rates of innovation in recent decades are associated with the disruption of this military-industrial culture of collaboration. Finally, drawing on lessons from this history of military-industrial relations, I examine the opportunities and challenges that the new "war on terrorism" presents for efforts to improve vaccine innovation and supplies.

Biographical Sketch

Kendall Hoyt received a B.A. degree in Biological Psychology and English Literature from Duke University in 1993 and a Ph.D. in the History and Social Study of Science and Technology from the Massachusetts Institute of Technology in 2002. She has worked at the White House Office of Science and Technology Policy, McKinsey and Company, and the Center for the Management of Innovation and Technology at the National University of Singapore. She is currently a Postdoctoral Fellow at the Belfer Center for Science and International Affairs at Kennedy School of Government at Harvard University.

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Archive Abbreviations

AP	Aventis-Pasteur Archives, Swiftwater, PA
MA	Merck Archives, Whitehouse Station, NJ
NA	National Archives II, College Park, MD
NAS	National Academy of Sciences, Committee on Biological Warfare Files, Washington DC
LC	Library of Congress, Vannevar Bush Papers, Washington, DC
WR	Walter Reed Army Institute of Research, Joseph Smadel Reading Room Collection, Silver Spring, MD

Introduction

A spate of anthrax infections contracted from letters sent through the U.S. mail system propelled biodefense to the top of the list of national security concerns in 2001. Prior to these events, few national security experts were concerned with the status of the national vaccine supply or with the problems of vaccine innovation. These problems, if they were noticed at all, were perceived as a public health issue affecting those in developing countries, the very old, and the very young.

As federal officials now rue insufficient national stocks of anthrax and smallpox vaccines, it has become clear that the problems of vaccine innovation and supply affect everyone. Newly appreciated as fundamental to national security, these issues are likely to receive a larger amount of attention and resources. As is natural in any urgent situation, government officials have focused on the immediate dilemma: "where can I find this vaccine and how long will it take?" This natural response may drive, however, stopgap solutions that fail to address the causes of innovation and supply problems. Since today's "war on terrorism" is unlikely to have a finite time frame that lends itself to short-term solutions, it is essential to explore novel and sustainable arrangements for vaccine development.

To this end, I examine the historical conditions that have contributed to high rates of vaccine innovation in the U.S. during the twentieth century. Empirical analysis of vaccine license data demonstrates that the highest rates of innovation were achieved during the 1940's. Historical analysis of this data indicates that a large percentage of these innovations were the direct result of World War II vaccine development programs. Participation in these programs fostered a uniquely productive culture of collaboration between the military and industrial vaccine developers, which persisted during the postwar era, fueling innovation rates through the 1960's and early 1970's. By the mid- 1970's, however, the historical circumstances and cultural factors that sustained high rates of military-industrial collaboration began to change, causing rates of vaccine innovation and vaccine stocks themselves to dwindle.

Poor economic incentives for vaccine development are often cited as the reason for falling rates of innovation. This explanation is correct but incomplete, since economic incentives for vaccine development were poor during the 1940's and 1950's as well, when innovation rates were high. I demonstrate that vaccine innovation is closely tied to levels of military-industrial collaboration and that declining rates of innovation in recent decades are associated with the disruption of this military-industrial culture of collaboration. Finally, drawing on lessons from

this history of military-industrial relations, I examine the opportunities and challenges that the new security environment presents for efforts to improve vaccine innovation and supplies.

Sources of Technological Innovation

This examination of historical patterns of vaccine innovation, like many other studies in the history and management of technology, converges on a single question: what is the source of technological innovation? This question takes many forms within studies on the history and management of technology. Does innovation stem from the insight of an individual scientist? Or does it derive from some combination of scientific, technological, and social factors over which the scientist exercises partial control? To what degree has the industrial research laboratory become a source of technological innovation? Under what circumstances does innovation stem, not from the firm itself, but rather from inter-institutional forms of collaboration? And finally, to what extent do the answers to these questions change as the historian follows a technology through time?

Traditionally, the history of vaccine development has been told from the perspective of the scientist, with reference to his discoveries and contributions to public health.[1] These tend to be heroic accounts that reinforce the notion that individual scientists single-handedly and methodically conquered infectious diseases. Scientists deduced a theory of germs, which led to the development of bacteriology and immunology, which, in turn, permitted them to identify, target and treat infectious diseases with increasing efficacy, and so the story goes.

A handful of social histories of vaccine development provide exceptions to this narrative tradition of heroic scientific progress. Notable among these is Bruno Latour's account of Pasteur's microbes and Evelynn Hammonds' account of New York City's struggle against diphtheria.[2] Both histories illustrate the social forces outside of the science-scientist nexus that have contributed to vaccine development. These histories temper the heroism of traditional accounts by ascribing agency to a variety of non-scientific actors outside of the laboratory. In so doing, they challenge the notion that the path from the laboratory to effective disease treatments

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[1] H. Dowling, *Fighting Infection; Conquests of the Twentieth Century* (Cambridge: Harvard University Press, 1977); R. Fisher, *Edward Jenner, 1749-1823* (London: Andre Deutsche, 1991); A. Silverstein, *A History of Immunology* (San Diego: Academic Press, Inc., 1989); H. J. Parish, HJ, *A History of Immunization* (London: E & S Livingstone Ltd., 1965); S. Plotkin and B. Fantini, eds., *Vaccinia, Vaccination, and Vaccinology: Jenner, Pasteur, and Their Successors* (Paris: Elsevier, 1995).

[2] B. Latour, *The Pasteurization of France* (Cambridge: Harvard University Press, 1988); E. Hammonds, *Childhood's Deadly Scourge; The Campaign to Control Diphtheria in New York City, 1880-1930* (Baltimore: Johns Hopkins University Press, 1999).

is linear and inevitable, and they provide a glimpse of a larger sociotechnical system for vaccine development that exists beyond the scientist and his laboratory.

During the World War II era, the institutional and social networks for vaccine development grew to such an extent that it is difficult to approach the historical development of this technology without reference to the larger sociotechnical system that supported it.[3] In other words, both the technology and its social context conspired to determine historical outcomes. These co-determinative dynamics are particularly evident in the history of vaccine development after World War II. As the science and business of vaccine development matured, manufacturers forged tightly-knit collaborative relationships with scientists, engineers, and physicians in academia and government, bringing them into their own expanding research and development (R&D) laboratories.

This shift from individual-based accounts to broader renditions of technological development that take a wider range of institutions into account is consistent, for example, with Paul Uselding's approach to the history of technology in the twentieth century. He observes that, prior to the emergence of the industrial laboratory in the late nineteenth and early twentieth century, the history of technology could be told in terms of the individual inventor with reference to his/her personal relationships and cultural context. However, once in-house R&D became a prominent feature of the industrial landscape, he argues, these factors became less relevant as the history of technology and business were, increasingly, endogenously determined.[4]

Despite this observation, I know of only one other study that approaches the history of late twentieth century vaccine development as the study of an industry-based sociotechnical system: Galambos and Sewell's *Networks of Innovation.*[5] Galambos and Sewell trace the history of vaccine innovation within Merck and Company (and its predecessors, the Mulford Company and Sharp & Dohme) from 1894 to the present day. The history of vaccine development is told through the eyes of the company and attends to the effects of firm capabilities (i.e., management and leadership characteristics) on innovation, thereby mitigating the appearance of scientifically or technologically determined account of vaccine development.

Nonetheless, Galambos and Sewell continue to rely, in part, on linear, science-driven accounts of technological development. For example, they attribute Merck's history of successful vaccine

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[3] The notion of a sociotechnical system is often invoked by historians of technology to imply a softened stance toward the question of technological determinism. For a full account of the issues surrounding deterministic approaches to the history of technology see R. Smith and L. Marx, eds., *Does Technology Drive History? The Dilemma of Technological Determinism* (Cambridge: MIT Press, 1994).

[4] P. Uselding, "Business History and the History of Technology," *Business History Review* 54 (1980): 443-452.

innovation to its ability to reorganize research programs around advances in basic science. These reorganizations produced waves of innovation that constitute what the authors call the bacteriology cycle (late 1800's to the 1920's), the virology cycle (1940's to the 1980's), a brief bacterial polysaccharide cycle (1960's and 1970's), and finally the molecular biology cycle (beginning in the 1970's). Thus, in their account, basic scientific discoveries determine industrial research programs that produce the innovation cycles they describe. According to this formulation, vaccines developed at Merck and it's predecessors are a rational reflection of science-driven technology cycles, and a straightforward function of economic opportunity, the available stock of knowledge outside of the firm, and the ability of the firm to exploit existing stocks of knowledge.

Galambos and Sewell's understanding of vaccine innovation patterns reflects a brand of technological determinism that is characteristic of many company-centered histories of technological development. In other words, they argue that industrial innovation is a rational function of technological opportunity (or scientific understanding), firm R&D capabilities, and economic incentives.[6]

This mildly deterministic theory of technological innovation has received much support within literature on the management of technology as well. Giovanni Dosi, for example, has argued that innovation patterns reflect a series of rational choices made in response to the technological opportunities, the managerial capabilities, and the economic opportunities available to individual firms.[7] Similarly, Richard Foster, in his study of innovation patterns in industrial research laboratories, has argued that there are inherent limits to profitable growth from technological innovation and that scientific understanding is the underlying limiting factor. He observes that a firm initially experiences increasing returns to innovation but, as the technology matures, higher levels of R&D investment are required, and the firm begins to experience decreasing returns to

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[5] L. Galambos J. and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995).

[6] Historical examinations that interpret technological development patterns in industrial settings in this manner include: A. Chandler, *Scale and Scope; The Dynamics of Industrial Capitalism* (Cambridge: Harvard University Press, 1990); D. Mowery and N. Rosenberg, *Paths of Innovation* (Cambridge: Cambridge University Press, 1998); A. Chandler, *Scale and Scope: The Dynamics of Industrial Capitalism* (Cambridge: Harvard University Press, 1990); L. Reich, *The Making of American Industrial Research; Science and Business at GE and Bell, 1876-1926* (Cambridge: Cambridge University Press, 1985); D. Houndshell and J. Smith, *Science and Corporate Strategy: Du Pont R & D, 1902-1980* (New York: Cambridge University Press, 1988).

[7] G. Dosi, "Technological Paradigms and Technological Trajectories; A Suggested Interpretation of the Determinants and Directions of Technological Change," *Research Policy* 11 (1982): 147-162.

R&D investments.[8] Hence, the industry-level technological cycles and discontinuities that Galambos and Sewell describe.

Historical studies of industrial innovation also tend to black-box the ways in which firms gain access to this stock of scientific knowledge. Although Galambos and Sewell make frequent mention of the importance of the scientific "network" of inter-institutional relationships as a source of technological innovation, viewed from the firm level, this "network" takes on a nearly mystical role in vaccine innovation and the reader is left without a precise understanding of how this network functions. For example, they explain that access to new knowledge hinges on the ability of industry scientists and managers "to read the signals coming from the appropriate science and medical networks and guide their organizations through this type of transition to the next long cycle."[9] This perspective produces a partial and potentially misleading picture of twentieth century vaccine innovation, since it restricts inquiry to a small set of scientific or firm-centered factors when neither may offer an adequate explanation of the historical dynamics witnessed.

What is it about these inter-institutional relationships that inspires innovation? Are all forms of collaboration equally productive? What conditions encourage or inhibit productive collaboration? Unless the motivations of both institutions (the firm and its partner in collaboration) can be taken into account, and unless the mechanism by which collaboration inspires innovation can be articulated, it is difficult to provide a balanced picture of how the socio-technical system for vaccine innovation functions. To answer these questions, I chose not limit my study to a single scientist, vaccine, or company but instead to take a wider range of individuals, institutions, and motivations into account. This approach exposed unexpected factors and inspired new questions about the historical conditions that have fostered high rates of vaccine innovation.

Innovation and the Military

I began my investigation in a deductive manner by investigating the developmental and institutional history of all vaccines produced and licensed in the United States.[10] This comprehensive review revealed two curious trends. First, it became clear that research conducted and sponsored by the military made significant contributions to over half of the vaccines

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[8] R. Foster, "Timing Technological Transitions," ed. M. Horwitch, *Technology and the Modern Corporation: A Strategic Perspective* (New York: Pergamon Press, 1986).
[9] L. Galambos and J. Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995), 243.

commercially available in the United States. Second, this data revealed that innovation rates were highest when the percentage of military contributions was highest and innovation rates were lowest when the percentage of military contributions was lowest.[11] This second observation raises a new question: Are military contributions to vaccine development especially productive and, if so, why?

A number of historical studies have identified the military as a significant agent of technological innovation. In this vein, studies have examined everything from the effect of military preferences for uniformity and standards on American systems of manufacturing, to the role of the military in the development of the transistor, early computing systems, sonar systems, and Polaris missile submarines.[12] However, for every study that emphasizes the role military as an agent of innovation, there is another that emphasizes the opposite. For example, Martin van Crevald's historical survey of technology and war argues that, while military interest in a particular weapons system may have assisted technological development, no innovative defense technologies have ever originated in the military.[13] Barry Posen takes this observation a step further, arguing that the natural tendencies of military bureaucracies thwart the development and application of new technologies (and the strategies that contain them).[14] What is needed in the literature is a clearer understanding of the conditions under which military contributions to industrial research and development generate high rates of innovation and why they may be more productive than other forms of inter-institutional collaboration.

Empirical studies in the management of technology begin to answer this question. Luigi Orsenigo, in an examination of collaboration in the pharmaceutical industry, has shown that high rates of collaboration between large pharmaceutical companies and smaller biotechnology firms, universities, hospitals, and public/private research institutions correlate with high rates of

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[10] Surveys of this investigation are displayed in Chapter One (Table 4) and Appendix 1.

[11] Innovation rates are defined by the number of licenses issued for new or improved vaccines per decade. This measure is broadly consistent with methods used to measure innovation in vaccine studies conducted by the Office of Technology Assessment (1979), the Institute of Medicine (1985) and the American Enterprise Institute (1997). See Chapter One for a detailed discussion of measurement issues.

[12] M. R. Smith, *Harper's Ferry Armory and the New Technology: The Challenge of Change* (Ithaca: Cornell University Press, 1977); T. Misa, "Military Needs, Commercial Realities, and the Development of the Transistor, 1948-1958," ed. M. R. Smith, *Military Enterprise and Technological Change* (Cambridge: MIT Press, 1985); E. Pugh, *Building IBM, Shaping an Industry and Its Technology* (Cambridge: MIT Press, 1984); D. Mindell, *Feedback, Control, and Computing Before Cybernetics* (unpublished manuscript); G. Wier, *An Ocean in Common* (Texas: A & M University Press, 2001);.H. Sapolsky, *The Polaris System Development* (Cambridge: Harvard University Press, 1972).

[13] M. van Crevald, *Technology and War: From 2000 B. C. to the Present* (New York: Free Press, 1989).

[14] B. Posen, *The Sources of Military Doctrine* (Ithaca: Cornell University Press, 1984).

innovation.[15] He hypothesizes that this is due to the interdisciplinary nature of drug development and wide range of expertise required to bring an effective drug to market. Vaccine development, like drug development, is a highly interdisciplinary endeavor, and thus industry stands to gain from a close working relationship with any institution that shares heterogeneous, yet complementary research and development capabilities.

Indeed, this is the principle behind Eric von Hippel's lead-user theory of innovation.[16] He questions the assumption that industrial labs are always the source of their own technological innovations and demonstrates the innovative advantages of collaborating with the individuals and organizations that use these technologies. This is related to Merritt Roe Smith's observation that the military, "in its role as a tester of products, has often set goals for private manufacturers and thereby influenced the innovative process."[17] Von Hippel suggests a slightly more active role for his lead-users, however, arguing that "lead-users face needs that will be general in a marketplace but they face them months or years before the bulk of that marketplace encounters them, and lead-users are positioned to benefit significantly by obtaining a solution to those needs."[18] Given this orientation, von Hippel observes that lead-users often invent a solution, build and test a prototype, and, with the cooperation of manufacturers, conduct wide-scale tests and applications of the new technology.[19]

Von Hippel's observations are consistent with the military's role in the history of vaccine development. I demonstrate that the military's extensive experience with, and need for, infectious disease control made them a "lead-user" of vaccine technologies. With advanced record keeping systems and high rates of infectious disease within controlled populations, military installations also offered both a testing ground and market for new vaccines. These observations shed light on the question of why military-industrial collaboration might be more productive than other forms of inter-institutional collaboration.

A close examination of military-industrial relations in the history of vaccine development also illuminates the impact of the Office of Scientific Research and Development (OSRD) and other government-sponsored R&D programs on postwar industrial history. A number of studies examine the role of World War II R&D successes in fueling the postwar boom in federal funding for research and much is understood about how federal money and political objectives have

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[15] L. Orsenigo et. al., "Technological Change and Network Dynamics: Lessons From the Pharmaceutical Industry," *Research Policy* 30 (2001): 485-508.
[16] E. von Hippel, *The Sources of Innovation* (Oxford: Oxford University Press, 1988).
[17] M. R. Smith, ed., *Military Enterprise and Technological Change* (Cambridge: MIT Press, 1985), 18.
[18] E. von Hippel, *The Sources of Innovation* (Oxford: Oxford University Press, 1988), 107.
[19] Ibid., 19.

shaped industrial and academic research agendas.[20] Historical studies of industrial R&D and technological development patterns during this period tend to offer abstract examinations of the interplay of technological forces and capitalistic systems. In particular, studies of this nature focus on the role of anti-trust law and economies of scope among leading industrial firms in inspiring the growth of in-house industrial R&D during the postwar period.[21] Houndshell and Smith's historical study of Du Pont, for example, indicates that Du Pont augmented investments in in-house R&D in response to increasingly strict antitrust policies that discouraged large firms from acquiring firms in related industrial or product areas.[22]

Far less is understood, however, about how the direct experience of individuals participating in World War II R&D programs shaped the practice and ideology of industrial R&D after the war. While Uselding is correct in his observation that the history of particular technologies has become embedded in industrial settings, it is not accurate to assume that this trend diminishes the relevance of the individual and his/her relationships within a particular cultural environment. An examination of Merck and Company's postwar vaccine program offers a unique perspective on this question, given the high number of future Merck directors and employees that became personally acquainted with one another through OSRD. This example traces the immigration of personal relationships, ideologies, and R&D practices forged during the war into the postwar industry for vaccine development. In particular, this case highlights the enduring role that non-economic factors such as a sense of public duty, and feelings of personal obligation played in industrial R&D investments during the postwar period.

In addition to theoretical questions about the source of technological innovation, the history of vaccine development raises a practical question. Namely, "what are some of the characteristics of historically successful vaccine R&D programs?" Much has been written on the history and lessons of OSRD and other large-scale efforts to organize research and development for national defense. In particular, a number of studies have examined the organizational, scientific and technological lessons and legacies of OSRD.[23] These histories hinge on an analysis of

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[20] D. Price, *The Scientific Estate* (Cambridge: Harvard University Press, 1965); D. Kevles, "Principles and Politics in Federal R & D Policy, 1945-1990" *Science—The Endless Frontier* by V. Bush (Washington, D.C.: National Science Foundation, 1990); S. Leslie, *The Cold War and American Science* (New York: Columbia University Press, 1993); B. Smith, *American Science Policy Since World War II* (Washington, D.C.: The Brookings Institution, 1990).

[21] D. Mowery and N. Rosenberg, *Paths of Innovation* (Cambridge: Cambridge University Press, 1998); A. Chandler, *Scale and Scope: The Dynamics of Industrial Capitalism* (Cambridge: Harvard University Press, 1990).

[22] D. Houndshell and J. Smith, *Science and Corporate Strategy: Du Pont R & D, 1902-1980* (New York: Cambridge University Press, 1988).

[23] I. Stewart, *Organizing Scientific Research for War: The Administrative History of the Office of Scientific Research and Development* (Boston: Little, Brown and Company, 1948); J. P. Baxter, *Scientists Against*

organizational and engineering feats conducted under the aegis of OSRD and other government organizations in non-biological fields such as the development of radar, the atomic bomb, fire control systems, and penicillin, to name a few.

Vaccine development, while a successful chapter in the history of OSRD sponsored research, has not received much attention in the study of World War II research programs. This is understandable for two reasons. First, vaccine research comprised a small portion of the activities conducted under OSRD. For example, the total dollar value of contracts for the study of infectious and tropical diseases amounted to ~$1.9 million out of a total ~ $450 million for all contracts performed under OSRD from 1941-1946.[24] Second, unlike radar, fire control, and nuclear weapons, biological weapons never became a factor in World War II. Further, military and civilian populations never encountered the widely feared reprise of the 1918 influenza pandemic. Thus, it was not immediately apparent to historians that the lessons from the organization of vaccine development for war would have particular relevance for the future. Indeed, by the late 1960's, after Nixon dismantled the U.S. biological warfare program, and the late1970's, after smallpox was eradicated from the globe and infectious disease rates reached an all-time low in the U.S., this assessment appeared to be increasingly accurate.[25]

The relevance of such a study has become increasingly clear, however, as security experts turn their attention to the number of biological threats posed by terrorists groups. According to Secretary of Defense, Donald Rumsfeld, biological threats currently rank highest among the range of threat agents occupying the attention of security experts.[26] A greater understanding of the factors that have contributed to historically successful vaccine development programs would offer a valuable guide to efforts to organize research and development for the purposes of biodefense today.[27]

Time (Cambridge: MIT Press, 1947); R. Rhodes, *The Making of the Atomic Bomb* (New York: Simon and Schuster, 1986); D. Mindell, *Feedback, Control, and Computing Before Cybernetics*, (unpublished manuscript); L. Owens, "The Counterproductive Management of Science in the Second World War: Vannevar Bush and Office of Scientific Research and Development," *Business History Review* 68 (1994): 4.

[24] I. Stewart, *Organizing Scientific Research for War: The Administrative History of the Office of Scientific Research and Development* (Boston: Little, Brown and Company, 1948), 104.

[25] D. Gordon, D. Noah, and G. Fidas, *The Global Infectious Disease Threat and Its Implications for the United States*, National Intelligence Estimate, 99-17D, CIA, (January, 2000); Figure 17, Trends in Infectious Disease Mortality Rates in the United States.

[26] "If I were asked, among those nuclear, chemical, and biological, which did I think was the more likely and the more worrisome to me at the moment, I probably would say biological. It can be done in relatively small places with dual-use equipment, and there are a variety of delivery mechanisms. Some biological weapons involve contagions, and that's a terribly dangerous thing." Donald H. Rumsfeld, Secretary of Defense, interview by Brian Williams, MSNBC, Department of Defense News Briefing, March 28, 2002.

[27] Biodefense refers to a system of surveillance, detection, preventative, and therapeutic strategies designed to prevent or mitigate potentially destabilizing natural and/or deliberate biological attacks.

War, Disease, and the Role of the Military in Vaccine Development

On the eve of the anthrax attacks of 2001, a series of reports warned of a growing national security threat from natural and manufactured forms of disease.[28] These reports professed that the very idea that infectious disease threatens national security is novel and unprecedented. For example, one states that "health has rarely, if ever, been defined as a national security issue. Yet today's world, in which globalization and the information revolution bring people and problems together in surprising ways, finds health and security intersecting with greater frequency."[29] The perceived novelty of this insight is underscored by the tendency of security experts to classify infectious disease as a "non-traditional" threat.

On the contrary, it is difficult to imagine a more traditional threat to military organizations. As one historian observed: "more than one great war has been won or lost not by military genius or ineptitude, but simply because the pestilence of war- from smallpox and typhoid to cholera, syphilis, diphtheria, and other scourges –reached the losers before they infected the winners."[30] War and disease have gone hand in hand for centuries, and historians have written volumes on this topic.[31] These accounts tend to focus on the effects of epidemics on manpower, morale, and ultimately, on the outcome of military campaigns. The military is portrayed in these accounts, however, as a passive consumer of new technologies and techniques of infectious disease control. With the exception of a few "in house" historical accounts of military medicine, the active role of the military in the development of new vaccine technologies remains relatively unexplored.[32]

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[28] D. Gordon, D. Noah, and G. Fidas, *The Global Infectious Disease Threat and Its Implications for the United States*, National Intelligence Estimate, 99-17D, CIA, (January, 2000); CSIS International Security Program and the Chemical and Biological Arms Control Institute, *Contagion and Conflict: Health as a Global Security Challenge* (January, 2000); Department of State, *Patterns of Global Terrorism: 2000*, April 2001; OMB, *Annual Report to Congress on Combating Terrorism* (July, 2001); GAO, *Combating Terrorism; Selected Challenges and Related Recommendations*, GAO-01-822, (Sept. 20, 2001).

[29] CSIS International Security Program and the Chemical and Biological Arms Control Institute, *Contagion and Conflict: Health as a Global Security Challenge* (January 2000), vii.

[30] A. Chase, *Magic Shots* (New York: William Morrow and Company, 1982), 197.

[31] W. McNeill, *Plagues and Peoples* (New York, Doubleday, 1976); H. Zinnser, *Rats, Lice, and History* (Boston: Little, Brown and Company, 1934); R. Major, *Fatal Partners: War and Disease* (New York: Doubleday, Doran, and Company, 1941); P. Steiner, *Disease in the Civil War, Natural Biological Warfare in 1861-1865* (Springfield, Ill., 1968); A. Crosby, *Epidemics and Peace, 1918* (Westport, CT: Greenwood Press, 1976).

[32] Examples of these "in-house" histories include: *Preventative Medicine in World War II*, Office of the Surgeon General, (Washington, D.C., 1955); N. Covert, *Cutting Edge: A History of Ft. Detrick, MD. 1943-1993* (Ft. Detrick, MD: HQ U.S. Army, 1993); T. Woodward, *The Armed Forces Epidemiological Board; Its First 50 Years* (Falls Church, VA: Office of the Surgeon General, 1990); J. R. Engelman, *Two Hundred Years of Military Medicine* (Ft. Detrick, MD: The Historical Unit, U.S. Army Medical Department, 1975).

Nonetheless, just as military organizations have long been preoccupied with the problems of weapons manufacturing and, later, the development and systems of information and machine control, so too have they been pre-occupied with the problems of disease control.[33] Whether at peace or at war, military settings encourage higher rates of infectious disease than do civilian settings. Training camps, for example, are ideal for breeding infectious disease. They bring men from different geographical regions into close contact with one another, and training conditions cultivate populations of stressed, under-slept, malnourished and wounded individuals. These conditions breed new diseases and magnify the effects of common diseases, rendering childhood ailments such as measles a greater problem for military than for civilian populations. Armed conflict exacerbates the problem; for centuries it has introduced disease into new regions and produced social dislocations that bring civilian populations with different immunological profiles into contact with one another, boosting the incidence and spread of infectious disease.[34]

Military organizations are also familiar with the threat of manufactured forms of disease. Evidence of biowarfare, or the intentional and hostile use of disease, dates to antiquity. Historical reviews of the topic describe the contamination of enemy wells with human and animal corpses as a common practice among retreating armies since the ancient Greeks.[35] In the twentieth century, military organizations have invested heavily in the development of biological weapons; the US, USSR, and Japan made heavy investments towards the middle of this century, and countries such as Iraq, Iran, Syria, Libya, and North Korea are suspected of making investments more recently. These last five countries are also suspected sponsors of terrorism, an indication that the ostensibly unique threat of bioterrorism takes its form and materials from traditional military research programs.

Given the historical relationship between effective disease control and military success, it should come as no surprise that U.S. military organizations have explored biodefense strategies since the Revolutionary War, with vaccines forming the backbone of biodefense plans. In the Revolutionary War, for example, smallpox was cited as a factor in the failure of the Continental

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[33] M. R. Smith, *Harper's Ferry Armory and the New Technology: The Challenge of Change* (Ithaca: Cornell University Press, 1977); D. Mindell, *Feedback, Control, and Computing Before Cybernetics* (unpublished manuscript).

[34] A. Crosby, *Ecological Imperialism; the Biological Expansion of Europe, 900-1900* (Cambridge: Cambridge University Press, 1986).

[35] M. Wheelis, "Biological Warfare before 1914," eds. E. Geissler and J. E. van Courtland Moon, *Biological and Toxin Weapons: Research Development and Use from the Middle Ages to 1945, SIPRI Chemical and Biological Warfare Studies* (Oxford: Oxford University Press, 1999); V. Derbes, "De Mussi and the Great Plague of 1348: A Forgotten Episode of Bacteriological War," *JAMA* 196, no. 1 (1966): 59-62.

Army to capture Quebec. In an effort to protect against similar future losses, General Washington gave orders for the variolation of his entire army in 1777.[36]

Military organizations continued to suffer tremendous losses to infectious disease in the Civil War and later in the Spanish-American War, where the ratio of disease to battle casualties was approximately five to one.[37] Typhoid fever accounted for the majority of disease casualties, with 20,738 reported cases in the Spanish-American War. Finding these losses unacceptable, the U.S. Army supported the research of Major Fredrick Russell, who succeeded in developing the first effective typhoid fever vaccine several years after the war.

It was not until World War I that the development of rudimentary vaccines, improved sanitation and vector control evened the ratio of disease to battle casualties. This achievement was immediately overshadowed, however, by the 1918 Spanish Influenza Pandemic that claimed twenty million lives worldwide and accounted for 80% of US Army casualties at the close of World War I.[38] As with smallpox in 1776 and typhoid in 1898, influenza was poorly understood and caught the military unprepared.

Due in large part to this experience with influenza at the close of World War I, and in part to biowarfare concerns, the military's approach to biodefense shifted markedly on the eve of World War II. Reactive biodefense strategies such as the Army's de facto search for a typhoid vaccine gave way to proactive vaccine development programs that tried to anticipate disease threats before they materialized. Federal investments in military medical personnel, training and research ballooned with the onset of World War II. The federal government coordinated massive infectious disease research and vaccine development programs through intra- and extra-mural projects conducted through the OSRD and the Surgeon General's Office (SGO). The operational success of these vaccine development programs is measured by the fact that battle casualties outranked disease casualties for the first time in the history of the Armed Forces.[39] More directly, however, these programs developed an exceptional number of new and improved vaccines for the Armed Forces.

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[36] Variolation preceded the use of Jenner's smallpox vaccine, which was not developed until 1796. The practice of variolation introduced dried pus from smallpox pustules through a break in the skin. An estimated 2-3% died from full-blown cases of variolation-induced smallpox. (E. Fenn, *Pox Americana: The Great North American Smallpox Epidemic* (New York: Hill and Wang, 2001).)

[37] S. B. Hays, Surgeon General, forward to *Preventive Medicine in World War II,* vol. IV, (Washington, D.C., 1958).

[38] T. Francis, Jr., "Influenza in the U.S. Army Medical Service," *Preventative Medicine in World War II,* vol. IV, (Washington, D.C., 1958): 85-87.

[39] The development and administration of penicillin and DDT contributed to the reduction of disease casualties during World War II. S. B. Hays, Surgeon General, *Preventative Medicine in World War II,* vol. IV, ed. John Boyd Coates, Jr., (Washington, D.C., 1958).

The innovative success of World War II vaccine development programs is illustrated in Chapter One, which provides a detailed empirical analysis of historical patterns of vaccine innovation, cataloguing the number, type and source of all new product licenses since 1903. Due to problems with data availability prior to 1938, analysis is limited to four major eras: the World War II era (1940-1949), the postwar era (1950-1975), the post-Vietnam era (1975-1989), and the present era (1990- present). The World War II era displays the highest rate of innovation, with the majority of significant innovations during this period deriving from World War II vaccine development programs. High rates of collaboration between military and industrial institutions continued through the postwar era, which was also characterized by relatively high rates of vaccine innovation. The post-Vietnam era was marked by a series of disruptions to these collaborative vaccine development networks and a corresponding decline in rates of innovation and levels of supply. The present era has been marked by still lower rates of innovation and supply. This era is still in its early stages, however, and the mood of this period, particularly after the events of September 11th, has begun to resemble the U.S. on the eve of World War II. Specifically, this era displays renewed concern for the destabilizing effects of infectious disease on national security and attention to the problems of vaccine innovation and supply.

Historically, the military has relied on private industry to assist in the late stage development, manufacture, and licensing of vaccines of military significance. This arrangement worked well during the World War II and postwar era but faltered over the past thirty years as companies, citing low margins, terminated long-held agreements to manufacture vaccines for the military. While the list of vaccines required by the Department of Defense includes a few commercially viable vaccines such as Hepatitis A and B, it contains a larger number of unprofitable vaccines against diseases with low natural incidence such plague, smallpox, and anthrax. Increasingly, the military has been forced to turn to smaller companies with less experience and fewer manufacturing resources to furnish these "limited use vaccines" or to terminate their supplies altogether. Philip Russell, former Commander of the U.S. Army R&D Command, has noted that, in light of recent DOD difficulties in procuring an anthrax vaccine, "it is becoming clearer and clearer that the government contracting mechanism is very poorly suited to assuring the supply of vaccines that are not economically attractive to the large manufacturers . . .."[40]

[40] P. Russell, "Vaccines for the Protection of the U.S. Forces: Research Success and Policy Failures," presentation to the Institute of Medicine: Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military, (Washington, D.C., April 3, 2000).

The "lack of an economic rationale" is the most commonly accepted reason given for failing systems of vaccine supply and innovation.[41] However, this explanation appears to be incomplete, since economic incentives for vaccine development were poor during the 40's and 50's as well, when innovation rates were high. What then has changed? Instead of asking "why is the traditional system of government contracting for vaccine development and supply failing and why are innovation rates falling?" federal planners should be asking, "why did the old system work in the first place?"

Chapter Two begins to answer this question by examining World War II vaccine development programs to reveal what made them effective in spite of poor economic incentives for commercial participation. Part of the success of these programs must be attributed to the urgency that surrounded the inception and mission of OSRD and SGO research and development programs. However a larger share of their success must be attributed to the organization of the programs themselves and to the collaborative relationships that they spawned. Of all the collaborative relationships formed, perhaps the most productive existed between military scientists, most notably those at the Army Graduate Medical School (later known as the Walter Reed Army Institute of Research or WRAIR), and industrial research scientists.

In an effort to understand the precise manner in which military-industrial collaboration fueled vaccine innovation, Chapter Three takes a detailed look at the relationships between individuals at National Drug, Merck, and WRAIR, examining their collective efforts to develop a meningitis vaccine and to improve the influenza vaccine. These cases depict the culture that surrounded vaccine development in the postwar era and demonstrate how the ideologies and practices that sustained personal networks of collaboration between military and industrial scientists continued to fuel vaccine innovation.

WRAIR scientists continued to make significant contributions to industrial vaccine development after the postwar era, but their opportunities to do so have diminished since the 1970's. Chapter Four explores the series of legal, economic, and political changes that disrupted the postwar culture for vaccine development.

In the private sector, a wave of product liability suits in the 1970's and '80's began to raise the cost and risk of vaccine development and vaccine manufacturers began to exit the industry in droves. After a decade of large-scale consolidation in the 1980's, the handful of large pharmaceutical firms that retained vaccine divisions possessed quasi-monopolies over individual vaccine product lines. Oddly, though, innovation rates continued to fall through the '80's and

[41] T. Monath, presentation to the Institute of Medicine: Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military,

'90's despite the economic opportunities of industrial consolidation and the technological opportunities afforded by advances in molecular biology.

These trends may be better understood with reference to the observation that military-industrial relations became strained towards the end of the Vietnam War. Industry began to question whether an overt association with military medical research offered a wise public relations strategy for an industry that relied on public trust, and Congress began to question the breadth of DOD funded research. Simultaneously, WRAIR lost its ability to draft top scientists at the end of the Vietnam War and began to lose its reputation as a "center of excellence" for infectious disease research. The DOD increasingly failed to support industry production costs for vaccine development, and manufacturers began to refuse low margin military contracts. Over time, industry stopped manufacturing vaccines of military significance, opportunities for military-industrial collaboration diminished, and overall rates of vaccine supply and innovation began to fall.

Chapter Five examines more recent transformations to the military-industrial culture for vaccine development and their effect on innovation and supply. By the mid-1990's, reduced levels of investment in infectious disease research and vaccine development began to seem shortsighted as a series of events raised the specter of bioterrorism. The 1995 Aum Shinrikiyo sarin gas attack in a Tokyo subway, followed by the Oklahoma City bombing a month later, awakened the Clinton Administration to the possibility that terrorist groups may attempt chemical or biological attacks on U.S. soil.[42] These events prompted a series of initiatives within the federal government to prepare for biological threats, and launched a new era in the history of vaccine development, an era characterized by renewed federal attention to the problems of vaccine innovation and supply for the purposes of national defense.

Renewed attention to the national security implications of disease extended to naturally occurring infectious diseases as well. For example, in April of 2000, the National Security Council classified AIDS as a security threat, placing it alongside national threats such as weaponized biological agents and other chemical and nuclear weapons of mass destruction.

Although there was evidence of renewed industry and government commitment to vaccine development by the mid-1990's, the airliner and anthrax attacks of 2001 mobilized the federal government and the pharmaceutical industry with a renewed sense of urgency, generating a spirit of cooperation that is reminiscent of industry-government relations on the eve of World War II.

(Washington, D.C., April 3, 2000).

[42] G. Koblentz, "Overview of Federal Programs to Enhance State and Local Preparedness for Terrorism with Weapons of Mass Destruction," BCSIA discussion paper, 2001-5, John F. Kennedy School of Government, Harvard University, (April, 2001).

Just as government officials in the 1940's worried about insufficient stocks of tetanus, typhus, yellow fever, and influenza vaccines, today they are concerned about low stocks of anthrax and smallpox vaccines. Similarly, just as Vannevar Bush (director of the OSRD) was besieged with offers of assistance from every large vaccine manufacturer after the bombing of Pearl Harbor, Tom Ridge (director of the Office of Homeland Security) has fielded similar offers from a host of pharmaceutical industry executives and lobbyists.[43]

This chemistry of urgency, patriotism, and opportunism was successfully translated into productive vaccine development programs during World War II. Is it possible to achieve the same results today? I demonstrate that urgency, in the absence of other non-market factors once present in earlier eras, will not suffice. Drawing on lessons from historically successful (and unsuccessful) vaccine development programs in this manner, I examine the opportunities and challenges that today's "war on terrorism" presents for efforts to improve vaccine innovation and supply.

[43] L. Wayne and M. Petersen, "A Muscular Lobby Tries to Shape Nation's Bioterror Plan," *New York Times*, November 4, 2001.

Chapter One: Historical Patterns of Vaccine Innovation

An empirical analysis of vaccine license data indicates a distinct trend in historical patterns of vaccine innovation since World War II. [1] The 1940's stand out as the period with highest rate of innovation. Since this time, however, innovation rates have declined in each subsequent decade. Reports examining the problems of vaccine innovation and supply have focused on the role of poor economic incentives to explain this decline. However, historical evidence indicates that economic incentives were poor when innovation rates were high (in the 1940's and 1950's), and were more favorable when innovation rates were low (in the late 1980's and 1990's). It appears, then, that a series of non-market factors have played an important role in driving historical patterns of vaccine innovation. In particular, a combination of empirical and historical evidence indicates that military-industrial collaborative vaccine development ventures may have generated historically high rates of innovation.

I. Methodology

Data Sources

The most direct and consistent way to measure historical patterns of innovation in the vaccine industry is to record the number of new and improved product licenses granted over time.[2] Unfortunately, publicly available vaccine license data is inaccurate and incomplete. An examination of the early history of individual vaccine companies, for example, revealed that many early product licenses, representing significant vaccine innovations, had not been included on lists of vaccine license data published by the FDA. This was troubling, given that most historical and empirical analyses of vaccine innovation have been based on the incomplete data provided by these FDA lists.[3]

Through the Freedom of Information Act (FOIA) I was able to obtain a more comprehensive list of all vaccine licenses issued since 1903 from the FDA's Center for Biologics Evaluation and Research (CBER). Unlike the FDA's currently published list, this list included vaccines that are no longer licensed or

[1] Vaccine innovation is measured by the number of licenses issued for new and improved product introductions per decade. A "new vaccine" is defined as the first safe and effective vaccine licensed to prevent a disease for which no form of active immunity was previously available. An "improved vaccine" is defined by enhancements to the safety and efficacy of a pre-existing vaccine.

[2] Given that living organisms and their derivatives were not patentable before 1980, license data offers a more direct and consistent measure of twentieth century innovation patterns than patent data. (*Diamond v. Chakrabarty*, Case 447. U.S. 303).

[3] Examples include: Office of Technology, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979); Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985). NAS); H. Grabowski, and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997); L. Galambos and J. Sewell, *Networks of Innovation* (Cambridge: Cambridge Press, 1995).

marketed in the United States. CBER warned, however, that they could not guarantee the accuracy of original vaccine approval dates before 1987, which is the date they assumed responsibility for the regulation of biologics and began to maintain their own database.[4]

CBER's reluctance to guarantee the accuracy of their data is understandable in light of the history and practices of the institutions responsible for the regulation of biologics. The name and/or location of the institution responsible for the regulation of biologics has changed at least seven times since the first for vaccine licenses were issued in 1903. From 1903-1930, licenses were issued from the Public Health Service Hygienic Laboratory. From 1930-1937, the Hygienic Laboratory issued licenses under the aegis of the NIH. From 1937-1955, responsibility for the regulation of biologics shifted to the Laboratory of Biologics Control (LBC). The LBC operated within the NIH until 1948, at which point it was absorbed by the National Microbiological Institute (later renamed the National Institute of Allergy and Infectious Diseases). From 1955-1972, the Division of Biologics Standards within NIH issued licenses. From 1972-1982, licenses were granted through the Bureau of Biologics within the FDA. In 1982-3 this became the Center for Drugs and Biologics. Finally, in 1987, CBER was created within the FDA to provide exclusive oversight and regulation of biologics exclusively.

Each regulatory body was concerned with maintaining an accurate record of currently licensed vaccines at a particular point in time, but not with maintaining records for licenses that had expired or for companies that had left the industry. Consequently, each time responsibility for the regulation of biologics shifted, data was lost or re-entered according to the practices of the inheriting organization. These reporting practices had the effect of under-reporting historical rates of innovation and over-emphasizing more recent contributions. It was therefore necessary to reconstruct a database with correct original approval dates in order to obtain a historically accurate picture of vaccine innovation patterns.

[4] Susan Raigrodski, CBER, interview with author, March 2, 2001.

Table 1: Institutions responsible for vaccine regulation

Date	Institution
1903-1930	Public Health Service Hygienic Laboratory
1930-1937	Hygienic Laboratory becomes part of NIH
1937-1948	Laboratory of Biologics Control- NIH
1948-1955	National Microbiological Institute- NIH
1955-1972	Division of Biologic Standards- NIH
1972-1982	Bureau of Biologics- FDA
1982-1987	Center for Drugs and Biologics- FDA
1987-Present	Center for Biologics Evaluation and Research- FDA

One strategy for reconstructing an accurate set of vaccine license data is to obtain lists of currently licensed vaccines dating back several decades. According to CBER, however, these lists were discarded over the years.[5] Some PHS publications proved useful in efforts to trace the introduction of vaccines back to original manufacturers and license dates, but these documents were published irregularly and they often lacked sufficient information about the vaccine to determine if license entries represented innovative activity.[6] In other words, one cannot always discern from these publications whether a license was issued for an improved version of a vaccine or for a version already in production elsewhere.

Previous attempts have been made to compile a more complete set of license data by filling requests with CBER to review the original approval letters issued to vaccine manufacturers. For example, Ronald Rader of the Biotechnology Information Institute submitted hundreds of Freedom of Information Act applications (FIOA's) to CBER for information regarding original approval dates. He found that "CBER/FDA has lost (or destroyed) most basic listings, license certificates, archives and other backup for the licensing activity of NIH DBS and earlier biologics regulators . . . Compounding this situation, CBER/FDA has lost capabilities for retrieving pre-1970's approval-related records, including approval letters, license certificates and other historically significant documents."[7]

In the absence of a reliable central repository for vaccine license data, I examined a wide variety of alternative primary and secondary resources to fill in the gaps in CBER's database. I scoured industry and

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[5] Ibid.

[6] *Biological Products: Establishments Licensed for the Preparation and Sale of Viruses, Serums, Toxins and Analogous Products, and the Trivalent Organic Arsenic Compounds*, Public Health Service, Publication No. 50. (Bethesda, MD, published sporadically from 1903-1937); *Establishments and Products Licensed Under Section 351 of the Public Health Service Act*, NIH (later FDA), (Bethesda, MD, published sporadically since 1938).

[7] R. Rader, *Biopharma: Biopharmaceutical Products in the U.S. Market* (Rockville: Biotechnology Information Institute, 2001).

federal archives for product records and letters referring to company vaccine licenses.[8] I cross-checked historical evidence gathered on vaccine license data against several anthologies and histories of vaccine development.[9] I also checked the accuracy of my historical data and CBER's data against publications issued from each agency responsible for the regulation of biologics over the past century.[10] Through these methods, I corrected several dozen entries and was able to add 66 license entries that had been lost over the years in agency shuffles.[11] The results of this exercise are detailed in Appendix 1.

Despite these additions and corrections, the data presented in Figures 1 and 2 is incomplete for the period prior to the passage of the Food Drug and Cosmetic Act of 1938, which, in addition to imposing stricter safety regulations, encouraged meticulous record keeping. For these reasons, my analysis of historical patterns of vaccine innovation begins with the 1940's.

Early studies on the problems of vaccine innovation and supply

By the late 1970's, the federal government began to sponsor a handful of studies to examine the condition of U.S. systems for vaccine innovation and supply. Congress, medical professionals, and industry became interested in this topic after a large number of vaccine manufactures began to exit the industry in the mid- and late 1970's. Due to the irregularities of vaccine license record-keeping described above, these studies struggled to provide an empirically consistent analysis of vaccine innovation.

The Office of Technology Assessment (OTA) issued one of the earliest studies on the topic of vaccine innovation and supply in 1979.[12] This study was commissioned by Congress in response to a series of

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[8] Merck Archives, (contains records from Mulford Labs, and Sharp and Dohme), Whitehouse Station, NJ; Aventis-Pasteur Archives (contains records from Pocono Labs, Swiftwater Labs, National Drug, Merrell-National, Connaught, and the Salk Institute), Swiftwater, PA; NA II (NIH and FDA records), College Park, MD; Walter Reed Army Institute of Research, records in the Joseph Smadel Reading Room, Silver Spring, MD.

[9] S. Plotkin and E. Mortimer, *Vaccines*, 2nd ed. (Philadelphia: WB Saunders Co., 1994); H. J. Parish, *A History of Immunization* (London: E & S Livingstone Ltd., 1965); S. Plotkin and B. Fantini, eds., *Vaccinia, Vaccination, and Vaccinology: Jenner, Pasteur, and Their Successors* (Paris: Elsevier, 1995); A. Chase, *Magic Shots* (New York: William Morrow and Company, 1982).

[10] *Biological Products: Establishments Licensed for the Preparation and Sale of Viruses, Serums, Toxins and Analogous Products, and the Trivalent Organic Arsenic Compounds*, Public Health Service, Publication No. 50. (Bethesda, MD, published sporadically from 1903-1937); *Annual Reports of the Public Health and Marine Hospital Service of the United States*, Treasury Department, U.S. Government Printing Office; *Establishments and Products Licensed Under Section 351 of the Public Health Service Act*, NIH (later FDA), (Bethesda, MD, published sporadically since 1938).

[11] CBER's list contained 252 vaccine licenses. This excluded licenses issued to foreign companies and excluded vaccines licensed in bulk for further manufacturing use. Using the same criteria for inclusion and exclusion, my final list contained 318 licenses.

[12] Office of Technology, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979).
This report was prepared by the OTA staff which consulted industry representatives (Eli Lilly, Merck, and Lederle Laboratories), government agencies (BOB, CDC, NIAID, National Center for Health Statistics, Bureau of the Census), and Universities (Duke University, Harvard University, University of Pennsylvania, and the University of California, San Francisco).

disturbing vaccine industry trends that emerged in the 1970's. In an effort to outline these trends, the report noted heavy consolidation in the vaccine industry with the number of licensed manufacturers dropping from 37 in 1967 to 18 in 1979. Of the 18 licensed to manufacture vaccines, only 8 were actively manufacturing vaccines for the U.S. market and these 8 companies held 70% of the then currently active product licenses.[13] The OTA study also observed that the number of licensed biological products on the market dropped from 385 in 1968 to 150 in 1979.[14] This is a measure of supply rather than innovation, however, since it measures the quantity of products on the market rather than the number of licenses representing new and improved vaccine products.

Due to the problems with vaccine license data, the OTA was not able to demonstrate declining levels of vaccine innovation. Nonetheless, dramatic reductions in the number of licensed manufacturing establishments bred concern that innovation would eventually suffer. In an attempt to outline the reasons for these signs of decline, the report highlighted a number of economic disincentives stemming from high competition among producers and low margins in the industry. The study also faulted a rash of product liability cases in the 1970's that increased the cost and risk of participating in the vaccine business.[15]

While the OTA study heightened awareness of the innovation and supply problems facing the vaccine industry, no significant action was taken in response to its findings. As the vaccine industry continued to show signs of strain, with more firms leaving the market, and reduced R&D investments, the Institute of Medicine (IOM) followed in 1985 with another study outlining the problems of vaccine innovation and supply. Recognizing a growing tension between industry's need to divest themselves of an unprofitable business and society's need for an adequate supply of safe and effective vaccines, the IOM report committee observed that the market demand for vaccines was not sufficient to support socially optimal levels of vaccine innovation. It stated: "our reliance on market incentives to ensure vaccine availability may lead to a failure to meet public health needs. Also, these incentives may not result in optimal levels of vaccine innovation."[16]

Like the OTA, the IOM was not able to substantiate their concern that poor economic incentives were causing vaccine innovation rates to suffer. Again, this failure was due to the difficulties of obtaining historically accurate vaccine license data. The OTA and IOM vaccine innovation studies based their

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[13] Ibid.

[14] "Biologicals" refer to a category of products that includes bacterial and viral vaccines, antigens, antitoxins, toxoids, serums, plasmas, and blood derivatives for human use.

[15] The OTA was also concerned that the rash product liability suits would undermine government and industry support for large-scale immunization programs. Specifically, the OTA was concerned that, in the wake of the Swine Flu Affair of 1976 (see Chapter 4), the media was giving an unbalanced picture of the risks and benefits associated with vaccination. Thus, this study also offered the OTA an opportunity to apply cost-effectiveness analyses to particular vaccination campaigns in an effort to evaluate the costs and benefits of immunization on a more rational scale.

[16] Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C., National Academy Press, 1985), v.

findings on lists of currently licensed vaccines. Given the considerable difficulties in obtaining historically accurate records of vaccine license data, the decision to proceed based on abbreviated lists of currently licensed vaccines is understandable, since this information was readily available and easily verifiable. However, this approach systematically underreports new product licenses that have since been revoked, replaced, or renamed, and therefore underestimates innovation rates from earlier decades. Furthermore, FDA reporting practices have inflated the record of innovative activity in recent decades. Since the 1970's, the FDA has issued new licenses for activities that do not represent innovative activity, such as changes to the name of a vaccine or the transfer of a license between companies. These superficial changes account for 65% of the new licenses issued since 1970.[17]

When one takes incomplete license data and FDA/CBER reporting practices into account and examines innovation patterns based on historically researched and analyzed license data, the historical patterns of vaccine innovation look very different from those depicted in the OTA and IOM reports. For example, to measure innovation, the OTA tabulated the number of licenses representing new vaccines over time.[18] Basing their analysis on a list of currently licensed vaccines provided by the Bureau of Biologics in 1979, they examined 49 vaccine introductions since 1903.[19] Their study showed no significant changes in the historical rate of vaccine innovation. Using this same methodology, the IOM used the FDA's 1983 list of currently licensed vaccines, which indicated only 34 significant vaccine introductions since 1903. Their study therefore suggested that vaccine innovation rates had increased considerably since the 1940's. These findings are an artifact of inaccurate FDA data. For example, a significant portion of the original license data was lost when records were transferred from the Bureau of Biologics (BOB) to the Center of Drugs and Biologics in 1982. In lieu of the missing data, vaccines were re-entered into the FDA database according to their more recent approval dates, creating the false impression that there was a spate of innovative activity in the 1970's.

To illustrate the way in which vaccine license data sources bias the perception of innovation patterns, I applied OTA and the IOM methodologies for selecting new vaccine introductions to my own data set of historically researched vaccine license data (Table 2). Clear differences in innovation patterns emerged based on the vaccine license data used. As predicted, reliance on lists of currently available vaccines, particularly after NIH-FDA shift in 1982, systematically over-reported recent innovations and under-reported earlier innovations.

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[17] See Figure 2.

[18] "New vaccines" are defined by the OTA and IOM studies as the first recorded license for a previously unavailable vaccines, antitoxins, or combinations thereof.

[19] This particular list also includes product introductions from foreign companies.

Table 2: Historical patterns of vaccine innovation based different vaccine license data sets

New Vaccine Product Introductions			
	OTA (1979)[20]: BOB, "Currently Licensed vaccines in 1979"	IOM (1985)[21] FDA, "Currently licensed vaccines in 1983"	Historically researched vaccine license data[22]
Before 1940	10	Not recorded	11
1940-1949	9	4	11
1950-1959	10	2	9
1960-1969	10	10	10
1970-1979	10	14	8
1980-1989		4 (1980-1983)	2
1990-1999			5

Thus, while incomplete data sets led the OTA to conclude that there was no change in the rate of innovation from the 1940's through the 1980's and IOM to report that innovation had improved during this period, Table 2 demonstrates that when one applies OTA/IOM methodologies to a more complete set of vaccine license data, it becomes clear that innovation rates have in fact been falling since the 1970's. The failure of these studies to demonstrate a clear decline in innovation rates may have contributed to the failure of government officials to respond to OTA or IOM recommendations to improve national systems of vaccine innovation and supply.

Biases arising from a lack of historical data are also evident in a recent report on the vaccine industry by the American Enterprise Institute (AEI), which asserted that the 1980's and 1990's were characterized by an industry-wide "renaissance" of vaccine innovation.[23] The authors based this claim in part on evidence of renewed levels of vaccine R&D investments within the pharmaceutical sector and on higher levels of collaboration between the pharmaceutical and biotechnology sectors.[24] They demonstrated that the portion of company R&D budgets devoted to biologicals fell from 5% in the early 1970's to less than 2% in the early 1980's, and that investments rebounded after 1986 to 4-5% in the early 1990's.[25] The

[20] Office of Technology, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979), 31. See Table 5.
[21] Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985), 50. See Table 4.3.
[22] See Appendix One for the list of historically researched license data.
[23] H. Grabowski and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997), 8.
The AEI study examined industry incentives to invest in vaccine R&D in an effort to evaluate the effects that a 1994 proposal for the government to buy and stockpile pediatric vaccines (Vaccines for Children Program) would have on commercial vaccine innovation patterns. The AEI consulted members of the CDC, FDA, Merck, Wyeth-Ayerst, and Aviron.
[24] Ibid., 8.
[25] Ibid., 9.
Grabowski and Vernon assert that vaccines comprise the majority of products represented in the "biologicals" category.

authors concluded that these increases reflected excitement in the industry stemming from the application of biotechnology to vaccine development and improved economic incentives following the passage of the Vaccine Compensation Act in 1986.

Just as the OTA and IOM studies failed to demonstrate a connection between adverse industry trends and innovation levels, the AEI study fails to provide adequate evidence that positive industry trends (in the form of renewed levels of industry R&D investments) have translated into higher levels of innovation. Again, this failure stems from a dearth of historically accurate license data. Under the circumstances, the authors rely on individual anecdotes to extrapolate industry-wide trends. As proof of a "renaissance" in vaccine innovation, they cite a handful of individual cases of new vaccine development: "new and improved vaccines, including combinations, have been introduced over the past decade for Haemophilus influenza type b, hepatitis A and B, varicella, and pertussis."[26] Contrary to these individual observations, when one examines a historically accurate set of vaccine license data, it becomes clear that the overall rate of significant innovations in recent decades has been, on average, lower than any other decade in the past fifty years (see Figure 1).

Results

Historically accurate vaccine license data and innovation patterns are displayed in Figures 1 and 2. Whereas Table 1 merely records the first introduction of a new vaccine, a large portion of vaccine innovation consists of making incremental improvements to the safety and efficacy of a product. To reflect this, Figures 1 and 2 include vaccine licenses issued for significant improvements to previously existing vaccines. Each license issued is classified according to the level of innovative activity represented.[27] There are five categories of vaccines that represent innovative activity in Figure 1. These licenses are designated with a "C", "I", "P", "A", or occasionally "R" in Appendix 1. "C" designates licenses that represent "component innovation" or the introduction of new antigenic material in a vaccine.[28] "I" indicates "incremental innovations" or improvements to the purity or immunogenicity of the antigenic material contained in a vaccine. Incremental innovations may also include significant changes to the dosage and a new indication for a vaccine. For example, an altered dose of the BCG (tuberculosis) vaccine was licensed in 1990 to treat bladder cancer. "P" refers to "process innovations", or improvements to the method of vaccine delivery or manufacture. Examples include the reformulation of the adenovirus vaccine from an injected to an oral vaccine, or the transformation of the hepatitis B vaccine from a plasma-

[26] Ibid., 8.

[27] See Appendix 1 for this list of all vaccine licenses by innovation type.

[28] These terms are derived from typologies used by Rebecca Henderson and James Utterback to distinguish among innovation types. See R. Henderson and K. Clark, "Architectural Innovation: The Reconfiguration of Existing Product Technologies and the Failure of Established Firms," *Administrative Science Quarterly* 35 (1990): 9-30;

derived vaccine to a recombinant vaccine derived from yeast cells. "A" refers to "architectural innovations" that combine elements of previously developed component innovations. Examples include the development of a combined measles, mumps, and rubella vaccine. "R" refers to "radical innovations" in which a vaccine incorporates both component and process innovations. One such example is the development of pneumococcal capsular polysaccharide vaccine in 1948, which incorporated a new component using a novel process.

There are also two categories of vaccines that do not represent innovative activity. For example, in many cases, regulators issued licenses for superficial name changes or license transfers associated with industry consolidation. Similarly, in 1990's, the FDA began to issue license supplements for trivial changes to the indication, dosing, or formula of a vaccine. These licenses are designated "LT" (license transfer) and "IS" (Incremental- Supplementary), respectively. Neither LT or IS licenses represent significant innovative activity and they are therefore excluded from Figure 1.[29] Figure 1 represents licenses in all five remaining categories, which reflect some degree of innovative activity.

J. Utterback, *Mastering the Dynamics of Innovation* (Boston: Harvard Business School Press, 1994).

[29] I have also excluded licenses issued to vaccines that had been developed outside of the U.S., thereby creating a data set that is representative of vaccine innovation in the U.S.

Figure 1: Licensed Vaccines Representing Innovative Activity

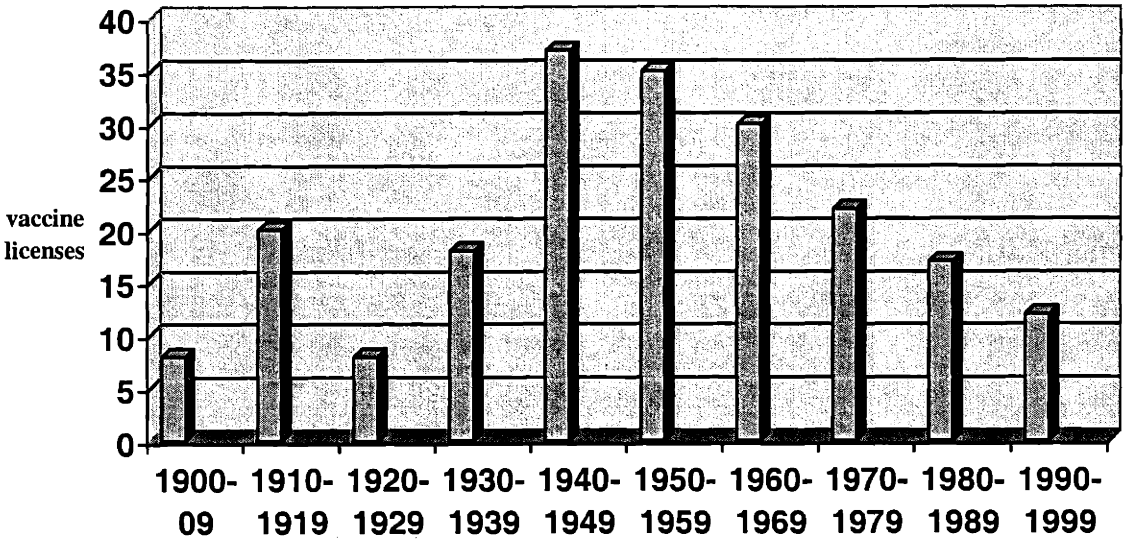
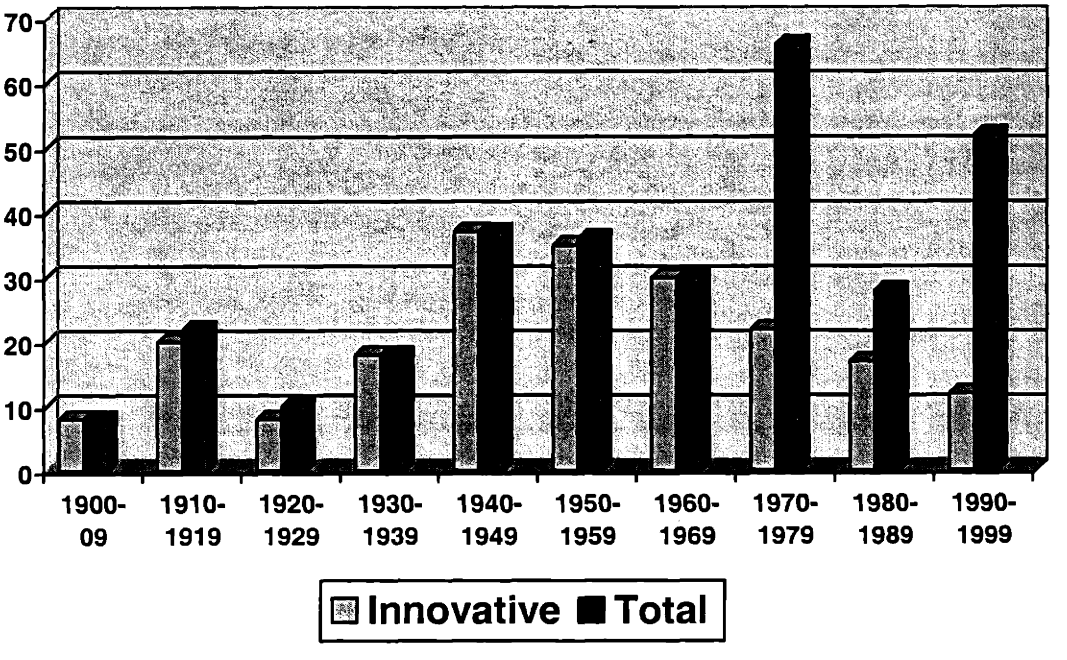


Figure 2: Total Licenses verses Licenses Representing Innovative Activity



Licenses representing non-innovative activity form a significant portion of licenses issued since the 1970's [Figure 2] for several reasons. First, due to heavy industry consolidation during this period, many licenses for previously developed products were transferred to new or merged companies, with each transfer resulting in a new license for the new owner. Second, as discussed above, when the FDA assumed responsibility for the regulation of biologics from the NIH in 1982, they lost many original approval dates and replaced these with more recent approval dates for older vaccines, accounting for the apparent spate of innovative activity in the 1970's. Finally, as vaccine regulations became more stringent in the 1980's and 1990's, the FDA began to require approval in the form of product license supplements for minor changes to the formula, dosing, or indication for a vaccine.

The license data in Figure 1 clearly demonstrates that the 1940's experienced the highest rate of vaccine innovation and that each subsequent decade has witnessed a steady decline. These findings support the concerns that motivated the OTA and IOM reports and cast doubt on more recent claims that the vaccine industry is experiencing a rebirth of innovative activity.

II. Why are vaccine innovation rates declining?

The most common reasons given to explain changing rates of vaccine innovation focus on the presence or absence of economic incentives. The OTA, IOM and AEI reports, for example, rely almost exclusively on the presence or lack of market incentives to explain innovation and supply trends. The OTA, for example, noted that vaccine sales are limited by the national birth rate and that this limited demand cannot support a large number of producers.

Product liability

The OTA study also observed that the rising costs from legal liability and tighter federal regulations undercut profits from vaccine sales, thereby discouraging industry investment in vaccine R&D. The IOM report shared the OTA's concern over rising legal liability costs, a trend that began after the swine flu affair in 1976. Data provided to the IOM committee from one pharmaceutical company indicated that their vaccine operations, which contributed less than 5-15 % of overall sales, were responsible for 40% of all liability claims.[30] Such data left little doubt in the minds of committee members that the pharmaceutical industry would prefer pharmaceutical to vaccine investments in the future, thereby jeopardizing future rates of vaccine innovation.[31]

[30] Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985), 53.

Government regulation

The IOM also asserted that stricter regulatory control over the manufacture of biologicals raised the cost of vaccine development and thus served as a disincentive to investment. A 1962 congressional amendment to the Food, Drug and Cosmetic Act introduced proof of efficacy requirements in addition to improved safety regulations. Initially, the OTA noted that this amendment had no visible effect on number of licensed products and establishments; "during the next five years, the number of licensed products dropped very little from 369 to 385 and the cumulative number of licensed establishments dropped by two."[32] One reason for this may be that this new legislation proved difficult to enforce. The regulatory standards for biologicals were stipulated in a fragmentary fashion under portions of both the Public Health Service Act and the Food Drug and Cosmetic Act. Further, the FDA did not have authority to enforce these new safety and efficacy standards on vaccines already on the market. It was not until 1972 that the FDA combined PHS regulations with the 1962 amendments to create a uniform set of standards for vaccine safety and efficacy. Based on these standards, in 1973 the FDA began to exercise its authority to remove vaccines from the market that were not in compliance with these standards. Pharmaceutical companies consulted by the IOM commission argued that, once these regulations were more strictly enforced in the 1970's, it raised their cost structures making it more difficult for U.S. manufacturers to compete internationally against foreign firms.

Pharmaceutical companies did not provide information on their cost structure for vaccine development and thus it is difficult to test the validity of these claims. However, there is some empirical evidence to suggest that these regulations had a negative effect on innovation and supply. Based on an analysis of vaccine license data in Appendix 1, between 1973 and 1980, 53 vaccine licenses were revoked. Though the data does not indicate reasons for revocation, this is significantly higher than the 22 vaccine licenses that were revoked in the 8 years prior (1965-1972).[33] However, it is not clear that a large number of these revocations can be attributed to higher regulatory standards. A large number of these revocations apply to Eli Lilly, Dow Chemical, and other large license holders who exited the vaccine business at this time. Furthermore, these companies cited high liability costs rather than the costs of adhering to stricter regulatory standards as the reason for their departure.

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[31] See Chapter Four for a more complete discussion of the effects of product liability on industry incentive structures during this period.

[32] Office of Technology, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979).

Market structure

The monopsony power of the government was also a source of concern for the authors of the IOM report. As the largest single buyer of vaccines (government purchases account for approximately 50% of all pediatric vaccine sales), the government has the power to drive down the price of vaccines, thereby creating another disincentive for industry investment. Supporting the claim that the government has the power to drive down vaccine prices, the AEI report observed that the ratio of public to private prices for major childhood vaccines such as DTP and MMR ranged from 25 to 54 percent in 1997.[34] They too were concerned with the impact of the market structure on incentives for industry investment in vaccine development.

The AEI report also identified a broad range of economic disincentives that compound the problems of market structure. It explained that vaccine development requires high capital investments, that these investments generate a lower rate of return than investments in drug development, and that vaccine investments are hard to recoup. Much of the argument is based on the fact that vaccines, unlike pharmaceuticals, have dual licensing requirements, meaning that, in addition to obtaining product licenses, a vaccine plant must obtain and renew an establishment license to operate. For this reason, a pharmaceutical company must begin investing in vaccine plant construction at an earlier date than for drugs. The AEI report argues that, given the time value of money, vaccine plant investments generate a lower internal rate of return than do pharmaceutical plant investments. The maintenance costs are higher for vaccine plants as well, since plants are subject to chronic FDA inspections to ensure that they satisfy requirements for Good Manufacturing Processes and a new establishment license is required each time a new vaccine reaches Phase III clinical trials. Moreover, because the process of scaling-up vaccines from pilot to commercial production is complex and can often result in a vaccine with different safety and efficacy qualities, the FDA strongly recommends that companies scale-up manufacturing before the vaccine ever enters Phase III trials.[35] This practice requires heavy up-front investments for a vaccine that may not receive approval. Furthermore, because the manufacture of biologicals can produce more variable outcomes than the manufacture of chemicals, the FDA periodically tests individual vaccine batches before they are released. This rigid control over the production process leaves little room to introduce manufacturing process improvements and limits manufacturing learning curve effects. Finally, the AEI report argues that investments in vaccine development are harder to recover, because it is difficult to decontaminate vaccine plants and convert them to other uses.

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[33] These numbers do not include smallpox vaccine license data; these licenses were cancelled in the late 1970's in response to eradication of the disease, not in response to higher regulatory standards.

[34] H. Grabowski and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997).

Vaccines verses pharmaceuticals

Perhaps the greatest source of economic disincentive is inherent in the concept of a vaccine itself. A product that is supposed to offer long-term immunity after a minimal dose confounds a host of profit-making strategies employed by pharmaceutical companies, who would prefer high-volume repeat sales to recuperate R&D investments and to profit from economies of scale and manufacturing learning curves. Further, private medicine and the pharmaceutical industry have always preferred therapeutic measures to the preventative measures favored by institutions like the Public Health Service and the military that strive to practice population-based medicine. One industrial research scientist explains: "Curative measures are more profitable in general because demand is always highest in the face of a salient illness. The need for curative measures is more chronic than outright prevention, which kills its own market after the first few immunizations. The vaccine industry puts itself right out of business."[36]

III. The limits of market-based accounts of vaccine innovation

Although economic disincentives play a role, they do not fully account for historical patterns of vaccine innovation for one simple reason: market conditions were unattractive in the 1940's and 1950's when innovation rates were particularly high, and relatively more attractive in the late 1980's and 1990's when innovation rates were particularly low.

The AEI study faults the rising cost of R&D and government regulation for the "slump" experienced in the 1970's. However, vaccine development in the 1940's entailed heavy-up front research costs as well. Indeed, before cell-culture techniques were perfected in the 1950's, research and development costs may well have been higher in the 1940's, than in the 1970's, because researchers had to use less efficient and more expensive animal models to grow viruses.

Similarly, although regulatory standards were not as strict in the 1940's as the 1970's, vaccines have always been at a comparative disadvantage to pharmaceuticals and larger companies have always had the option of shifting investments out of their vaccine divisions and into their less strictly regulated drug divisions. For example, vaccines, unlike pharmaceuticals, have been subject to dual licensing requirements (both the product and the establishment that produces it must be approved) and to individual

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[35] Phase III trials represent the last stage of FDA testing after efficacy has already been determined in a group of 100-200 human subjects. In Phase III, vaccine candidates are tested on large groups of human subjects (between several hundred and several thousand) to assess safety, efficacy, and optimal dosages for a wider demographic.
[36] Dr. James Sorrentino, former vaccine research scientist at the National Drug Company in Swiftwater, PA, interview by author, May 25, 2001.

batch testing from the moment that the federal government assumed responsibility for the regulation of biologicals in 1902.

Finally, though no precise figures are available, one can assume that monopsony power dynamics also existed during the 1940's; the civilian market for vaccines was still quite small and government purchases for military vaccines were at record highs in this time period. According to records from the National Drug Company, nearly 100 percent of its output supplied the Armed Forces during World War II.[37] After a brief slump immediately after World War II, the government became the largest single buyer of vaccines again during the Korean War, accounting for fifty percent of all sales at National Drug. Large government contracts brought sales at National Drug to an all-time high of $2 million in 1951, yet the low prices negotiated for these contracts diminished margins considerably. By 1953, A.B. Collins, President of National Drug, acknowledged that net earnings were falling despite record sales. During the 1940's and 1950's vaccines were sold for pennies on the dose. It was well understood that the vaccine industry did not generate significant margins, and many companies maintained vaccine divisions out of a sense of public and patriotic duty. One industrial research scientist observed that, even in the 1970's, "all pharmaceutical companies had a vaccine business and looked at it as a public service by the company, not as huge revenue generators--which they weren't."[38]

Curiously, by the late 1970's and early 1980's, rates of innovation began to fall at the same time that prices rose and the vaccine business became more profitable. Dr. Donald Metzgar, a vaccine research scientist at Aventis-Pasteur (formerly Connaught) since 1966, offers some insight into what was going on during this time period.[39] He explains, "ironically, Connaught began to make more money on vaccines when litigation became so prevalent. We couldn't get insurance because the price had gotten so high . . . Connaught started to charge more money to cover self-insurance needs. There was a period of time when we didn't sell anything- almost drove ourselves out of the market. Eventually, other companies began to look at what we were doing and followed suit."[40]

Pricing data from that time period support his claim. Data provided by the CDC demonstrates that vaccine prices rose at a relatively faster rate than drug prices during this period (roughly 1978 to 1982).[41] Data for vaccines sold to the federal government indicates that, after a series of price decreases during the

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[37] J. Widmer, *The Spirit of Swiftwater* (Swiftwater, PA: Connaught Laboratories, 1997), 45.
The National Drug Company is a Philadelphia based drug company with a biologicals division in Swiftwater, PA since 1926.

[38] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.

[39] Dr. Metzgar joined the National Drug Company in 1966 when it was a division of Richardson-Merrell. Richardson-Merrell donated the National Drug division to the Salk Institute, which, in turn, sold the division to Connaught in 1978. After a series of mergers, the division became part of Aventis Pasteur in 1999.

[40] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.

[41] Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985), 60. See Table 4.10

1970's, prices jumped considerably after 1978.[42] One can assume that price jumps in private vaccine markets were even steeper, since consumers in these markets had less bargaining power than the government.

Margins on vaccine sales continued to grow through the 1980's and 1990's. After Congress passed the National Vaccine Compensation Act of 1986 to limit industry liability for vaccine injuries, the government placed a surcharge on the sale of all vaccines to create a fund to manage liability claims. This legislation removed the need for industry to self-insure through price hikes. And yet pharmaceutical companies continued to raise their prices.[43] This is due, in part, to changes in the competitive landscape for vaccines. Consolidation gave surviving firms a greater controlling share of the market. The four largest remaining firms-- Merck, Wyeth-Lederle (division of American Home Products), Aventis-Pasteur, and GlaxoSmithKline-- went from controlling 50% of the U.S. market in 1988 to controlling 75-80% in 2001.[44] Further, several of these firms developed monopolies in non-competing product lines. Merck, for example, became the sole supplier of combined measles, mumps and rubella (MMR) and varicella vaccines, Wyeth-Lederle of combined diphtheria, tetanus, and pertussis (DTP) and conjugate pneumococcal vaccines, and Aventis-Pasteur of the meningitis, polio, and yellow fever vaccines.

Industry consolidation did not merely improve the profitability of the market; there is also evidence that companies responded by re-investing in higher levels of vaccine R&D.[45] Why then did innovation rates continue to suffer? It appears that market factors by themselves do not explain these trends in vaccine innovation and one is led to consider non-market factors.

In an effort to understand what some of these non-market factors may be, I shifted my attention from the macroscopic view afforded by vaccine license data to focus on the developmental history of individual vaccines. In the course of doing so, I was struck by the large number of vaccines that were developed or sponsored by military medical research programs. To illustrate the scope of military contributions to commercial vaccine development, I have provided a brief developmental history of vaccines licensed in the United States (Table 4). Most notably, this table demonstrates that that the military has made significant contributions to well over half (18) of the vaccines licensed to fight 28 distinct diseases since the turn of the century.[46] The heaviest concentration of military contributions occurs during the 1940's

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[42] Ibid. See Tables 4.9 and 4.10.

[43] DTP vaccine pricing was an exception to this trend; H. Grabowski and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997), p. 3, Table 1-1 "Private catalogue prices and Federal contract prices per dose for children's vaccines, 1985-1996 (dollars)."

[44] *The New York Times*, July 2001; A. Bateson and M. Bekier, "Vaccines Where They Are Needed," *McKinsey Quarterly*, Special Edition (2001): 103.

[45] H. Grabowski and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997).

[46] This list merely highlights the initial development of the vaccine and significant improvements to its safety and efficacy. For the sake of simplicity, this list does not include combination vaccines such as DTP and MMR and it does not represent the early development of anti-toxins.

with many vaccines coming out of World War II vaccine development programs. Vaccine license data in Appendix 1 reveals that 26 out of the 37 vaccines licensed during the 1940's (70%) derived from World War II vaccine development programs [Table 3].

The decades following World War II did not witness the same degree of military-industrial collaboration in commercial vaccine development. For reasons discussed in Chapter Four, the opportunities for military-industrial collaboration have diminished since the late 1970's. As the rate of military-industrial collaboration diminished, so too did overall rates of innovation [Table 3]. However, though military contributions have decreased in number in recent decades, they have not diminished in significance. For example, in the 1980's, WRAIR worked closely with SmithKline-Beecham to license the first hepatitis A vaccine. DOD labs overseas were also used in the 1980's and 1990's to perform clinical trials that led to the licensure of a hepatitis B vaccine and a new generation Japanese encephalitis vaccine.

I.V. Conclusions

The vaccine license data presented in Figures 1 and 2 is more comprehensive than any other publicly available data set and offers the best existing approximation of historical patterns of vaccine innovation since 1940. Analysis of this data reveals that military research made significant contributions to well over half of all major vaccines developed in the U.S.. Furthermore, the data demonstrates that the highest rates of innovation (1940's) correspond with the highest rates of military-industrial collaboration, whereas the lowest rates of innovation (1980's and 1990's) correspond with the lowest rates of military-industrial collaboration. These findings suggest that military-industrial collaboration has exerted a significant and positive influence on vaccine innovation since World War II. In an effort to understand the precise manner in which military-industrial collaboration influenced historical patterns of vaccine innovation, subsequent chapters explore the historical circumstances and cultural factors that sustained these collaborative relationships.

Table 3: Innovation Trends and Military Contributions

Decade	Number of licenses representing innovative activity	Percent of licenses derived from military sponsored research (numbers rounded)
1940	37	70%
1950	35	49%
1960	30	53%
1970	22	36%
1980	17	24%
1990	12	8.3%

Table 4: Development History of Vaccines Licensed in the United States

Disease or Pathogen	First Isolation	Vaccine developed	Licensure	Innovation Type	Military Contribution
Adenovirus	1953 Hilleman and Werner (WRAIR) isolate RI-67 from adenoidal tissue of recruits at Fort Leonard Wood	1959-60 Inactivated vaccine developed at WRAIR[47] 1964 live vaccine-Type 4: Dr. Chanock at NIAID[48] and WRAIR Type 7[49]	**1957** Parke-Davis[50] Inactivated vaccine **1980** Wyeth-live oral enteric coated- human diploid and green monkey kidney cell lines	Component Process	Clinically recognized by AEB '41-43 Virus identified and isolated; inactivated vaccine developed by WRAIR Developed live enteric coated oral vaccines in collaboration with NIAID
Anthrax	*Bacillus anthracis*: 1876 Koch	1881 Pasteur live attenuated vaccine for animals 1948 Gladstone (Lister Institute) and USAMRIID: formaldehyde inactivated vaccine for humans; alum precipitated, bacteria-free antigen: grown in synthetic liquid medium	1950 Merck 1965 MPBI produce for DOD **1970** MBPI	 Process-new strain and manufacturing process: less reactogenic	1948 Gladstone and Ft. Detrick scientists developed pilot vaccine 1950 Merck scale-up attenuated vaccine for USAMRIID sponsored field trials 1980- USAMRIID tests efficacy against inhalation form on monkeys
Cholera	*Vibrio cholerae:* Koch 1883	1896 Kolle: rudimentary agar grown, heat inactivated, whole cell vaccine	**1917** Lilly-inactivated **1952** Wyeth - agar grown, phenol inactivated (in current use) **1968** Bayer-live oral vaccine: enteric coated tablets	Incremental[51] Process-chemically inactivated Process	1940's: Army Medical School selected and standardized the strains (Inaba and Ogawa serotypes) used in commercial vaccine production
Diphtheria	*Corynebacterium*	1922: Park, TAT mixtures	1922 New York Public Health	Process –first sub-unit vaccine	1954: Army studies indicate that smaller doses

[47] Hilleman discovered that formalin failed to kill SV40 Simian viruses in the inactivated vaccine, which are oncogenic in hamsters. This prompted the search for an alternative vaccine.
[48] Chanock et al., "Immunization by Selective Infection with Type 4 Adenovirus Grown in Human Diploid Tissue Culture," *JAMA* 195 (1966): 445.
[49] F. Top et al., "Immunization with Live Types 7 and 4 Adenovirus Vaccines," *Journal of Infectious Disease* 124 (1971): 148-160.
[50] Vaccines that have been licensed have the date of licensure highlighted in bold type.
[51] Though this is the first recorded license for cholera, the Lilly vaccine is not significantly different from the original Kolle vaccine.

	diphtheriae: Klebs 1883 Loeffler 1884 (Institute of Infectious Disease, Berlin)	1923: Glenny, Hopkins- formalinized toxoid[52] 1928 Glenny, precipitation with alum adjuvant enhances immunogenicity	**1927** Parke-Davis diphtheria toxoid **1949** Parke-Davis, National Drug diphtheria toxoid adsorbed[53]	Process- active immunization Process- improved immunogenicity	of toxoid reduced reactogenicity without compromising immunogenicity; permitted the development of combined diphtheria tetanus toxoids[54]
Haemophilus influenzae B: source of bacterial meningitis for children under 5 (also causes pneumonia and Otitis media infections- but vaccine does not protect against these non-typeable NTHi strains)	1892	1920's Avery developed methods to conjugate polysaccharides and proteins to improve immunogenicity[55] 1980, Schneerson and Robbins (BOB) revived work on conjugated vaccines[56]	**1985** Lederle, Connaught, Praxis: unconjugated HIB vaccine **1987** Pasteur Merieux Connaught	Component- does not elicit immunity in infants who are at greatest risk for the disease Process- conjugation improves immune response by inducing proliferation of helper T-cells; safe for children under 18 months.	
Hepatitis A	1976- HM-175 strain isolated in Australia Host line developed by NIAID: Isolate strain and adapt host line	Inactivated Inactivated	**1995** SKB **1996** Merck	Component Process- first use of nuclease enzyme in purification process: improves purification	1985 first pilot lot dev. at WRAIR. 1986 WRAIR demonstrate immunogenic in humans 1987 WRAIR transfers manufacturing capability to SKB, trains corporate

[52] A. Glenny and B. Hopkins, "Diphtheria Toxoid As an Immunizing Agent," *British Journal of Experimental Pathology* 4 (1923): 283; In this same year, Gaston and Ramon developed a toxoid that did not need to be administered in conjunction with an antitoxin.

[53] According to CBER data, the first license for diphtheria toxoid adsorbed was approved in 1949. However, some army records indicate earlier use of adsorbed diphtheria toxoids.

[54] G. Edsall, J. Altman, and A. Gaspar, "Combined Tetanus-Diphtheria Immunization for Adults," *American Journal of Public Health* 44 (1954): 1537.

[55] O. T. Avery and W. F. Goebel, "Chemo-Immunological Studies on Conjugated Carbohydrate Proteins," *Journal of Experimental Medicine* 50 (1929): 533.

[56] R. Schneerson et al., "Preparation, Characterization, and Immunogenicity of HIB Polysaccharide-Protein Conjugates," *Journal of Experimental Medicine* 152 (1980): 361.

[57] P. Provost and M. Hilleman, "Propagation of Human Hepatitis A Virus in Cell Culture in Vitro," Proceedings *of the Society of Experimental Biological Medicine* 160 (1979): 213-221.

	to human diploid cells 1979- Hilleman and Provost: first successful attempt to grow HepA in cell culture[57]			without compromising yield[58]	scientists, assists with scale up of pilot procedures under no-dollar agreement. 1988 AFRIMS and Thai ministry of health- large scale trials in Thailand; USAMMDA coordinates licensure application for SKB
Hepatitis B	1960's: HbsAg- Hep B surface antigen isolated by Blumberg et al. (Wistar Institute), linked to disease, and developed serological test to measure presence of antigen and its antibodies[59]	Inactivated sub-unit vaccine- plasma derived Recombinant- engineer yeast cell line (portion of HBV gene coding for HBsAg into yeast cell) to express surface antigen similar to HBsAg isolated in plasma of chronic HBV carriers	**1981** Merck : HBVax **1986** Merck rHBVax[60] **1989** SKB rHBVax	Component- Process- first recombinant vaccine- safer: carries no risk of infection associated with the use of human blood products	AFEB sponsor etiological studies in 1960's-'70's; conduct early clinical efficacy demonstrations of HBvax[61]
Influenza	1933 Laidlaw isolated A strain (National Institute for Med. Res., London)[62] 1940 Francis isolate B strain (Rockefeller Institute) 1949/50- Francis isolate C strain[63] 1957 WRAIR (Hilleman,	1942 Sharp and Dohme manufactured the first inactivated vaccine on the basis of SGO and AFEB commissioned research during World War II- clinical trials on troops in 1943 treat with organic solvent or detergent or disrupt viral envelop 1960-69 Kilbourne	**1945** Lederle and Parke-Davis: split viron; Sharp and Dohme, Lilly: whole cell **1970**- National Zonal Centrifugation split and sub-unit purification **1971**	Component: lost effectiveness after 1947 due to antigenic shift in the population Process: reduced previously high levels of reactogenicity- encouraged general use of the vaccine Process: reduces reactinogenicity at expense of immunogenicity Process: first	AEB Influenza Commission develop and test first inactivated vaccine 1947: WRAIR determined need for annual adjustment of antigenic content 60's Zonal centrifugation technology transferred from military labs to National Drug

[58] Merck received Industrial Bioprocess Award in 1998, from the American Chemical Society for the developing a process to use nuclease enzymes to purify the Hepatitis A virus. This process improves purity and safety without compromising yields.

[59] Blumberg et al., *Science* 197 (1977): 17.

[60] rHBax: Merck: collaborated with scientists at UCSF to clone HbsAg: (W. J. Rutter, H. M. Goodman et al., "Vaccines Containing Hepatitis B S-Protein," assigned to the University of California, U.S. patent 5 (March 23, 1993): 196,194.

[61] W. Szmuness et al., "Hepatitis B Vaccine: Demonstration of Efficacy in a Controlled Clinical Trial in High Risk Populations in the U.S.," *New England Journal of Medicine* 303 (1980): 833.

[62] W. Smith, C. H. Andrews, and P. Laidlaw, "A Virus Obtained from Influenza Patients," *Lancet* 2 (1933):66-60.

[63] T. Francis et al., "Identification of Another Epidemic Respiratory Disease," *Science* 112 (1950): 495.

	Buescher) isolate and characterize Asian Influenza [H2N2?] strain used in commercial vaccine	(NY Med College) reassort genes from new variants and high yield strains	Reassorted vaccines	genetically engineered vaccine: reduce time between variant strain identification and vaccine preparation, also requires fewer eggs, limiting production costs	
Japanese Encephalitis	Isolated from human case in 1935 and maintained by continuous mouse brain passage: formalin inactivated, un-centrifuged 10% suspension of infected mouse brain	Lyophilized, formaldehyde inactivated Japanese encephalitis virus cultured *in vivo* in mouse brain Osaka University added successive refinements over the years[64]	**1992** Research Foundation for Microbial Diseases of Osaka University- license also granted to Connaught/BIKEN consortium	Process- more immunogenic	AEB- Sabin develop vaccine 1945 Squibb; Sharp and Dohme increase production (not licensed) Transfer the tech to Japan during occupation. 48-'51 inactivated, chick embryo derived – less immunogenic '52-55 WRAIR (Buescher, Scherer) vector studies DOD encouraged RFMD to file for US license and sponsor and conduct clinical trials of JEVax in Thailand[65]
Lyme Disease	*Borrelia burgdorferi*	Rather than induce immunity in humans, vaccine produces antibodies that are ingested by the deer tick and that neutralize spirochete in the	**1998** SKB recombinant OspA (outer surface protein of *Borrelia burgdorferi)* Developed in Europe	Component- (removed from the market in 2001)	

[64] K. Takaku et al., "Japanese Encephalitis Purified Vaccine," *Biken Journal* 11 (1968): 25-39.
[65] C. Hoke et al., "Protection against Japanese Encephalitis by Inactivated Vaccines," *New England Journal of Medicine* 319 (1988): 608-614.

		tick gut			
Measles	1954 Dr. John Enders et al, Children's Hospital, Boston- isolated culture taken from Dr. Edmunston	1958 Enders, Katz, Milovanovic passaged Edmonston strain in human tissue cultures- then adapted to propagation in chick cultures. Merck developed Lyophilized live attenuated viral vaccine	**1963** Merck Rubeovax **1968** Merck Attenuvax	Component and Process- Merck attenuated Edmunston strain further Process: 40 additional passages created the less reactogenic Moraten strain	Enders develop vaccine under Army contract at Harvard Medical School[66] AFEB commission on viral infections sponsor testing of live and inactivated vaccines
Meningococcal Meningitis	*Neisseria meningitidis* Weichselbaum (Vienna) Second most common cause of bacterial meningitis accounting for 20% of all cases	1906 Flexner, Jobling (Rockefeller Institute) produced horse derived antisera until sulfa drugs became available in 1938	**1974-5** Merck and National: meningococcal polysaccharide vaccines A and C. **1981-2** Connaught (formerly National) and Merck A/C/Y/W135 Combined	Component Component	Late 60's-70's: Group A and Group C isolated and vaccines developed at WRAIR
Mumps	1934-5 Johnson, Goodpasture 1963 Hilleman isolated Jeryl Lynn strain from his daughter- strain used in vaccine	1948 Weller, Enders grow in chick embryo culture, attenuate through embryonated egg passage 1963- Jeryl Lynn strain passaged in chick embryo cultures	**1950** Lilly and Lederle- inactivated **1967** Merck Lyophilized, live attenuated	Component Process- longer lasting immunity, suitable for infants	
Pertussis	1906 *Bordetella pertussis:* Bordet, Gengou	1942 Kendrick (Michigan Dept Public Health) alum precipitated vaccine	**1914** Bayer, Lederle etc. whole cell pertussis vaccine **1948** Bayer Pertussis Adsorbed **1991** Lederle combines aP component (Takeda Chem Industry, Japan) into DTaP vaccine	Component Process- more immunogenic Architectural	

[66] Preventative Medicine Research Division of the U.S. Army, Annual Report, FY '63, August 27, 1963. NA: RG 112, E. 1015. B.106.

Plague	1894 *Pasturella pestis* Kitasato and Yersin: Hong Kong epidemic	1895 Yersin, Calmette heat-killed, phenolized	**1942** Cutter Labs (Bayer) whole cell formalin inactivated	Process- prior vaccines of unproven efficacy, Meyer reduced the dose to reduce reactogenicity	OSRD sponsored Meyer's vaccine research at Hooper foundation UCSF 1960- military use demonstrated efficacy in Vietnam
Pneumococcal Pneumonia	1881 *Streptococcus pneumoniae* Dr. George Sternberg 1923-24 Heidelberg, Avery identify polysaccharide capsules responsible for virulence Austrian (UPenn) late 60's isolated new strains and provided seed cultures for Merck vaccine	1964 Austrian demonstrated 17% of pneumococcal pneumonia cases resistant to penicillin NIAID sponsored research between Dr. Austrian (UPenn) and Lilly to dev. new vaccine After production problems and high reactogenicity, Austrian turned to Hilleman in 1970 to develop new polyvalent vaccine-clinical trials in South African gold mines	**1948** Squibb polyvalent polysaccharide vaccine-discontinued in '56 due to rising use of antibiotics **1977** Merck polyvalent capsular vaccine **1979** Lederle polyvalent capsular vaccine **2000** Lederle-pneumococcal 7-valent conjugate vaccine (Dip CRM 197 protein)[67]	Radical- First capsular polysaccharide vaccine Component- new strains Process- induces long term immunity (via T-cells) and can be used in children under 2.	1881 AMS isolated pneumococcus bacterium 1945 AMS performed first large scale, double blind, randomized field trial to demonstrate efficacy for a vaccine[68] AMS encourage Squibb to license and manufacture vaccine
Polio	1909 Poliomyelitis Lewis, Flexner (Rockefeller) etiology, mode of infection 1949 Bod (Hopkins) identify 3 types poliovirus	1949 Enders, Robbins, Weller (Harvard Univ., Children's Hospital) propagate virus in human tissues early '50's:Salk (Univ. Pittsburgh) inactivated vaccine(IPV) grown in monkey kidney cultures 1954 NFIP coordinated clinical trial for Salk IPV. 1948 Koprowki et al, Wistar Institute dev first live-oral vaccine (OPV)-	**1955** Merck (Sharp and Dohme), Parke-Davis Cutter, Pittman Moore, Wyeth, Lilly-IPV **1960** Merck-IPV[69] **1961** Pfizer-live oral type 1, 2, and 3 **1963** Lederle-OPV trivalent	Component- first commercially manufactured polio vaccine-inactivated, lower immunogenicity, lower reactogenicity Incremental- higher purity and potency Incremental- more immunogenic Architectural	

[67] Conjugate vaccine originally developed by Praxis, which was acquired by Lederle in 1989.

[68] C. MacLeod et al., "Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides," *Journal of Experimental Medicine* 82 (1945): 445. (7,730 recruits on base randomized for this trial.)

[69] Merck withdrew vaccine after discovered contamination with SV40 from monkey kidney cells.

		1953-55 Sabin OPV 1960 Hilleman, Charney adjust antigenic components of Salk vaccine to improve antibody response			
Rabies	1884 Roux, Pasteur isolate from rabbit 1940 Leach, Johnson (Berkeley) isolate from human brain 1964 Koprowski adapt virus to human diploid cell culture[70]	1884 Roux, Pasteur: desiccated rabbit spinal cord, saline suspension- demonstrate efficacy of this attenuated vaccine on child	**1915** Lilly (rabbit brain) **1942** Parke-Davis **1980** Wyeth Rabie-vax- inactivated: cell line and process dev at Wistar Institute	Incremental Process- of non-nerve tissue origin- less reactogenic, yet less immunogenic Process- human diploid cells- fewer foreign proteins, less reactogenic	
Rocky Mountain Spotted Fever *Rickettsia rickettsii*		1924 Rocky Mountain Labs (PHS) in Hamilton, MT early work on vaccine	**1942** Lederle		
Rotavirus	NIAID identify virus	1984 Clark, Offit, and Plotkin of Wistar Institute, Children's Hospital of PA and NIAID dev first monovalent reassortment vaccine- later develop additional reassortment compounds- first grown in fetal rhesus diploid cells 1987 CRADA (NIAID-Wyeth) for further vax dev	**1998** Wyeth-Lederle Live, oral, tetravalent, attenuated, lyophilized	Component- withdrawn in 1999 due to increased incidence of intussusception	
Rubella (German Measles)	1938 Hiro 1961 Parkman et al (WRAIR) and Weller, Neva (Harvard School Public	Merck and DBS (NIH) adapt virus to grow in bovine kidney cells (would not grow in chick cultures)and	**1969** Merck- live attenuated lyophilized	Component	Parkman, Buescher and Artenstein (WRAIR) isolate rubella virus in collaboration with Harvard School of Public Health[71]

[70] T. Wiktor, M. Fernandez, and H. Koprowski, "Cultivation of Rabies Virus in Human Diploid Cell Stain WI-38," *Journal of Immunology* 93 (1964): 353-366.

[71] P. Parkman, E. Buescher, and M. Artenstien, "Recovery of Rubella Virus from Army Recruits," *Proceedings of the Society of Experimental Biological Medicine* 111 (1962): 225-30.

	Health) identify another strain 1962 Merck identifies Benoit strain (HPV-77) Plotkin et al: Wistar Institue dev RA 27/3 strain	attenuate through duck embryo cultures Cultured in human diploid lung fibroblasts	**1978** Merck- live attenuated	Incremental- less reactogenic in adults	Strain and virology techniques developed at WRAIR were used to develop the commercial vaccine
Smallpox	Wyeth vaccine uses strain isolated by the New York Board of Health	1796 Jenner Calf lymph vaccine 1933 Goodpasture cultivate variola virus in chick embryo tissue cultures[72] Collier (Lister Institute) perfect freeze-dried process 1973 produce stable freeze dried vaccine in monolayers of primary rabbit kidney- clinical trials impossible without efficacy surrogates	**1903** Bayer, Pocono Labs glycerinated calf-lymph **1944** Lilly, Merck, Wyeth: calf-lymph	Process- lower bacteria counts, less reactogenic Process- lyophilization- more stable for transport	1882 Jenner cowpox vaccine adopted by US Army; Sternberg demonstrates serum associated immunity; suggests mechanism of a neutralizing antibody to vaccinia virus[73] 1940's: Army Blood Program develops Lyophilization technique. 1949 AFEB sponsors studies to apply technique to stabilize vaccine for shipment[74]
Tetanus	*Clostridium tetani*: 1884 Nicolaier (Gottingen)	1890 Kitasato, Behring grow pure cultures with anaerobic methods- demonstrate protective effects of animal source antitoxin 1927 Ramon, Zoller: active immunization with toxoid (Institute Pasteur)	**1933** Parke-Davis, Sharp & Dohme Tetanus toxoid (inactivated toxin)	Process- active immunization	Routine military vaccination during World War II provided informal proof of efficacy and paved the way for commercial use after the war.[75] 1944 American Academy of Pediatrics recommended routine administration AFEB commission on immunization (directed by J. Smadel) CMR (Dr. Mueller, HMS) Reduced reactinogenicty by synthesizing

[72] Ernest Goodpasture is credited with the early development of tissue culture techniques in the 1930's. He was at Johns Hopkins but later become the scientific director of the Armed Forces Institute of Pathology.
[73] J. R. Engelman, *Two Hundred Years of Military Medicine* (Fredrick, MD: U.S. Army Medical Department, 1964).
[74] Army Medical School, Small pox vaccine, 1949; also, Minutes, 3rd annual meeting of the Commission on Immunization, (March 21, 1949) Armed Forces Epidemiology Board. NA: RG 112, E. 1035, B. 83.
[75] Only 12 cases of tetanus were reported in the U.S. Army between 1939 and 1945, 6 of which consisted of soldiers that had not been actively immunized. (H. J. Parish, *A History of Immunization* (London: E & S Livingstone Ltd., 1965).)

			1934 National – Tetanus toxoid adsorbed	Process- first recorded use of alum as adjuvant	alternative to peptones originally found in broth cultures. Determined superiority of alum vaccine used by Navy over non-adsorbed vaccine used by Army
Tuberculosis	1883 Tubercule Bacillus- Kolle 1924 *Mycobacterium bovis* aka *BacilleCalmette-Guerin* (Pastuer Institute)	1902 Behring 1906 Calmette and Guerin whole cell attenuated live. Tice strain (derived from BCG) dev. by Univ. Illinois in mid- 30's 1929- Pearl noticed anti-tumor effect	**1950** University of Illinois- first freeze-dried, live, attenuated vaccine (Tice strain) **1990-** Connaught (Toronto) licensed to use BCG to treat bladder cancer	Process- more stable, safer Incremental- new indication	
Typhoid	*Salmonella typhi* Pfieffer, Kolle ; Wright 1896	1896 Pfieffer; Wright : heat inactivated, phenol preserved 1909 Russell modified version used in German and British Armies Whole cell heat inactivated, phenol preserved[76] Live attenuated oral Purified Vi polysaccharide vaccine	**1908** Lederle- whole cell inactive **1989** Swiss Serum and Vaccine Institute, Berne live-attenuated oral **1994** Pasteur Merieux- purified Vi polysaccharide inactivated	Incremental: less Reactogenic Process: requires 4 doses, more immunogenic Process: less reactogenic but short term efficacy- works less well for infants	1898 Typhoid Board identify vector [human contact and flies] Maj. Walter Reed demonstrates pathogenesis of typhoid bacillus 1909 Dr. Russell, US Army Medical School develops vaccine and conducts first clinical studies[77] 1911 made compulsory for military World War I demonstrates efficacy[78]
Typhus	1916 *Rickettsia prowazeki* Rocha Lima (Hamburg) 1942- Plotz isolate soluble	1937 Zinnser incubate infected chick embryo on agar slopes- inactivate with formalin or phenol 1938 Harold Cox (Parke-Davis)	**1942** Parke-Davis, Eli Lilly, Sharp & Dohme, Lederle, PHS	Process- growth on agar slopes permits large-scale production (formerly had to maintain louse farms)	Original formulation lost potency. 1940: US Typhus Commission- under direction of Harry Plotz: isolate, purify, grow, produce, and test new typhus vaccine, pool

[76] This was the first effective typhoid vaccine according to: (J. R. Engelman, *Two Hundred Years of Military Medicine* (Fredrick, MD: U.S. Army Medical Department, 1975).)

[77] Based on visit to German and British military.

[78] During the Spanish American War of 1898, the U.S. suffered 20,738 cases of Typhoid Fever. Following routine administration of the vaccine in 1911, the U.S. suffered only 1,529 cases of the disease. (R. Rader, *Biopharma* (1998), 265.)

	polysaccharide antigen from rickettsial antigen.	adapted to grow in chick embryo[79]	**1967** Lederle	Process- less reactogenic, yet less immunogenic as well	US/UK research and epid info[80] CMR and AMS develop fractionation procedures to isolate antigens from rickettsial bodies. WRAIR studies later determined that this purified vaccine was of insufficient potency
Varicella (Chicken Pox)	1970 Dr. Takahashi et al live Oka Strain, Osaka Univ. Merck derived more attenuated and stable Oka/Merck strain from the Oka/BIKEN strain	Passaged through human embryonic cells, grown in embryonic guinea pig fibroblasts: subsequently passaged in human MRC-5 diploid cells and propagated in human fibroblast cultures	**1995** Merck – live, attenuated, lyophilized	Component	
Yellow Fever	1900-02 Yellow Fever Commission (directed by Walter Reed) demonstrates transmission via *Aedes aegypti* mosquito; infer presence of filterable virus 1937 Max Theiler (Harvard) isolated and developed Asibi strain; 17D- safer than live mouse brain substrate previously used	Live attenuated- passage through chick embryo tissue culture [81] (Rockefeller Institute) – previous killed vaccines not effective	Rockefeller Foundation supplement vaccine production for US military during World War II 1942 Rocky Mountain Laboratory of PHS- dev aqueous base **1952** license transferred to National Drug **1968** National Drug	Process: transferred 17D strain from chick tissue culture to the developing egg itself using Goodpasture techniques- facilitated mass production- Safer, human serum removed from vaccine Process- safer, free of avian leukosis virus	Identify vector Infer presence of virus when discovered that the use of (non-approved) serum-based YF vaccine during World War II caused hepatitis B- initiate research that permitted industry to shift from serum based vaccines

[79] H. Cox, "Use of Yolk Sac in Developing Chick Embryo as Medium for Growing Rickettsia of RMSF and Typhus Groups," *Public Health Report* 53 (1938): 2241-2247.
[80] "Typhus Vaccine Development," (Washington, D.C.: Army Medical School, 1946). NA: RG 112, E. 1035, B. 83.
[81] M. Theiler and H. Smith, "The Use of Yellow Fever Virus Modified by In Vitro Cultivation for Human Immunization," *Journal of Experimental Medicine* 65 (1937): 787.

Chapter Two: World War II Vaccine Development Programs

The 1940's demonstrated unprecedented rates of vaccine innovation. The majority of significant innovations introduced during this period derived from World War II vaccine development programs. A close examination of the inception, organization, and function of these programs reveals why organized vaccine development efforts were so successful during this period.

I. Better welfare through warfare? The inception of World War II biodefense programs

Suffering heavy troop losses to disease in the Revolutionary, Civil, and Spanish-American Wars, military planners had long since learned to respect the threat disease poses to military objectives.[1] With the onset of the World War I, therefore, the U.S. military looked for assistance from the United States Public Health Service (PHS), which had actively been appropriating and in many cases developing laboratory and sanitary techniques generated from the bacteriological revolution at the turn of the 20th century. Recognizing the importance of infectious disease control to the maintenance of effective military operations, President Wilson signed an executive order in April 1917 assigning the PHS to the U.S. Armed Forces.[2] The duties of commissioned public health officers consisted primarily of the application of sanitary and mosquito control measures to recruitment camps, where typhoid and malaria were often rampant. At the time, the number and status of laboratory scientists within the military were still limited, and these scientists rarely sought collaborative research relationships outside of the military context, either with academia or with industry.

Between World War I and World War II, few funds were made available to the Medical Department for research and the department retained "but a small nucleus of officers with research experience."[3] As World War II brewed in Europe, however, the federal government began to make unprecedented investments in infectious disease research. This development is often attributed to the military's experience with the influenza pandemic at the close of World

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[1] In the Spanish American War, for example, the ratio of disease to battle deaths was 5:1. S.B. Hays, Surgeon General, *Preventative Medicine in World War II,* vol. IV, ed. John Boyd Coates, Jr., (Washington D.C., 1958).

[2] F. Mullan, *Plagues and Politics: The Story of the U.S. Public Health Service* (New York: Basic Books, 1998), p. 70.

[3] Brig. General James Simmons, Chief of Preventative Medicine Service, SGO, U.S. Army, statement for presentation, December 14, 1944, before the Senate Sub-Committee on Wartime Health and Education. NA: RG 165, E. 488, B. 183.

War I, which was responsible for nearly 20 million deaths worldwide. Military populations were particularly hard hit. According to one estimate, influenza accounted for nearly 80 percent of the war casualties suffered by the U.S. Army during World War I.[4]

Thomas Francis Jr., chairman of the Influenza Commission, which coordinated research on the influenza vaccine during the Second World War, noted how the onset of World War II immediately recalled the specter of the 1918 influenza pandemic: "The appalling pandemic of 1918 in the last months of the exhausting conflict of World War I, with massive mobilization of armies and upheaval of civilian populations, has irrevocably linked those two catastrophes. It demonstrated that virulent influenza may be more devastating to human life than war itself . . . the onset of another war inevitably recalled the specter of 1918 and the possibility that . . . [it] would again result in the epidemiologic conditions which would heighten the severity of influenza to a catastrophic level."[5]

Dr. Francis was not alone in his thinking. Many shared his concern that a new war would unleash another influenza pandemic along with a host of other familiar and perhaps unfamiliar infectious diseases and federal investments in military medical personnel, training, and research ballooned with the onset of World War II. Funding for Army medical research alone increased more than one hundred percent between 1940 and 1942.[6] In particular, the government began to make unprecedented investments in large-scale, federally coordinated vaccine development programs. Intramural and extramural research projects were administered through the U.S. Army's Surgeon General Office (SGO), the Committee for Medical Research (CMR) division of the Office of Scientific Research and Development (OSRD) and, in some cases, the War Research Service (WRS).[7]

The SGO, through the Preventative Medicine Division, directed in-house research programs through a network of international laboratories and through the Army Medical Graduate School (AMS) in Washington DC. These programs were chiefly concerned with the diagnosis, prevention, and treatment of typhoid dysentery, typhus, and syphilis. In 1941, attesting to widespread fears that war would encourage another influenza pandemic, the Secretary of War

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[4] Department of Defense, *Addressing Emerging Infectious Disease Threats: A Strategic Plan for the Department of Defense* (Washington, D.C.: Walter Reed Army Institute of Research, 1998), 23.

[5] T. Francis Jr., "Influenza in the U.S. Army Medical Service," Preventative *Medicine in World War II,* vol. IV (Washington, D.C., 1958), 85-87. See also T. Woodward, *The Armed Forces Epidemiological Board: Its First 50 Years* (Falls Church, VA, 1990).

[6] The department received a total of $16,000 for 1940 and was slated for a total of $37,000 in 1942. No funds had been granted in 1925, 1926, or 1927. (*The Surgeon General's Report to the Secretary of War for the Fiscal Year of 1940).* NA: RG 112, E. 1014, B. 1.

[7] WRS development projects were transferred to the Chemical Warfare Service (CWS) in 1943.

also created a Board for the Investigation and Control of Influenza and other Epidemic Diseases (hereafter referred to by its later appellation, the Army Epidemiology Board or AEB).[8] Administered through the Preventive Medicine Division, this seven-member board directed ten commissions with a total of 100 civilian scientists conducting research on a range of diseases of military importance.

With the exception of the Respiratory Disease Commission Laboratory at Fort Bragg, NC, these scientists were contracted through the War Department on a part-time basis to conduct research at their home institutions. Commissions enlisted the top infectious disease specialists in the country from universities, hospitals, public health labs, and private research foundations to conduct epidemiological surveys and to develop and test preventative measures against diseases such as influenza, meningitis, encephalitis, acute respiratory diseases, measles and mumps, pneumonia, typhus and rickettsial diseases.[9] According to Dr. Bayne-Jones, Deputy Chief of the Preventative Medicine Division during the war, these AEB contracts were designed to permit the Army to outsource research they were not qualified to perform and gave the Army access to "valuable services and facilities in the leading institutions in the country."[10]

The CMR within the OSRD performed a similar function.[11] The CMR, chaired by Dr. Alfred Newton Richards (Chairman of Pharmacology at the University of Pennsylvania), was comprised of three presidential appointees and one representative each from the offices of the Secretary of War, the Navy, and the Federal Security Agency. The CMR was created primarily because the Division of Medical Sciences (DMS) at the National Research Council was not a government agency and therefore could not obtain congressional funding to administer a large-scale contract research program. The newly formed CMR drew heavily however from the expertise of the pre-existing DMS. Dr. Lewis Weed, Chairman of the DMS, was elected Vice Chairman of the CMR and the chairmen of each of the eight pre-existing medical committees were appointed as consultants to the CMR. Like the AEB, the CMR recommended and reviewed contract research performed by civilian scientists and administered through OSRD.

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[8] This board became known as the Army Epidemiology Board after the war. In 1949, when the board became responsible for Navy and the Air Force, it was renamed the Armed Forces Epidemiology Board.
[9] The Board oversaw Commissions on Acute Respiratory Diseases, Air-Borne Infections, Epidemiological Survey, Hemolytic Streptococcal Infections, Influenza, Measles and Mumps, Meningococcal Meningitis, Neurotropic Virus Diseases, Pneumonia, and Tropical Diseases.
[10] Brig. General S. Bayne-Jones, U.S.A, Deputy Chief, Preventative Medicine Service, SGO of the U.S. Army and Director of U.S.A. Typhus Commission. NA: RG 156, E. 488, B. 183.
[11] The CMR was created by executive order in June of 1941 to supplement the efforts of the National Defense Research Committee. Together these two committees formed the OSRD.

The AEB and CMR both produced large numbers of medical and technological innovations during the war. The most celebrated wartime innovations include the development of blood substitutes such as plasma, the mass production of penicillin, and the development of insect repellents and insecticides, most notably DDT.[12] Wartime contributions to vaccine development were equally impressive, with ten new and significantly improved vaccines resulting from World War II vaccine development programs.[13]

The SGO and OSRD published volumes on their wartime achievements, perpetuating an exalted vision of military medicine after the war.[14] These volumes often emphasized the technical achievements of wartime research whereas, at the end of World War I, ambitions for military medicine reflected a moralistic tone. In 1917, for example, a member of the PHS, buoyed by recent successes in containing traditional scourges such as typhoid and malaria, expressed the hope that "possibly some day the doctors who save life may outrank the generals who destroy it, and they will then clasp hands across the trenches and turn their combined strength against insects, parasites, and disease, the enemies of all men."[15]

By the 1940's, as the U.S. began to invest in biological warfare research, proponents of military medicine made fewer claims to moral superiority. As the SGO, the OSRD, and the WRS began to account for their activities after the war, they focused more heavily on their contributions to scientific achievement and technological innovation than on any role in reshaping the moral order. When James Simmons, Chief of the Preventative Medicine Division, addressed Congress in 1944, he limited his comments to the technological and organizational contributions of military medicine during the war: "Through this great organization practically all of the medical investigative resources and research workers of the country have been mobilized to assist the Armed Forces. The new knowledge made available has been applied immediately in the field."[16] The acquisition of new knowledge through wartime R&D, regardless of its military application, signified an achievement worthy of praise.

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[12] J.P. Baxter, *Scientists against Time* (Cambridge: MIT Press, 1947).

[13] A new vaccine is defined as the first safe and effective vaccine licensed to prevent a disease for which no form of active immunity was previously available.

[14] John Boyd Coates, Jr., ed., *Preventative Medicine in World War II*, SGO, Department of the Army (Washington, D.C., 1955); I. Stewart, *Organizing Scientific Research for War: The Administrative History of the Office of Scientific Research and Development* (Boston: Little Brown and Company, 1948); J.P. Baxter, *Scientists against Time* (Cambridge: MIT Press, 1947).

[15] Samuel Grubbs, a surgeon with the U.S. PHS, 1917, quoted in F. Mullan, *Plagues and Politics: The Story of the U.S. Public Health Service* (New York: Basic Books, 1998), 58.

[16] Brig. General James Simmons, Chief of Preventative Medicine Service, SGO, U.S. Army, statement for presentation before the Senate Sub-Committee on Wartime Health and Education, December 14, 1944. NA: RG 165, E. 488, B. 183.

This shift in emphasis from the moral to the technological and organizational contributions of military medicine may have reflected a growing recognition that few of these wartime innovations offered unambiguously positive outcomes for society. Indeed, for many members of the SGO, CMR, and WRS engaged in vaccine research, there was the inescapable fact that some medical men made more progress in learning how to spread disease than in learning how to prevent it.

Reflecting on World War II in relation to the larger the history of war and technology, William McNeill described how "a growing government bureaucracy, made more powerful by the threat of war, nurtured and coordinated these developments to produce a flood of technological innovation directed at national welfare and warfare objectives."[17] Furthermore, said McNeill, there was "moral ambivalence implicit in every increase in human power to manage and control our natural and social environment."[18] Though he did not examine the moral ambivalence of World War II vaccine development programs, it is difficult to imagine a World War II project that embodied a more contradictory mix of national welfare and warfare objectives.[19]

Wartime advances in methods for growing high-yield plague and typhoid cultures, for example, could be used either to improve vaccine production or to accelerate the development of biological weapons. Indeed, scientists were often contracted by the federal government to ensure that their inventions were available for *both* purposes. Dr. Dubos, a microbiologist, and Dr. Hoberman, an infectious disease specialist, for example, led two projects at Harvard Medical School during the war.[20] The public was aware only of the first, which attempted to improve typhoid vaccines. The second, code-named project "Y," determined methods for the mass production of the Shiga bacillus. As was often the case, the offensive objectives of these projects turned out to be easier to accomplish than the defensive ones. Whereas Dubos' group never made significant progress in the development of a more effective vaccine, they succeeded in developing production processes that produced high yields of the bacilli in record periods of time. [21]

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[17] W. McNeill, *The Pursuit of Power: Technology, Armed Force, and Society Since A.D. 1000* (Chicago: University of Chicago Press, 1982), 360.

[18] Ibid.

[19] Atomic weapons research suffered from moral ambiguity as well. Unlike biological weapons programs, however, the Manhattan Project did not contract large number of physicians that had taken the Hippocratic oath.

[20] Dr. Rene Dubos spent the majority of his career as a microbiologist at Rockefeller University. From 1942-1944 he was a Professor of Pathology and Tropical Medicine at Harvard Medical School.

[21] They devised a method of forced aeration in which flowing air columns permit complete oxidation of the nutrients boosting culture growth. Dubos' group could obtain maximum yields with this method within 12 hours. R. Dubos, reporting in G. W. Merck, *Activities of the U.S. in the Field of Biological Warfare* (October 31, 1945). NA: RG 165, E. 488, B. 182.

Dubos was well aware that other scientists under OSRD contracts were also attempting to obtain high yields of bacterial cultures for offensive and defensive purposes and, with the help of OSRD, his new method was rapidly transferred to other scientists working on similar problems under vaccine development contracts.

In addition to Drs. Dubos and Hoberman, a number of other scientists were contracted to improve the technologies of disease prevention and creation simultaneously. Dr. Karl Meyer, a biochemist at the George William Hooper Foundation in San Francisco, accepted contracts through the CMR and WRS to develop vaccines and weapons with plague-causing bacteria. Dr. Norman Topping, a research scientist at the National Institute of Health, accepted similar contracts to work with typhus. Dr. Lee Foshay, a professor in the Department of Bacteriology at the University of Cincinnati, and Dr. Cora Downs, a professor in the Department of Bacteriology at the University of Kansas, each worked within their respective labs on ways to prevent and induce tularemia. Dr. Forest Huddelson, from the Department of Bacteriology at Michigan State College worked on Brucellosis weapons and vaccines; Dr. Griffiths from the National Institute of health was contracted to develop cholera weapons and vaccines. Moral dilemmas were inherent in the task at hand. To test vaccines, scientists had to produce infectious agents to perform challenge studies; to handle biowarfare agents responsibly, lab workers had to develop vaccines. The line between defensive and offensive research was thus exceedingly thin.

Though it is hard to know how each individual resolved this moral tangle of welfare and warfare objectives, Dr. Meyer's comments offer some insight. He justified his work by deciding that he would not proceed with offensive research until he developed effective defensive measures. When the WRS research project was proposed to Meyer, he responded, "irrespective of what we may ultimately be able to accomplish in the offensive direction I am more than ever convinced that we must first and foremost plan to and develop the defensive. The risk to workers is too great to venture even a pilot experiment on a small scale."[22]

While Meyer succeeded in developing an effective plague vaccine before he moved on to methods of weaponization, he proved to be an exception. According to activity reports from the WRS advisory committee, few of the other scientists under WRS contracts succeeded in developing effective vaccines because, in many cases, the diseases under study were poorly understood.[23] Many scientists may originally have used rationales similar to those espoused by Dr. Meyer. In their final activity reports, however, many were forced to acknowledge that their

[22] K. Meyer, letter to E. B. Fred (December 18, 1942). NAS: CBW Files.
[23] "Research Program of the War Research Service" (1944). NAS: CBW files.

attempts to mass-produce and devise methods for the dissemination of various pathogens had been successful, whereas their efforts to develop vaccines had failed.[24]

The moral ambivalence of World War II biodefense programs cannot be attributed to scientific factors alone. Offensive and defensive research programs were co-dependent for strategic and organizational reasons as well as scientific ones. Biowarfare research and vaccine development programs were hatched at the same table; they shared a similar rationale for existence and pursued similar strategies. Biodefense planners in the SGO did not distinguish between the threat of natural and manufactured forms of disease. In devising a defense strategy, they considered both forms equally, reasoning that, "the devastation wrought by the natural partnership of war and pestilence has scarred the face of history so deeply that it is only logical that military men in search of offensive weapons should consider the intentional use of disease producing agents."[25] Indeed, in earlier eras, there was often some confusion as to what was and was not a natural outbreak. The Spanish Influenza pandemic of 1918 had been so severe, so unprecedented, and so devastating to U.S. troops in particular that a number of OSS intelligence reports intimated that the Germans had deliberately unleashed it.[26]

The question of whether the U.S. should prepare for biological warfare was reportedly first raised by Vannevar Bush in conversation with Dr. Lewis Weed (then Chairman of the Division of Medical Sciences, NRC).[27] Dr. Weed, in turn, presented the issue at a meeting of the Health and Medical Committee of the Council of Medical Defense in October of 1940. This initiated a cascade of events in which the NIH and the NAS were asked to study the issue and evaluate the threat of biological warfare. A committee of special consultants held at the NIH concluded that "biological warfare was not considered practicable or as constituting a menace to the country."[28] Over the previous several years, however, members of the SGO had been developing a very different opinion on the matter.

Dr. James Simmons, Chief of the Preventative Medicine Division, was an early proponent of initiating a U.S. biodefense program. While stationed in Panama in 1934, he was reportedly "so impressed with the hazard of yellow fever and its possible intentional introduction that he

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[24] "Research Program of the War Research Service" (1944). NAS: CBW files; Historical Report of WRS, (November, 1944-Final). NA: RG 165, B. 185.
[25] *History of the Relation of the SGO to BW Activities*. NA: RG: 112, E. 295A, B. 13.
[26] *Digest of Information Regarding Axis Activities in the Field of Bacteriological Warfare* (January 8, 1943). NAS: CBW Files.
[27] The WBC Committee, "An account of its initiation and early activities" (May 15, 1944). NAS: CBW Files. There is no record of precisely what V. Bush said to Dr. Weed.
[28] Ibid.

prepared an informal plan to counteract such a move in the event of war."[29] In January 1941, Simmons again suggested that yellow fever might be used against U.S. troops for military purposes and recommended mandatory yellow fever vaccinations for all servicemen in tropical stations. The SGO procured a non-approved yellow fever vaccine in which pooled human serum was used as a stabilizer. In their haste, they administered the vaccine, which had not been tested for safety, and soon afterward troops began to contract "serum sickness" from the vaccine.[30] Although the SGO stumbled on their first attempt to protect U.S. troops from biological attacks, biodefense planning did not lose momentum.

A series of intelligence reports fed anxieties that Axis nations were investing in biological warfare capabilities.[31] For example, there were reports in 1939 that a Japanese doctor attempted to acquire Yellow Fever virus from the Rockefeller Institute in New York. When he failed to obtain the virus by request, he purportedly attempted to bribe an employee.[32] There was also reliable evidence that in 1941 the Japanese had trained over 2,000 parachute troops as a "bacteriological warfare battalion." But it was not until 1941 that the infamous OSS "Bern Report" implicated the Germans in biological warfare activities. According to the report, Professor Menk from the School of Tropical Medicine in Hamburg, Germany, had been working in a lab near Paris on the weaponization of botulinum toxin. While the report contained several widely recognized inaccuracies, the report was sufficiently disturbing to biodefense planners to justify launching a series of federal biodefense and biowarfare programs.[33]

In response to these reports, Simmons sent an urgent memo to Harvey Bundy, Special Assistant to the Secretary of War, stating that "serious consideration should be given to the advisability of developing facilities within the Medical Department for intensive research on methods for preventing diseases of man, lower animals, or plants that might be introduced

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[29] G. Dammin and E. Robinson, "Medical Laboratories," in *Preventative Medicine in World War II,* vol. IX: Special Fields, Medical Department of the U.S. Army, ed. Col. Robert Anderson, SGO, Department of the Army, (Washington, D.C., 1969), 578.

[30] It was later determined those vaccinated had contracted Hepatitis B from serum used in the yellow fever vaccine. This finding offered the first evidence that there was a distinction between infectious and serum forms of the disease.

[31] *Digest of Information Regarding Axis Activities in the Field of Bacteriological Warfare* (January 8, 1943). NAS: CBW Files.

[32] An intelligence digest indicates that in 1942 another Japanese doctor attempted to obtain the virus from a lab in Brazil. (*Digest of Information Regarding Axis Activities in the Field of Bacteriological Warfare* (January 8, 1943). NAS: CBW Files).

[33] Reflecting on the inception and administration of the U.S. BW program in World War II, Dr. Ernest Goodpasture, a member of the WRS advisory committee, later concluded, "It seems to me that we have been all along acted more by an emotional reaction than by a very critical analysis of the situation." Ernest Goodpasture, letter to Perry Pepper (October 16, 1946). NAS: CBW Files.

artificially by military enemies."[34] By this time, Surgeon General Dr. Thomas Parran had taken this issue to the public. Addressing a 1942 Mayor's conference, Parran presented the threat of biowarfare in stark terms, asserting that "the enemy has planned and, in my opinion, will use bacteriological warfare whenever possible." Such tactics, he warned, "can be as deadly as mustard gas or explosives." He went on to urge the Mayors "to begin at once to take every possible precaution and to get expert advice."[35]

Henry Stimson, then Secretary of War, asked Dr. Weed to appoint another elite group of biologists to assess the threats and opportunities posed by biological warfare. Dr. Weed formed a joint committee of members from the NRC and the NAS. This committee, known as the War Bureau of Consultants (WBC) consisted of Dr. A.N. Richards (chairman of the CMR) Lt. Col. Jacobs, GSC; Col. ME Barker CWS; Col. JS Simmons, MC; Dr. Ross Harrison, Chairman of the NRC, and Dr. Weed. By this time however, the question was no longer whether the U.S. should proceed with a BW program but who would be responsible for various components of it. It was agreed from the start that, to whatever extent possible, these programs must be kept nominally, if not institutionally, separate.

The SGO took public responsibility for biodefense programs concerned with the search for vaccines to protect the troops from natural and manufactured forms of infectious disease. The WBC committee suggested the formation of a civilian agency to supervise and coordinate biowarfare R&D for the military, PHS, Dept of Agriculture, FBI and the OSS. Vannevar Bush, director of OSRD, recalled that responsibility for the WRS was passed around like a hot potato: "Mr. Stimson did not want this thing in the War Department, and I did not want it in OSRD. So we inserted it in an agency headed by Paul McNutt. I don't think Mr. McNutt knew he had it."[36]

Biological warfare research was thus taken "under the wing and the cloak of the Federal Security Agency" with the innocuous title of the War Research Service (WRS).[37] The offensive aspects of the U.S. BW program were placed in a civilian research service at this time, "for the purposes of security and for protecting the armed services from public involvement in biological warfare."[38] The WRS formed two civilian advisory committees to consider the offensive and

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[34] G. Dammin and E. Robinson, Medical Laboratories, in *Preventative Medicine in World War II,* vol. IX: Special Fields, Medical Department of the U.S. Army, ed. Col. Robert Anderson, SGO, Department of the Army, (Washington, D.C., 1969), 579.
[35] *The New York Times*, January 13, 1942.
[36] V. Bush, *Pieces of the Action* (New York: William Morrow and Company, 1970), 209.
[37] G. W. Merck, "Peacetime Implications of Biological Warfare," *The Merck Report* (July 1946). MA.
[38] G. W. Merck, letter to F. Jewett, President of the NAS, (April 21, 1944). NAS: CBW Files.

defensive aspects of biological warfare respectively. They "would in effect be one, but . . . separate reports would be prepared for transmittal to the OSG and the CWS, respectively."[39]

Maintaining strict separation between the programs proved difficult. A memo regarding U.S. biodefense programs candidly admitted, "it is impossible, however, to visualize all the possibilities inherent in bacterial warfare if the question is considered purely from the defensive standpoint. The assumption of an offensive viewpoint is absolutely necessary."[40] The WBC report concluded, "it is believed that such warfare is of sufficient importance to warrant asking the help of the OSRD."[41] Thus offensive research objectives began to creep into biodefense research programs from their inception and a number of OSRD vaccine projects, such as the development of plague, botulinum toxoid, typhoid, and, to some extent, influenza vaccines were motivated by biowarfare concerns.

George Merck, director of the WRS, and later a special consultant to the Secretary of War on biological warfare (BW), was acutely aware of the moral ambivalence inherent in biodefense research. Following the war, however, when he returned to his duties as president of the pharmaceutical company that bears his name, he chose to focus on the positive spinoffs from BW research activities. In a 1946 article regarding U.S. biowarfare activities he asserted that "there cannot help but be important advances in knowledge -- many of them fundamental -- and gains in scientific achievement -- many of them capable of practical application. In fact, it is quite impossible for work to be done in this field without such results. It is inherent in the nature of the work. Perhaps no other type of warfare can bring with it such a guarantee of good: economic advantages in agriculture, parallel gains in animal husbandry, and, above all, vital contributions to the fight against human ills and suffering. . . . While we perfect a biological weapon, we perfect the defense against it, thereby destroying the weapon. Would that all weapons of war could be liquidated from the earth as simply as this."[42]

Better welfare through warfare? In light of the final WRS activity reports, Merck's arguments appear mildly disingenuous. Heightened concern for biological threats during this period did, however, provide the impetus for unprecedented military investments in vaccine research and development activity, influencing innovation rates for the next several decades.

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[39] The WBC Committee, "An Account of Its Initiation and Early Activities" (May 15, 1944). NAS: CBW Files.
[40] Memo to V. Bush, "*B.W.*" (February 27, 1942). NA: RG 227, E. 1, B. 35.
[41] Memo to H. H. Bundy, Special Assistant for the Secretary of War, from SGO, "Comments on Biological Warfare" (August 18, 1941). NAS: CBW Files.
[42] G. W. Merck, "Peacetime Implications of Biological Warfare," *The Merck Report* (July, 1946). MA.

II. Patriotism and Opportunism

World War II vaccine development programs were highly productive. As Chapter One demonstrates, the highest rates of innovation in the twentieth century were experienced during the 1940's, and the majority of these innovations derived from these development programs. For example, World War II vaccine development programs developed new or significantly improved vaccines to prevent 10 of the 28 diseases for which vaccines have been developed in the U.S. The AEB, the AMS, and CMR developed the first licensed vaccines for influenza, pneumococcal pneumonia, and plague. The U.S. Typhus Commission within the SGO, with the assistance of the CMR and the AMS, developed an entirely new typhus vaccine after establishing that the former vaccine had lost potency. The CMR, the AEB, and the WRS/CWS developed the first botulinum toxoid and the first Japanese encephalitis vaccine.[43] Finally, the AMS also made significant improvements to the yellow fever, cholera, smallpox, and tetanus vaccines. In particular, these improvements facilitated the wider use of tetanus and smallpox vaccines in the general population after the war.

Why were vaccine development efforts so much more productive during this period than any other period in the twentieth century? There are at least three reasons. The first must be attributed to unique historical circumstances surrounding World War II. The sense of urgency surrounding infectious disease threats during World War II bred a complex mix of patriotism and opportunism that encouraged unprecedented levels of cooperative research and development in biomedicine. Second, enthusiasm for cooperative research was productively harnessed through targeted research and development programs under the OSRD and the military. Third, World War II vaccine development programs encouraged interdisciplinary collaboration (and on the job interdisciplinary training) between the lead-users of vaccines (the military) and their manufactures which, in turn, encouraged high rates of innovation.

Cooperation under the threat of war

The bombing of Pearl Harbor in 1941 thrust the U.S. into World War II and brought a sense of urgency to biodefense plans that had been underway since 1940. As we saw from the previous section, between the 1940 and 1942, biodefense planners stopped evaluating the risks against the benefits of initiating a BW research program and launched into full-scale offensive and defensive preparations for biological warfare. This sense of urgency was not limited to the government

[43] These were not licensed due to the low natural incidence of these diseases in the United States.

however, and defense planners received myriad offers of assistance from the civilian sector. Relating his experiences as the director of CMR, Richards paid tribute to the "unselfish zeal, co-operative spirit, and the competence with which our civilian investigators, laying aside more agreeable pursuits, entered into the attack on problems whose solution was vital to our fighting forces . . . . Never before, we believe, has there been so great a coordination of medical scientific labor."[44]

Political scientist Barry Posen has noted that this phenomenon, in which civilians intervene in military affairs to initiate large-scale adaptive change within military organizations, is not unusual in the face of war. According to Posen, "fear of disaster or defeat prompts statesmen to question long-standing beliefs, to challenge service preferences, to alter budget shares, and to find new sources of military advice and leadership."[45] Similarly, he notes that "soldiers themselves are more likely to examine their traditional premises . . . It is the combination of civilian intervention and increased military open-mindedness that produces the results predicted [innovation]."[46] Although Posen refers to innovation in military doctrine and adaptive changes to grand strategies that integrate political ends with military and political means, his observations reflect the massive adaptive reorganization of military-civilian research and development networks that occurred in the face of World War II. A large portion of the adaptive reorganization of vaccine R&D occurred under the civilian-governed OSRD.

The inception and operation of OSRD was successful, in part, because under the threat of war, traditional barriers to collaboration between industrial, military, and academic institutions collapsed. Potential industry opposition to unprofitable contracts, academic opposition to disrupted research and teaching schedules, and government and military opposition to a technocratic reorganization of the nation's research and development apparatus were all set aside with the understanding that all arrangements would be temporary.

Irvin Stewart, deputy director of OSRD, believed this mentality – that all arrangements would be temporary- accounted for much of the organization's success. He wrote, "the organization was built on a temporary basis, drawing upon the best available men for relatively short periods of time without disturbing their regular academic or industrial trial connections in most cases. This was possible largely because of the pressure of impending and actual war which made men available whose service could not have been obtained on any comparable scale in normal times.

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[44] A. N. Richards, quoted in *Advances in Military Medicine, vol. I*, ed. E. C. Andrus et al., (Boston: Little, Brown and Company, 1948).
[45] B. Posen, *Sources of Military Doctrine* (Ithaca: Cornell University Press, 1984), 60.
[46] Ibid.

The leaders of OSRD were always keenly conscious of this fact, which however completely escaped many people on the outside who, seeing the success of OSRD called for its retention in peacetime. This could never be done. Once the pressure of war lifted, the key men upon whom its success depended responded to the more urgent calls of their regular activities and not all the king's horses nor all the king's men could hold the group together."[47]

From the outset, there were signs that this intense coordination of effort could not be sustained over the long term. Research and development contracts were issued on a "no loss, no gain" basis and they were not designed to be profitable. Contracts covered the cost of research to the performing institution in advance and occasionally calculated overhead to cover hidden costs of research.

There were, however, non-financial costs to cooperation as well. The war did not free investigators of their professional obligations. Richards noted that "although in most cases financial loss to the nonprofit institutions was avoided, there can be no question of the strain put on many of the investigators themselves."[48] This was especially true in universities and medical schools, where, in addition to performing research under war contracts, scientists were expected to train new doctors at an accelerated rate.

The vaccine industry's participation in wartime vaccine research, development, and manufacturing contracts is remarkable given large economic disincentives for doing so both before and during the war. The introduction of sulfa drugs in the 1930's and their success in combating bacterial infections bred widespread pessimism throughout the industry. By the late 1930's, many companies in the vaccine industry were reducing their investments, closing plants, and consolidating activities. For example, the National Drug Company, one of the oldest and most reliable vaccine producers for the military, had embarked on a retrenchment program in which they closed their Germantown plant and consolidated all activities into their plant in Swiftwater, Pennsylvania. According to an internal office memo, "the attitude at the time was that chemotherapy would eventually bring about the complete dissolution of the biological industry."[49]

Despite poor commercial prospects, with the onset of war manufacturers reversed their retrenchment programs and made the investments necessary to scale up production to supply both domestic and allied forces with vaccines. Large military orders did not, however, translate into

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[47] I. Stewart, *Organizing Scientific Research for War* (Boston: Little, Brown, and Company, 1948), 320.
[48] A. N. Richards, quoted in *Advances in Military Medicine, vol. I*, ed. E. C. Andrus et al., (Boston: Little, Brown and Company, 1948).

large profits for the vaccine industry. The government, as the largest single buyer of vaccines, was able to negotiate a lower price for military vaccines, and military orders were large but sporadic. Thus participating producers were forced to invest in the rapid expansion of facilitates to meet high volume orders, and then were left with excess capacity that would not be filled with subsequent orders in any predictable fashion. Further, many vaccines required by the military had limited commercial markets and were therefore unattractive to industry.

Faced with war, patriotism trumped profits and the military managed to procure nearly all of the vaccines it needed for World War II through commercial channels regardless of the economic disadvantages to industry.[50] This list includes not only vaccines for influenza and tetanus, which had a commercial future after the war, but a large number of limited-use vaccines, such as those for rocky mountain spotted fever, plague, botulism, Japanese encephalitis, and rabies.

Reflecting on the capacity of crisis to affect political and economic change, one historian wrote, "World War II constituted a crisis in which state and capital were vulnerable to an external military threat on one hand, and to internal pressures from below (due to a compelling need for working class labor, loyalty and sacrifice) on the other. In response to these threats, the state acted authoritatively and relatively autonomously vis-à-vis the capitalist class. Despite their suspicion of and hostility toward the state, capitalists were forced by the exigencies of war to submit to these statist, collectivist developments."[51] Government orchestrated collaborative vaccine development programs and widespread use of low margin contracts are examples of such "statist" developments in action.

There is little evidence, however, that leaders in the vaccine industry suffered the sense of grudging submission that this interpretation of World War II government-industrial relations would suggest. Rather, company presidents and research directors appeared genuinely eager and proud to assist the war effort. From its inception, the CMR was courted with offers of lab space, personnel and contract services. Vannevar Bush and Alfred Newton Richards, upon their appointments as chairmen of OSRD and CMR respectively, received countless letters from an array of pharmaceutical, chemical and biological houses offering congratulations on their recent government appointments and assistance.

For example, Randolph Major, Director of Research at Merck and Company, wrote Vannevar Bush to assure him that "if we can so arrange our program as to be of help in the Defense

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[49] Internal Memo, "A Recommendation for Future Expansion of the Swiftwater Laboratories" (February 18, 1948). AP.

[50] Exceptions included typhus, which was produced at the Army Medical School, and yellow fever, which was produced by the Rockefeller Institute and the PHS.

Program we shall be glad to do this."[52] Major sent a brochure detailing the research and manufacturing capabilities of the company. [53] Similarly, Hans Molitor, Director of the Merck Institute of Therapeutic Research, wrote to Richards, "to offer you whatever help or assistance the Merck Institute or I personally might be able to give you. Of course you are familiar with our general research program which is right in line with national defense, and with our facilities. However, since you were here last we have further grown, both in personnel and facilities."[54] Richards, prior to accepting his position on the CMR, had served as a scientific advisor to the Merck Institute under Molitor and relations between Merck and the CMR were friendly and familiar.

By all appearances, relations were cordial among institutions contracted to perform biological warfare research as well. According to Merck, the "majority of institutions approached recognized the importance of the biological warfare program and were eager to participate in this war effort. They generously loaned the services of their highly trained staffs and made available, free of charge, their laboratories and equipment."[55]

Cordial, if not enthusiastic, relations existed between the government and the pharmaceutical and vaccine industries, in part, because their interests were united by an external threat. The expectation of public relations benefits, coupled with the fact that the national emergency had a limited time horizon, may also account for industry's willingness to overlook the immediate economic hardships inherent in expanding operations to fill low-margin military contracts during World War II. However, there is also evidence that both industry and government perceived World War II with its calls for patriotic duty, as an opportunity to boost flagging industrial productivity. Thus, far from "submitting to these statist, collectivist developments," the vaccine industry may have seized upon them.[56]

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[51] Paul Adams, *Health of the State* (New York: Praeger Press, 1982), 148.

[52] R. Major, letter to V. Bush (July 21, 1941). NA: RG 227, E. 165, B. 58.

[53] Major took this occasion to remind Bush that "we have a staff of four hundred and fifteen people in our Research and Development Department of Merck and Co. Inc. at this time of whom forty-four are Doctors of Philosophy, forty-one are masters men and sixty-nine Bachelors of Science men." R. Major, letter to V. Bush (July 21, 1941). NA: RG 227, E. 165, B. 58.

[54] H. Molitor, letter to A.N. Richards, NA: RG 227, E. 165, B. 58.

[55] G. W. Merck, "Activities of the WRS in the Field of Biological Warfare" (October 31, 1945). NA: RG 165, E. 488, B. 182.

[56] In his account of OSRD, Larry Owens indicates that industrial relations within NDRC were often strained, raising the question of why this was not the case for biological and pharmaceutical relations with the CMR. Part of the reason may be due to the fact that biological materials were not patentable at this time and thus, there was no danger of the vaccine industry running into the patent disputes that Owen describes. Further, Owens indicates that NDRC- Du Pont relations, in particular, suffered from the company's distrust of OSRD intentions. It is possible that trust issues may have been diffused within the

Mobilizing for World War II paved the way for what was to become a large-scale R&D enterprise. The National Drug Company, for example, expanded its biological facilities five times over their original production capacity during World War II to furnish the military with smallpox vaccine, tetanus and gas gangrene antitoxin. According to the National Drug memo, in order to meet military contracts, "it was necessary also to forsake academic methods of production and to adopt more of the mass production methods found in other industries. We can well assume that our competitors were faced with many of the same circumstances and that they too have adopted the same principles of operation. Subsequent visits to their laboratories have substantiated this assumption."[57]

To motivate employees for this Herculean effort, the National Drug Company made the connection between vaccine production and national security direct and personal. On Dec 12, 1941, all employees received a memo entitled, "Remember Pearl Harbor." It is explained that, "With the actual declaration of hostilities, this plant becomes, from a medical standpoint, a vital link in the chain of National Defense, therefore it behooves us to observe all precautions to maintain an uninterrupted flow of production."[58]

In efforts to nourish employee's sense of patriotism to boost productivity, defense planners made explicit efforts to equate patriotism and productivity with freedom. To make employees feel like a legitimate component of the war effort, the military awarded several commercial vaccine producers with the Navy "E" award, first granted in 1906 for excellence in gunnery. Addressing members of the National Drug Company receiving the award, Lt. Col R.R. Patch illustrated the national security importance of vaccines, attempting to both motivate and reward overworked production crews with patriotic imperatives: "Some of you may have questioned whether you were doing your part in the war effort. Guns, tanks, planes and other agents of destruction are quickly recognized by everyone as war materials. But those things that save life or prevent the loss of life are not so easily recognized. Yet they may be just as important as the destructive implements. Those guns, tanks, and planes are useless without physically fit men to

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CMR due to the fact that the Director of CMR (Alfred Newton Richards) had established a familiar working relationship with industry as a senior scientific advisor to Merck and Company before the war. L. Owens, "The Counterproductive Management of Science in the Second World War: Vannevar Bush and Office of Scientific Research and Development," *Business History Review* 68 (1994): 4.

[57] Internal Memo, "A Recommendation for Future Expansion of the Swiftwater Laboratories" (February 18, 1948). AP.

[58] Internal Memo, "Remember Pearl Harbor" (December 12, 1941). AP.

operate them. You men and women have played an important role in preventing sickness and keeping men fit to fight."[59]

Employees presented with an "E" pin were informed of its significance and expected to wear it as a reminder of their mission. Lt. Commander A.V. Winchell instructed the audience that "as you wear this pin, and I hope you will wear it always, remember that the Army and the Navy presented it to you to realize that you were an integral part of our industrial-military team which will eventually inflict such a devastating defeat upon our enemies. And remember also that you are carrying with you the proudest tradition of our armed forces -- courage, honor, and purity of motive -- and that you hold the key to realize these ideals -- by strength, production, and excellence."[60]

The Under Secretary of Navy instructed that, with the presentation of each "E" award, all employees should be told that "by their unflagging spirit of patriotism . . . by their acceptance of high responsibility . . . by the skill, industry, and devotion they are showing on the production front of the greatest war in history . . . they are making an enduring contribution not only to the preservation of their country but to the immortality of human freedom itself."[61] Thus, in what may be described as a uniquely American brand of patriotism, high-volume industrial production and technological innovation were celebrated as the practical means to a lofty end.

Equating patriotism with production by associating one's business with the war effort also offered good public relations for industry. Merck and Company produced an advertisement during the war for pharmacists to post wherever Merck products were sold. The poster depicts a pharmacist dispensing medicine interposed between Merck's industrial complex, and the shadow of a saluting soldier. This image reveals all that Merck and Company wanted to convey to the public about the direct and essential role of their company in defending the nation's security by defending the nation's health.

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[59] "The 'E' Award: What it means to us," *The National Bulletin of the National Drug Company*, vol. 4, no. 1, (January 1944). AP.
[60] Ibid.
[61] Ibid.

Figure 3: The Pharmacist

Courtesy of Merck Archives, Whitehouse Station, NJ

Thus, defense and industrial planners collectively capitalized on unique historical circumstances, harnessing the sense of urgency wrought by the threat of war to forge unprecedented levels of military-industrial-academic cooperation and productivity. They were able to do this in part from the savvy public relations campaign in which they defined both the production and purchase of biological and pharmaceutical products as patriotic acts. However, a large part of their success stems from the fact that they pursued their objective – the rapid development of new and improved vaccines- with an administrative apparatus that was well suited to applied research and product development.

III. Organization of large-scale R&D for national defense

The government, under the auspices of OSRD, effectively capitalized on the urgency of war to channel the efforts of civilian institutions. Vaccine development programs, in particular, both within OSRD and within the military, took advantage of the sudden willingness of industry and academia to cooperate with the military, forging interdisciplinary teams from both sectors within and outside of the government.

The organizational structure and administration of these programs was well suited to targeted research and development objectives. Vaccine development requires contributions from a wide range of disciplines from immunology, bacteriology and virology, to epidemiology and bio-process engineering. Through advisory committees, the CMR, AEB, and WRS integrated a wide range of outside expert advice with early stage research and development activities in academic and government labs. These CMR and military-led research initiatives united individuals with a diverse range of expertise under a clear objective: to develop, test, scale-up, and manufacture a set of specified vaccines. The top-down organization of these programs also permitted the rapid integration and application of existing knowledge to vaccine production, thereby speeding the development process.

Top-down administrative structures also permitted strong communication and coordination of research objectives with the military services. Close coordination between product development and the needs of defense planners played a key role in the success of vaccine development programs. Individual members of the CMR held joint membership in the Division of Preventative Medicine in the Office of the Surgeon General, in the Navy Bureau of Medicine and Surgery, the Army Epidemiology Board, the Chemical Warfare Service, the Office of the Quartermaster General, and in the Office of the Air Surgeon. In this manner, the CMR ensured that military needs were well articulated and taken into account in all research and development planning

sessions. Research and military objectives were so well coordinated, in fact, that many vaccines were developed for specific military missions. The botulinum toxoid, for example, was developed for D-Day in response to OSS reports that the Germans may have loaded V-1 rockets with the toxin. Similarly, the Japanese encephalitis vaccine was developed in anticipation of a land invasion of Japan.[62]

Top-down coordination of vaccine development programs also accelerated traditional rates of technology transfer, as the OSRD, SGO, and WRS were in a position to transfer people, technology, and ideas to the projects that needed them most. For example, correspondence with Parke-Davis and Company during this period reveals that the SGO coordinated site visits between military and industrial labs, communicated expectations for regulatory standards between the NIH and industry, and provided specialized biological materials and technical equipment to industry. This correspondence also illustrates the central role the SGO as a clearinghouse for materials and technical advice.

Dr. Norbert Fell, Director of the Biological Manufacturing Laboratories of Parke-Davis and Company, was in regular contact with Dr. Paul Hudson, special consultant to the SGO, regarding the development of Bio-toxoid K types A and B, otherwise known as Botulinum toxoid.[63] At one point, Dr. Fell remarked, "During my last visit to Detrick, Dr. Nungster told me that there were several [Pfaudler] tanks . . . available at Detrick that were not in use and that if we ever needed one or two, it might be possible to obtain them."[64] Similarly, Dr. Fred Stimpert, Assistant Director of research at Parke-Davis, often wrote Dr. Hudson requesting materials and technical advice. On one occasion he asks, "Can you supply us with antitoxin for the LF tests? Also I wonder if you happen to have a source of antitoxin or antiserum which might be available for therapeutic use if found necessary. Another question that would be well to have cleared is the amount of formalin to be used in [Bio-toxoid K type] B."[65]

In addition to top-down transfer, a significant amount of technology transfer occurred in a bottom-up fashion. In a manner consistent with Bush's principles of scientific management, OSRD provided broad outlines to direct research, rather than micromanaging the activities of scientists. There is ample evidence to suggest that individual scientists contracted with the CMR

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[62] U.S. Department of the Army, *U.S. Army Activity in the U.S. Biological Warfare Programs,* vol. 1 (February 24, 1977).

[63] Dr. Paul Hudson was a Liaison Officer of the SGO with the Chemical Warfare Service on BW matters.

[64] Pfaudler tanks are glass lined or stainless steel jacketed high capacity tanks. Dr. Norbert Fell, letter to Dr. Paul Hudson (November 27, 1944). NA: RG 112. E. 295A, B. 3.

[65] Dr. Fred Stimpert, Assistant Director Research Department, Parke-Davis and Company, letter to Dr. Paul Hudson (March 3, 1944). NA: RG 112. E. 295A, B. 3.

and WRS were permitted to work out the details among themselves, communicate findings, and to share technology.

For example, letters from Dr. Dubos indicate that he was in conversations with Dr. Meyer, a fellow WRS contractee, regarding difficulties growing *Pasturella pestis* in large quantities. He wrote to Dr. E. B. Fred, a bacteriologist at the University of Wisconsin and Director of the WRS advisory committee asking for permission and funds to transfer the technology (aeration columns) that he and Dr. Hoberman had developed to Dr. Meyer's project. He also asked him to "consider with Mr. Merck and your committee whether it would be advisable to send Dr. Hoberman to Dr. Meyer's laboratory after we have completed the first phase of our work."[66]

In this and other cases, Dr. Fred often encouraged these technology and personnel swaps provided that all parties had security clearances. Similarly, Lt. Commander William Sarles, in a letter to E.B. Fred, indicated that "Drs. Dyer and Topping dropped in for a visit and suggested that we might be able to obtain fairly large quantities of typhus rickettsia material from Parke-Davis Company of Detroit. Parke-Davis will supply this material for experimental purposes without charge. . . . the man at Parke-Davis responsible for the production of the typhus vaccine, Dr. Stimpert, has been cleared and so Dr. Topping can deal directly with him. An arrangement of this type is necessary because the NIH has not been able to produce sufficient material to keep the Notre Dame laboratories fully occupied [these labs were performing tests to dry the vaccine to increase stability]."[67]

Contrary to glowing reports of OSRD's administrative prowess in the accounts provided by Irvin Stewart and James Baxter, there is evidence that OSRD was not always as effective at directing technology transfer efforts as it could have been.[68] OSRD/CMR administrators sometimes became overwhelmed, receiving too many reports to be able to effectively coordinate and integrate the results of all projects.[69] The organization was, however, in an excellent position to learn from its mistakes and to adapt. Bush and Stewart were always available to make quick contract decisions, since the system was not as heavily bureaucratized as it would have been if OSRD had been permitted to grow into an older and larger government agency. CMR directors

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[66] R. Dubos, letter to E. B. Fred (May 14, 1943). NAS: CBW Files.
[67] Lt. Commander William Sarles, letter to E. B. Fred (February 25, 1944). NAS: CBW Files.
[68] I. Stewart, *Organizing Scientific Research for War: The Administrative History of the Office of Scientific Research and Development* (Boston: Little, Brown, and Company, 1948); J. P. Baxter, *Scientists against Time* (Cambridge: MIT Press, 1947).
[69] Larry Owens made similar observations in his analysis of NDRC activities. (L. Owens, "The Counterproductive Management of Science in the Second World War: Vannevar Bush and Office of Scientific Research and Development," *Business History Review* 68 (1994):4, 530.)

encouraged feedback from their industrial partners and they profited from industry's frank assessments of the shortcomings of the organization.

Since the pharmaceutical industry was familiar with the task before CMR --how to apply research findings to product development efficiently and effectively-- they were quick to identify relevant problems and to offer advice. This dynamic was facilitated by the fact that powerful heads of industry, including George Merck, were represented within the biodefense administrative apparatus. Merck in particular, through his directorship of WRS and later as a special consultant on biological warfare, was in close and constant contact with Bush and Richards. Richards was also familiar with the personalities and practices within the pharmaceutical industry, as he had served as a scientific research advisor to the Merck Institute (research arm of Merck and Company) prior to World War II. Communication about issues affecting CMR-industry relations was open, direct, and frequent. For example, in 1943 Merck wrote Richards on the issue of technology transfer. He writes, "I have wanted for some time to plot with you a plan for activating more effectively the interchange of new information between the field and the laboratories. My own feeling is that while every impetus might be given at either end, it is likely to bog down somewhere in between unless a regular system is installed."[70] He relayed to Richards that rumblings within Merck and Company prompted his questions. In particular, Hans Molitor, Director of Research at Merck, had informed him that innovation could be better served by closer collaboration between laboratory and field scientists.[71]

Despite an ability to identify and discuss issues of technology transfer and the proper organization of R&D, the pressures of war may have made it difficult to respond in an effective and timely manner. It was clear by 1944 that some CMR divisions were still struggling to find ways to implement productive information sharing and technology transfer within a top-down administrative structure. Whereas university scientists may have been able to achieve adequate levels of information sharing simply by participating in normal academic communication channels, it appears that industry often had to rely on CMR and OSRD to bring them into the loop.

Also in 1944, Molitor wrote Richards to express frustration with the one-way flow of information from industry to OSRD in malaria research programs. He protested that "despite the

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[70] G.W. Merck, letter to A. N. Richards (September 30, 1943). NA: RG 227, E. 165, B. 58.

[71] Molitor relates to Merck the contents of a letter he received from Dr. Ravdin, a field scientist working for the Medical Corps. Ravdin writes: "Much water has gone over the dam since last I heard from you. I wish to thunder you would send me small amounts of the new things coming out for us to try. You can send 8 oz. packages without request forms. All goes well with me in the jungle." G. W. Merck, letter to A. N. Richards (September 30, 1943). NA: RG 227, E. 165. B. 58.

fact that all of us working on this problem have been cleared by the FBI, and that our laboratory is doing malaria research on a scale as large, if not perhaps larger, than any other laboratory in this country, we receive no direct information regarding the trends and accomplishments of other investigations done under OSRD Army or Navy sponsorship—apparently only because we are not operating under such a contract. Other research laboratories under industry sponsorship are in the same condition; they, as we, communicate findings of interest immediately to the OSRD but receive in return no information . . . it is strictly 'one-way' traffic, which can be of advantage to no one. . . . I fully realize that the problem of disseminating information is greatly complicated by the fact that some of the most active participants in this work are research laboratories of industrial firms, which normally are strong competitors. However, with goodwill on all sides (and I am sure that such good will exists) it should be possible to overcome these difficulties."[72]

Molitor's frustration reflects the tension that existed whenever OSRD attempted to apply its top-down governance structure to projects that required more than the straightforward application of previous findings. Malaria research, for example, was in its infancy and therefore required a more fluid administrative structure than the OSRD was equipped to provide. As individuals from a wide range of disciplines grappled with some of the more fundamental scientific issues standing in the way of effective therapeutic and preventative measures, it was essential to allow for some inefficiency.

Despite charges of "one-way" information flow, the OSRD effectively developed and delivered a high number of pragmatic vaccine innovations in a short time frame. In 1945, James Conant, former director of NDRC under Bush and then president of Harvard University, gave a succinct summary of the method and rationale behind OSRD's successful ventures. In a letter to the editor of the *New York Times* he writes: "There is only one proven method of assisting the advancement of pure science, - that of picking men of genius, backing them heavily, and leaving them *to direct themselves* [emphasis his]. There is only one proven method of getting results in applied science, -picking men of genius, backing them heavily, and *keeping their aim on the target chosen* [emphasis his]. OSRD . . . had achieved its results by the second procedure which is applicable to government-financed research in war time because the targets can be chosen with a reasonable degree of certainty. . . .its objective was not to advance science but to devise and improve instrumentalities of war."[73]

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[72] H. Molitor, letter to A. N. Richards (April, 1944). NA: RG 227, E. 165, B. 58.

[73] James Conant, President of Harvard University and then chairman of the National Defense Research Committee, Letter to the Editor of *The New York Times* in response to an unfavorable editorial regarding Bush's proposals in *Science: the Endless Frontier* (August 3, 1945). NA: RG 227, E. 2, B. 1.

As Conant's comments suggest, the success of World War II vaccine development programs was due less to scientific breakthroughs than to the ability of these programs to distill and apply existing knowledge for new vaccine candidates. In many cases, the basic knowledge required to develop a new vaccine had been available since the 1930's. Barriers to the development of these vaccines were therefore not scientific but organizational in nature and were best overcome by the coordination function provided by these targeted research and development programs. For example, the development of the first capsular polysaccharide vaccine was one of the most radical innovations to come out of World War II vaccine development programs. Not only did the vaccine prevent a previously unpreventable disease, it also used an entirely new method to confer immunity. As was the case with most of the World War II vaccine development successes however, a basic understanding of both the pathogen and the disease had already been well established before 1940.

In 1927 Wolfgang Casper and Oscar Schieman published research in a Berlin medical journal demonstrating that vaccines made from purified pneumococcal capsular polysaccharides would immunize mice against infection from the pneumococcal strains used to make the vaccine. This article offered the first evidence that substances other than proteins could have antigenic properties. The concept of a capsular vaccine was preferable to whole cell vaccines because the polysaccharide capsules themselves are, on their own, incapable of infecting the subject with pneumonia. Thomas Francis, Walter Tillet and Lloyd Felton conducted a series of laboratory and clinical studies to demonstrate the immunogenic properties of pneumococcal capsular polysaccharides at the Rockefeller Institute in the 1930's. Their research identified the particular antigens on polysaccharide capsules responsible for inducing an immune response, and determined how to isolate and purify these antigens to produce a vaccine. Pilot vaccines were tested during the 1930's on volunteers in the West Coast Civilian Conservation Corps.[74] These studies provided early evidence that types I and II polysaccharide vaccines offered sufficient levels of safety and efficacy.

Thus the primary task before the members of the pneumococcal commission became one of identifying which serotypes were most prevalent in military populations and developing and testing a vaccine containing these serotypes, the hard work of determining ways to purify

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[74] T. Francis and W. Tillet, "Cutaneous Reactions in Pneumonia: The Development of Antibodies Following the Intradermal Injection of Type-Specific Polysaccharides," *Journal of Experimental Medicine* 52 (1938):573; L. Felton, "Studies on Immunizing Substances in Pneumococci: Response in Human Beings to Antigenic Pneumococcus Polysaccharides Type I and II," *Public Health Reports* (1930): 53: 1833; G. Ekwurzel et al., "Studies on Immunizing Substances in Pneumococci: Report on Field Tests to Determine the Prophylactic Value of a Pneumococcus Antigen," *Public Health Reports* (1938): 53:1877.

polysaccharide capsules and to demonstrate their antigenic properties having already been completed. In essence, feasibility had been established, and the task remaining was one of coordinating the scientists, engineers, epidemiologists and physicians required to scale up production and to test the efficacy of the new vaccine -- a task World War II development programs were designed to do.

Similarly, much of the groundwork for an influenza vaccine had been laid prior to World War II. In 1933, Patrick Laidlaw, at the National Institute for Medical Research in London, isolated a filterable virus from a patient with influenza and determined that this agent produced flu-like symptoms in a ferret. This agent became known as influenza type A. In 1940 Thomas Francis, first isolated the type B strain of influenza. In the early 1940's Drs. Macfarlane and Burnet in Australia developed methods for growing the virus in developing chick embryos. By 1941, several virologists had determined ways to quantify and titrate influenza-specific antibodies.

Thus, by the time the SGO formed the Influenza Commission in 1941, investigators had already established the etiology of the disease and developed methods for the isolation, cultivation, and purification of the components for an influenza vaccine. With the basics thus established, the top-down administration of targeted research and development of an influenza vaccine was possible and proceeded apace. Though feasibility had been demonstrated in the lab, the SGO still required a vaccine that could be scaled up for industrial production and evaluated for safety and efficacy before it could administer a vaccine to the armed forces.

Thomas Francis, working as director of the Influenza Commission, worked in concert with CMR teams to develop a vaccine. CMR contracts were issued to investigate some of the more technical aspects of influenza vaccine development. Under these contracts, investigators determined conditions to improve virus yields from embryonated eggs, methods to improve titration accuracy, and ultracentrifuge and electrophoresis purification methods. In particular they determined that fractionation with a Sharples centrifuge offered the best method for concentrating and purifying the virus on a large scale relative to previously used elution and precipitation methods.[75] Once a suitable vaccine had been developed on a larger scale, Francis conducted field studies with the vaccine under the auspices of the AEB that provided the first reliable proof of safety and efficacy. A vaccine was available for general administration within the military within two years of initiating the research and development program.

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[75] By 1945, CMR's production methods were accepted by the Army as an alternative to red cell absorption and elution methods that were used in 1944. Industry began widespread adoption of CMR production guidelines by mid 1945 and expanded production to meet civilian markets by early 1946. CMR's Sharples

The experiences of the War Research Service (WRS) provide an interesting foil to the success of OSRD. While the WRS mimicked OSRD's administrative structure and targeted research strategies, it had a less impressive record in vaccine development. [76] This was due in part because of the secrecy restrictions placed on research, which prevented investigators and administrators from engaging in the same level of information sharing that was possible in unclassified vaccine development programs. More significantly, however, WRS investigators lacked a basic scientific understanding of the pathogens under study because they were often asked to work with more exotic, low incidence organisms, such as coccidioides, brucellosis, and tularemia that had not been extensively and systematically studied by the general scientific community.

As Conant had explained in his 1945 letter to the *New York Times*, it was neither possible nor desirable to exercise top-down control on vaccine development projects before a basic scientific understanding of the disease and organism had been established. Indeed, Merck discovered that his efforts to target vaccine research were often thwarted, since WRS investigators often found that they had to circle back to answer more basic questions of the disease before they could make any progress in developing a vaccine.

The experiences of Dr. Louis Julianelle at the Public Health Research Institute in New York City illustrate of some of the problems that beset WRS contractees.[77] Contracted to investigate the bacteriological and immunological aspects of anthrax, Dr. Julianelle found himself unraveling pre-existing knowledge of the disease more quickly than he could add to it. He first tested commercial antisera and determined that could not effectively mitigate anthrax infections. He also determined that sulfa drugs did not work well but that penicillin in high doses was effective antidote. Since penicillin was in short supply, he then attempted, without success, to develop vegetative, capsular, and spore vaccines.

Dr. Julianelle reported to the WRS that "text-book accounts all indicated that the subject was pretty well closed as far as immunization, and specific serum therapy was concerned. It came a good deal as a surprise to discover how incomplete or unreliable was indeed the existing knowledge. Consequently, it has been necessary to rework a number of the more fundamental

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centrifuge purification techniques were considered state of the art in the industry until the 1960's, when zonal centrifugation technologies were transferred from military labs to commercial industry.

[76] Botulinum toxoid was the only human vaccine that came out of the WRS program.

[77] Dr. Louis Julianelle, a bacteriologist, received his PhD. at Washington University Medical School in St. Louis.

phases of "N" [code for anthrax] with the result that progress has been slow and the lag period of relearning prolonged."[78]

In the absence of a clear understanding of development needs, the program had to yield to less efficient, bottom-up decision-making processes that were more suitable for basic research programs. To the dissatisfaction of some WRS advisory committee members (known as the ABC committee), the WRS program began to feel as though it lacked direction.[79] In the absence of visible progress in vaccine development, many scientists began to express their frustration. When the ABC committee was reformed to oversee the expansion of the BW program within the CWS in 1944, Dr. Perry Pepper, a physician at University of Pennsylvania Hospital and director of the new (DEF) committee, had a difficult time encouraging his colleagues from the former committee to renew their commitment.[80]

Dr. Ernest Goodpasture, a professor of pathology and viruses at the Vanderbilt University School of Medicine and a former member of the ABC committee, declined Dr. Pepper's invitation to join the DEF committee. Dr. Goodpasture responded that he had for some time tried to discern the objective of the ABC committee. "I have the feeling that no critical survey of existing potentialities in relations to military needs has been undertaken or at least has resulted in the definition of objectives suitable to guide the work in laboratories. It appears that the military interests are relying entirely on the laboratory worker to suggest application to military uses concerning which the laboratory investigator has no knowledge himself or direction from military experts."[81] Thus, despite best intentions, in the absence of a more fundamental understanding of the more exotic BW diseases under study, the need for more scientific research undercut targeted R&D objectives and demoralized WRS participants.

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[78] Quoted in WRS report for the ABC Sub-Committee, "The Research Program of the War Research Service" (May 13, 1944). NAS: CBW Files.

[79] The ABC Committee (1942-1944) was a joint National Academy of Sciences/National Research Council advisory committee established at the request of George Merck to advise WRS on scientific matters pertaining to biological warfare.

[80] Military investments in the U.S. BW program began to accelerate in December of 1943 when members of the OSS grew leery of Germany's new V-1 rockets. They feared that they might contain botulinum toxin within the warheads and that, by early 1944, the Germans might be getting desperate enough to use them. The BW program was transferred to the CWS within the War Department in 1944 as plans were made for the large-scale development of botulinum toxoid. Under this new arrangement, the new Camp Detrick program expanded to include field testing facilities and production plants in addition to research and development laboratories. At the height of the program, approximately 3,900 personnel were associated with the biowarfare defense mission of the special projects division of the CWS. (U.S. Department of the Army, *U.S. Army Activity in the U.S. Biological Warfare Programs,* vol. 1 (February 24, 1977).

[81] Ernest Goodpasture, letter to Perry Pepper (Oct. 16, 1946). NAS: CBW Files.

I.V. The military as a lead-user of vaccines

OSRD and other vaccine development programs conducted under the AEB and WRS were successful, in part, due to their proximity to the leading end-user of vaccines: the military. Conant explained that targeted "research of this nature, like that in industry, can be effectively organized and planned because there are very definitely defined objectives. And in the case of OSRD, defining these objectives was possible because of close cooperation and frequent consultation with the "users" – the Army and the Navy, those who had control and responsibility for achieving very specific ends."[82] In this manner, World War II vaccine development programs permitted industry to take full advantage of the military's experience with disease and vaccine technologies. This was an unintended yet positive outcome of World War II vaccine development programs.

Prior to World War II, there had been a strong divide between military and civilian scientists. Reflecting on pre-war state of military-industrial relations, Bush writes, "in this country it was not merely that the people turned aside from the paraphernalia for war. Civilians felt that this was a subject for attention only by military men; and military men decidedly thought so too. Military laboratories were dominated by officers who made it utterly clear that scientists or engineers employed in these laboratories were of a lower caste of society. When contracts were issued, the conditions and objective were rigidly controlled by officers whose understanding of science was rudimentary, to say the least."[83] This changed over the course of the war, as both industry and the military discovered that they had much to gain from collaborative vaccine development projects.

Over the course of the war, industry discovered that wherever targeted research was possible however, the military (i.e. military research scientists, military physicians and their patient populations) often proved a valuable collaborative partner that would accelerate vaccine development efforts. Collaborative ventures between the two produced a record number of new and improved vaccines in a short time. The success of these ventures is due in part to the fact that the military's extensive experience with, and need for, infectious disease control rendered it a "lead-user" of vaccine technologies. This term is often used in literature on the management of

[82] James Conant (president of Harvard University and then chairman of the National Defense Research Committee), Letter to the Editor of *The New York Times* in response to an unfavorable editorial regarding Bush's proposals in *Science: the Endless Frontier* (August 3, 1945). NA: RG 227, E. 2, B.1.
[83] V. Bush, *Modern Arms and Free Men* (Cambridge: MIT Press, 1968).

technological innovation to refer to "organizations or individuals that are ahead of market trends and have needs that go far beyond those of an average user."[84]

Indeed, the effects of infectious disease have always been exaggerated under military conditions, and the military has always had vaccine performance needs that exceed those of the general population. Recruitment camps pool individuals from different parts of the country with disproportionate types and levels of immunity. Training regimens compromise immune systems as they produce populations of physically exhausted and emotionally stressed individuals. When people live in close proximity in barracks, communicable diseases spread like wildfire. Consequently, respiratory and common childhood diseases such as measles, mumps and rubella present a greater threat in military contexts than in civilian life. In the field, troops are also subject to poor sanitation and unfamiliar disease vectors, such as mosquitoes that transmit yellow fever and malaria or arthropods that spread rickettsial diseases.

Scientists and physicians working in military contexts had extensive experience with disease and vaccines and were able to provide clear direction on research objectives and development needs, as was the case, for example, with the pneumococcal and influenza vaccines. They were adept at helping industry to bridge the "basic-applied" gap that existed between their knowledge of which pathogens cause disease and how to produce vaccines from them. Military scientists and physicians were skilled at identifying new diseases in military populations and defining their etiology. Since they were treating homogenous populations that ate, slept and worked under similar environmental conditions, they were quicker to identify population level characteristics that characterized new and familiar diseases.

Furthermore, unlike their academic counterparts, the military shared industry's product development orientation. They were skilled at isolating and culturing pathogens, and developing pilot lots of vaccine for testing. In this manner, they were strong where industry was weak. Once they were able to demonstrate the feasibility of a vaccine candidate in this manner, industrial scientists were then able to apply their talents to the problems of scaling up production for large-scale testing and licensing. Working together, military-industrial development teams managed to overcome and avoid hurdles that would have beset the development process if each group had worked in isolation.

Military installations, with their advanced record keeping systems and high disease rates within controlled populations, also offered a testing ground and market for new vaccines. One member of the Preventative Medicine Division noted that "the practitioner of military preventive

[84] E. von Hippel, W. Thomke, and M. Sonnack, "Creating Breakthroughs at 3M," *Harvard Business*

medicine has at his disposal information on morbidity of a quality not available in any other social organization; records of admission to hospital and quarters are a part of the military system. These data permit sound evaluation of non-effectiveness and of the reasons for discharge for medical disability."[85] Under these conditions, scientists were able to conduct clinical trials to test the efficacy of vaccines efficiently and reliably. Over the course of the war, the AEB conducted trials, affording the first reliable demonstration of the safety and efficacy of the newly developed plague, botulinum toxoid, Japanese encephalitis, pneumococcal, and influenza vaccines.

Dr. Francis, who directed trials within the Army Specialized Training Program Units (ASTP), explained how field trials at military installations afforded a unique opportunity to assess the efficacy of the early vaccines developed by the AEB Influenza Commission. The installations "were stable populations and subject to constant, uniform observations. It was possible to obtain participation of entire units so that vaccinated persons and controls could be properly designated rather than depending upon the less desirable and unpredictable basis of volunteers."[86] Together with the CMR, industry, and the SGO, Francis worked to standardize the vaccine production procedures, record systems, observation procedures, and the viral and serological tests that would permit the uniform clinical study of over 12,500 members of ASTP groups across the country. These men were vaccinated in October and November of 1943, just weeks before an influenza epidemic hit the nation.

By early January, the influenza board was able to provide the first conclusive evidence of an efficacious vaccine against epidemic influenza A, which permitted the SGO to recommend the vaccine in the event of another outbreak. An epidemic of influenza B in 1945 afforded an opportunity to demonstrate efficacy of the B strain as well. Naval and ASTP units were already under observation at the University of Michigan and Yale University when the B strain hit in November and December. Comparison of the hospital admission rates between vaccinated and unvaccinated groups were used to demonstrate efficacy of the vaccine.

The zenith of wartime clinical research was reached under the auspices of the AEB, when Dr. MacLeod performed the first double-blind randomized clinical trial to test the efficacy of a quadravalent vaccine for the military.[87] The study included 8,500 men at the Army Air Force

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Review (September/October, 1999).

[85] J. Gordon, "General Considerations of Modes of Transmission," Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts, *Preventative Medicine in World War II, vol. IV*, ed. Col. John Boyd Coates, Jr., MC (1958), 5.

[86] T. Francis, "Influenza," vol. IV of Communicable Diseases Transmitted Chiefly Through Respiratory and Alimentary Tracts, *Preventative Medicine*, ed. Col. John Boyd Coates, Jr., MC (1958), 121.

[87] C. M. MacLeod et al., "Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides," *Journal of Experimental Medicine* 82, no. 6 (1945): 445.

Technical School, half of whom received the vaccine and the other half received a placebo. At the end of a seven-month observation period, four men in the experimental group contracted pneumonia, whereas 26 men in the control group contracted the disease. The results were considered to offer a sufficient demonstration of efficacy, and only mild reactions to the vaccine had been reported. Dr. Michael Heidelberger, a Colombia-trained immunochemist who had also been part of the AEB commission, recalls that "the entire study, so beautifully organized and monitored under Colin M. MacLeod's direction, showed that epidemics of pneumococcal pneumonia in closed populations could be terminated within two weeks after vaccination with the polysaccharides of the causative types."[88] This study, according to Dr. Heidelberger, set the standard by which all future clinical trials would be held.

Even in the absence of well-planned clinical trials, the widespread use of a vaccine in military populations often offered de facto evidence of safety and efficacy. Military use of vaccines also revealed problems and guided improvements to vaccines before they were disseminated through the general population. Prior to World War II, for example, the value of tetanus vaccines was relatively unknown and thus the vaccines were not widely used in civilian populations. Widespread military use of and experimentation with the vaccine during the war, however, paved the way for general use after the war. In-house research conducted by the SGO Preventative Medicine Division identified peptones in the vaccine broth as the likely culprits for allergic reactions among personnel. In response to this finding, the SGO contracted Dr. Mueller at Harvard Medical School to develop a synthetic alternative to broths containing peptones. Once this had been accomplished, in 1941 Dr. Veldee, Chief of the Division of Biologics Control, wrote to the producers of tetanus toxoid to inform them of the problems with the vaccine and shared with them Dr. Mueller's formula for an effective synthetic alternative. The letter hinted that manufacturers would be wise to adopt Dr. Mueller's process formula if they wished to be eligible for military contracts in the future.[89]

Once industry adopted the new process formula, the military experienced such high rates of safety and presumed efficacy that, in the absence of formal clinical trials, the American Pediatric Association announced in 1944 that it recommended routine use of the vaccine in the general population. Similarly, administration of the yellow fever vaccine at the beginning of the war revealed the dangers of using human serum to stabilize vaccines, as many lots of the vaccine

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[88] Michael Heidelberger, "A 'Pure' Organic Chemist's Downward Path," *Annual Review of Biochemistry* 48 (1979): 1-21.

[89] M. V. Veldee, Chief, Division of Biologics Control, "To Licensed Manufacturers of Tetanus Toxoid" (October 3, 1941). AP.

contained hepatitis B contaminated serum. This pressed the PHS to develop a non-serum based version of vaccine in 1942.

In addition to initiating safety enhancements, military users often initiated improvements to the efficacy of these vaccines since they often had vaccine protection needs that were well in advance of those civilian populations. Thus, many of the companies that worked closely with OSRD and the AEB to develop vaccines found themselves at an advantage after the war, since their vaccines, if not entirely new to the market, reflected the highest standards of purity and potency.

As the nation's canary for future disease threats, however, the military has proven to be a highly sensitive indicator, sometimes so sensitive that close collaboration with the military has on occasion put industry on the bleeding edge rather than the leading edge of vaccine development. As was the case with the pneumococcal vaccine in World War II and meningococcal vaccines in the 1970's (and as may prove to be the case with anthrax vaccines), the military encouraged industry to develop vaccines well before commercial markets could support industry participation. In each case, industry had to terminate production of the vaccine. And in each case, the decision to terminate proved premature as civilian vaccine protection needs eventually caught up with those of the military.

The World War II development of a pneumococcal vaccine illustrates the point. Through the AEB and the AMS, the military continued to invest in a pneumococcal vaccine after both industry and academia had lost interest. After the antibiotic sulfapyridine was introduced in 1939, physicians began to substitute the pneumococcal antisera that were on the market for sulfonamides, which were less expensive, easier to administer, and considered safer and more effective against a wide spectrum of pneumococci. With this development, researchers who had been interested in developing a novel vaccine to induce active immunity to pneumococcal pneumonia began to focus their efforts elsewhere. However, given military incentives to reduce the overall number of sick-days for the armed forces, preventative measures remained more attractive to them than therapeutic ones, and the AEB formed the Commission on Pneumococcal diseases to continue research for a vaccine.

By 1944, the decision to continue pnuemococcal research proved to be a wise one, since training bases began to reveal some of the holes in the new antibiotic armamentarium. An Army Air Force training base in Sioux Falls South Dakota began to experience recurrent epidemics of pneumococcal pneumonia despite the use of sulfa drugs. Under the auspices of the AEB, Dr. Colin MacLeod and his team developed a pilot vaccine derived from isolates taken from military personnel. Based on their research, and at the behest of the Army, E.R. Squibb and Sons

proceeded to prepare a quadravalent vaccine for clinical trials. This was a risky proposition for Squibb, since it required them to build entirely new production facilities for a vaccine of unproven safety and efficacy. It is unlikely that they would have undertaken this project except for clear military need in a time of war.

By the war's end, pneumococcal pneumonia continued to pose a perennial threat to military installations and the vaccine required further development. Eager to obtain a regular supply of the vaccine, the Army medical branch asked Michael Heidelberger at the Columbia University School of Medicine to continue work on a capsular polysaccharide vaccine with pneumococci types I, II, V, and VII.[90] Subsequent studies by Dr. Heidelberger further demonstrated the safety and efficacy of hexavalent vaccines.[91] On the basis of Heidelberger and MacLeod's safety and efficacy data, the Army again urged Squibb to develop and market two hexavalent pneumococcal capsular polysaccharide vaccines. By 1945 Squibb had already poured millions into the building and staffing of new plants simply to produce the vaccine for clinical trials, so in 1948 they agreed to market one for adults and one for children, each containing a slightly different array of serotypes.

Despite the proven safety and efficacy of pneumococcal vaccines, they were a commercial failure. Antibiotic resistance to pneumococci was not yet as widespread in civilian populations as it had become in the military by the end of World War II. Doctors, convinced of the efficacy of antibiotics in treating pneumococcal infections, preferred therapeutic to preventative measures as a general rule.[92] As the use of antibiotics grew increasingly widespread, Squibb could no longer afford to stay in the pneumococcal vaccine business, and, in 1954, the company terminated production of the vaccines. Levels of antibiotic resistance in civilian populations eventually caught up with those of military populations and commercial interest in pneumococcal vaccines resumed by the 1970's, but it was far too late for Squibb to recover from its financial losses.

Regarding vaccine development from the perspective of lead-user innovation theories sheds light on the effects of institutional objectives and inter-institutional collaboration, not only on the rate, but also on the type of innovation produced. For example, in contrast to private medicine, military medicine is directed towards improving daily non-effectiveness rates. Thus, scientists working within military research organizations are highly motivated to devise population-based

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[90] The SGO was familiar with Heidelberger through some contract research he performed for the WRS during the war. He had participated in the WRS Blood Studies in which scientists were contracted to test blood samples of war prisoners for evidence of antibodies to anthrax and botulism antitoxin.

[91] M. Heidelberger et al., "The Human Antibody Response to Simultaneous Injection of Six Specific Polysaccharides of Pneumococcus" *Journal of Experimental Medicine* 88 (1948): 369.

preventative measures such as vaccines. Private medicine, on the other hand, tends to promote the use and development of individual therapeutic measures, which are more effectively used in the context of an individual doctor-patient relationship since care is initiated only after the patient has already contracted an illness. Though a doctor may perceive the public health value of population based measures, his/her ability to implement them on a wide scale is limited.[93]

As Squibb's early development of a pneumococcal vaccine demonstrates, military-industrial cooperation is likely to encourage higher rates of vaccine innovation and use, whereas industrial collaboration with institutions representing the interests of private medicine would have been more likely to encourage higher rates of therapeutic innovations. Given the high rates of military-industrial collaboration achieved through federal vaccine development programs during the war, it should come as no surprise that the 1940's witnessed higher rates of innovation than any other decade in the twentieth century.

V. Conclusions

Three factors explain the success of World War II vaccine development programs. First, the threat of disease to national security was perceived as clear and immediate. A sense of urgency and patriotism, coupled with the understanding that all arrangements were temporary, fostered unprecedented levels of collaboration among military, industrial, and academic scientists.

Second, World War II vaccine development programs provided a governance structure that was well designed to harness the enthusiasm and efforts of scientists within industry, academia, and the military. These programs provided top-down governance for large-scale, targeted R&D programs, resulting in the cross-fertilization and coordination of people, technology, and ideas, which facilitated the distillation and application of existing knowledge regarding potential vaccine candidates.

Third, in what was a positive, yet unintended outcome, World War II vaccine development programs paired industrial vaccine developers with their lead-users. As a "lead-user," the military

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[92] Office of Technology Assessments, "*A Review of Selected Federal Vaccine and Immunization Policies*" (Washington, D.C., 1979), 32.

[93] Other studies have noted political and professional motivations for this separation of preventative and curative medicine. Evelynn Hammonds history of diphtheria prevention in New York City at the turn of the century highlights this point (E. Hammonds, *Childhood's Deadly Scourge; The Campaign to Control Diphtheria in New York City, 1880-1930* (Baltimore: Johns Hopkins University Press, 1999) 207.
Paul Starr attributes this separation, not only to turf wars between public health and private medicine, but to an abiding American belief that "the state should not interfere with private business.""(P. Starr, *The Social Transformation of American Medicine*, (Basic Books: New York 1982), 196).

was well positioned to anticipate product development needs and to detect potential problems with existing vaccine candidates. Furthermore, unlike their academic counterparts, military research scientists shared with industry an interdisciplinary product development orientation while they were also engaged in early stage vaccine development activities. In this role, they were well suited to help industry bridge the gap between early and late stage vaccine development. For example, military medical scientists, most notably those at the Army Graduate Medical School (later known as the Walter Reed Army Institute of Research or WRAIR) were skilled at identifying new diseases in military populations, isolating and culturing the relevant pathogens, and developing pilot lots of vaccine for testing. Once the feasibility of a new vaccine candidate had been demonstrated, industrial scientists were then able to apply their talents to the problems of scaling up production for large-scale testing and licensing. Pairing these heterogeneous, yet complementary skills of military and industrial research, scientists accelerated vaccine development efforts during the 1940's. The product development advantages of collaboration, coupled with a pervading sense of social obligation and patriotic duty, forged alliances and engendered a "culture of collaboration" between military and industrial vaccine developers that, as the next chapter will demonstrate, continued to encourage innovation through the postwar period.

Chapter Three: The Legacies of World War II Vaccine Development Programs in the Postwar Era

By the 1950's, the urgency generated by the threat of world war had diminished, and the governance structure provided by World War II vaccine development programs had dissolved. Thus, two out of the three factors identified in the previous chapter as having contributed to high rates of vaccine innovation in the 1940's were no longer present. Nonetheless, military-industrial vaccine development networks remained intact, and relatively high rates of vaccine innovation persisted throughout the postwar era.

How did these networks sustain innovation throughout this era in the absence of strong economic incentives for industrial vaccine development or federal coordination? A close examination of the collaborative efforts of the Walter Reed Army Institute of Research, Merck and Company, and the National Drug Company to develop the influenza and meningitis vaccines reveals how military-industrial collaboration fueled vaccine innovation during this period. In particular, these cases demonstrate how participation in World War II vaccine development programs forged a set of personal friendships, ideologies, and R&D practices that formed the basis for a productive postwar culture of military-industrial collaboration.

I. Postwar Vaccine Industry: early prospects

Just as wartime research in electronics, aircraft design, and jet propulsion formed the base for the expansion of postwar industries, so too did wartime research in vaccine development transform the U.S. vaccine industry, formerly a cottage industry, into a full-scale research and development enterprise. In cooperation with the CMR, AEB, and WRS, U.S. companies developed ten new and improved vaccines in the 1940's. Furthermore, in a gesture that was symbolic of the growing independence and sophistication of the U.S. vaccine industry, the government began ship many of these vaccines to their European allies to assist in the war effort.

This marked a significant reversal in the international status of the U.S. vaccine industry. When World War I cut off American supply lines to European research and laboratory equipment, U.S. manufacturers struggled to provide the military with vaccines, toxoids, and antitoxins and were forced to acknowledge their dependence on their European counterparts. Dr. Richard Slee, director of the commercial vaccine laboratory in Swiftwater, Pennsylvania (which later became the National Drug Company) wrote to the director of Abbott Laboratories in Chicago with a confession: "America may be a very bright nation, but between you and I, we are

really nothing but a nation of assemblers and we have built up our reputation most largely on adopting European ideas, buying their stock, stamping it together and putting a nickel plate or polish on it and calling it a product of America."[1]

The expansion of research and development (R&D) based firms after World War II is a common theme in twentieth century U.S. industrial history.[2] However, the growth of the U.S. vaccine industry was not assured after the war. In fact, in the years immediately following World War II, prospects for U.S. vaccine manufacturers looked grim. After the war, most government contracts were terminated, leaving companies with excess production capacity, huge inventories, and insufficient commercial demand. Worse, wartime testing of biologicals demonstrated that a large number of widely sold antitoxins, toxoids, and vaccines were ineffective, and wartime advances in the development of sulfonamides and penicillin nearly eliminated demand for bacterial vaccines. Even some of the vaccines developed during the war, which were expected to have wide market appeal, were not doing well commercially. The influenza vaccine, for instance--though it prevented a widely feared viral disease that affected a large percentage of the U.S. population--was not popular on the market because it caused sore arms and fevers.

Commercial biological houses began to reconsider their pre-war retrenchment programs. According to an internal memo from the National Drug Company, "the major portion of government contract work was completed by the end of 1946. At that time the attitude of management . . . was somewhat pessimistic regarding the volume of biological business to be anticipated during the post-war era. Plans were made to consolidate facilities and some attempts to increase efficiency were made."[3]

There were, however, a few reasons for cautious optimism within the industry. In addition to rising birth rates, which signified growth in pediatric markets, there was evidence that widespread use of vaccines in the Armed Forces had reduced cultural barriers to immunization. As servicemen returned home, most of whom had received multiple immunizations with no ill effects, vaccines gained a reputation within the general population as a harmless, routine, medical intervention.[4] "War" the memo notes, "was the greatest test of the efficacy of biologics," and it

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[1] Dr. Slee, letter to Dr. Biehm (1915), quoted in J. Widmer, *The Spirit of Swiftwater*, (Swiftwater: Connaught Laboratories, 1997), 29.

[2] A. Chandler, "The Competitive Performance of U.S. Industrial Enterprises since the Second World War" *Business History Review* 68 (Spring 1994): 1-72; D. Mowery and N. Rosenberg, *Paths of Innovation* (Cambridge: Cambridge University Press, 1998).

[3] Internal Report, "A Recommendation for Future Expansion of the Swiftwater Laboratories" (February 18, 1948). AP.

[4] Although the postwar period represents a time of relative cultural acceptance of vaccines, vaccine technologies have never diffused through U.S. populations and medical communities without opposition and a variety of anti-vaccinationist groups have been active since the development of the first smallpox

spurred cultural acceptance of vaccines among doctors, scientists and the general public. Thanks to wartime immunization programs, 12 million men returned to their homes with at least some knowledge of how and why they are used."[5] Public education campaigns further encouraged public acceptance. The report notes that, "the American public is becoming better informed through current periodicals, movies, and broadcasts about the 'shots' that they formerly dreaded and now more than often request."[6] While the commercial future of vaccines remained ambiguous in the immediate postwar years, the vaccine industry waited and watched events unfold in Washington.

Cold War investments in vaccine research

Significant political changes following the war hinted at brighter prospects for military-sponsored vaccine research as well. The contributions of OSRD to the war effort provided ample political justification for continued federal investments in science and technology. Arguments for continued federal support for research were based on the premise, made famous by Vannevar Bush's report to the President, *Science -- the Endless Frontier*, that a strong scientific base is an investment in the economic health and security of the nation.

Federal support for biomedical research had strong advocates after the war. Regarding federal aid for biomedical research, Alfred Newton Richards, former chairman of the CMR and president of the National Academy of Sciences, observed, "the experience of OSRD has proved that none of the universities which were called upon for OSRD work could afford to undertake it on the scale which the emergency demanded at the expense of its own resources. Hence, if the concerted efforts of medical investigators which have yielded so much of value during the war are to be continued on any comparable scale during the peace, the conclusion is inescapable that they must be supported by government."[7]

James Simmons, Chief of the Preventative Medicine Service, argued for continued sponsorship of medical research as well, contending that "the security of the nation depends on the health and physical strength of all its people, both military and civilian, and that a continuing

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vaccine in 1796. For an account of the activities of the Milwaukee Anit-Vaccinationst Society in 1892, see J. Leavitt, *The Healthiest City: Milwaukee and the Politics of Health Reform* (New Jersey: Princeton University Press, 1982).

[5] Internal report, "A Recommendation for Future Expansion of the Swiftwater Laboratories" (February 18, 1948). AP.

[6] Ibid.

[7] Draft report of the OSRD Medical Advisory Committee, "Effect of War on Medical Education and Research" submitted by Walter Palmer, Chairman of the Committee to Vannevar Bush, (April 25, 1945). NA: RG 227, E. 2, B. 1.

program of research in military medicine is essential to its security."[8] In an appeal to protect research budgets from changes in future political and security climates, he went on to explain that "the need for medical research by and for the Army bears no direct relationship to the size of the Army. The medical problems of a future war will be the same regardless of the size of the Army during the intervening years."[9] Richards and Simmons' arguments were well received for, as Bruce Smith has argued, the postwar period was characterized by a high level of "consensus" on the question of whether federal investments in science and technology improved the security of the nation, the health of the economy, and the human condition.[10] All that remained for the argument was a clear articulation of where and how to support this research.

A number of proposals for a national foundation to support scientific research were debated in congress for several years following the war.[11] When the shape of OSRD's successor, the National Science Foundation (NSF), was finally agreed to in 1950, it was clear that the NSF would support only non-targeted forms of biological research. Responsibility for the sponsorship of more applied forms of research would fall partly on military research institutions and partly on the NIH. This was not the arrangement that either Bush or Richards had envisioned for federal support of medical research. They favored instead an independent agency (which they called the "National Foundation for Medical Research"), which would disperse grants-in-aid to medical schools and universities. In their view, no pre-existing agency, including the NIH, was "sufficiently free of specialization of interest to warrant assigning to it the sponsorship of a program so broad and so intimately related to civilian institutions."[12] Concerned that federal planners might grant too much credit for wartime innovations to the military labs themselves, Bush and Richards wanted to turn the government's attention back to the universities. In support of this point, Richards wrote: "It must be emphasized that there is little in war medicine that did not have its roots in civilian studies and practice. The pressure of war served chiefly to accelerate

[8] Brig. General James Simmons, Chief of the Preventative Medicine Service, OSG, U.S. Army, statement for presentation, December 14, 1944, before the Senate Sub-Committee on Wartime Health and Education, under the Chairmanship of Senator Claude Pepper. NA: RG 165, E. 488, B. 183.
[9] Ibid.
[10] B. Smith, *American Science Policy since World War II* (Washington, D.C.: The Brookings Institution, 1990).
[11] For a historical account of the politics surrounding the acceptance of a national science program during this period see: D. Kevles, "Principles and Politics in Federal R & D Policy, 1945-1990: An Appreciation of the Bush Report" preface to V. Bush, *Science—The Endless Frontier* (Washington, D.C.: National Science Foundation, 1990). See also J. Kleinman, *Politics on the Endless Frontier* (Durham: Duke University Press, 1995).
[12] V. Bush, *Science—The Endless Frontier* (1990; reprint, Washington D.C.: National Science Foundation, 1945).

the development and large scale application of discoveries particularly applicable to military needs."[13]

By the postwar era however, this trend began to reverse itself, and it began to appear that there was little in civilian vaccine development that did not have its roots in military research programs. A review of new vaccine development since 1950 reveals that military sponsored research continued to make significant contributions in the second half of the twentieth century.[14] Military research labs contributed to the development of eight out of fourteen new vaccines licensed during this period: the adenovirus, anthrax, hepatitis A, hepatitis B, Japanese encephalitis, measles, meningococcal meningitis, and rubella vaccines.[15] Of these eight vaccines, five were developed in the postwar period: the adenovirus, anthrax, measles, meningococcal, and rubella vaccines. Research conducted in military labs during this period also contributed to incremental innovations in the development of the influenza vaccine and combined diphtheria tetanus vaccines.[16]

This high number of significant contributions from military research labs may be attributed in part to shifting patterns of federal funding for military medical research after World War II. When Bush's and Richards' proposed successor agency for the CMR failed to materialize, federal support for vaccine research began to flow to pre-existing government research organizations such as the NIH and, most notably, the Army Medical Graduate School (AMS). OSRD contracts were transferred to the Army Medical Research and Development Board and World War II vaccine development projects were subsumed into in-house research programs at the AMS and Fort Detrick.

The Rise of WRAIR

By 1947, the Army Medical Research Development budget accounted for one fifth of the entire federal budget ($28 million) for research in medical and allied sciences.[17] This stands in stark contrast to the status of medical research within the War Department prior to World War II. According to one report, the entire research and development budget for the Quartermaster Corps

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[13] Draft report of the OSRD Medical Advisory Committee, "Effect of War on Medical Education and Research" submitted by Walter Palmer, Chairman of the Committee to Vannevar Bush, (April 25, 1945). NA: RG 227, E. 2, B. 1.

[14] See Table 4, Chapter One, for specific details on the contributions of military research.

[15] A new vaccine is defined as the first safe and effective vaccine licensed to prevent a disease for which no form of active immunity was previously available. I do not include the Rotavirus vaccine in this total, which was licensed in 1998 but withdrawn in the following year for causing bowel obstruction in infants.

[16] See Table 4, Chapter One, for specific details on the contributions of military research.

[17] Final Report on Review of Medical and Biological Programs within the Department of Defense, Institute of Defense Analysis (August 1962): B-3. NA: RG 319, E. 181, B. 1.

totaled $1,000 in 1939.[18] With sustained infusions of federal funding, the AMS expanded their facilities throughout the 1950's and in 1955 renamed the research branch of the AMS the Walter Reed Army Institute of Research (WRAIR). By 1958, the Army Research and Development Board was reorganized into the U.S. Army Research and Development Command, a network of military labs and installations performing medical research, which expanded to include fourteen laboratories in the U.S. and overseas.

Cold War anxieties surrounding the threat from nuclear and biological warfare fed these investments in military medical research and development. According to a memo arguing for an expanded research program at WRAIR in 1959, "if we are to fight the kind of ground war that is projected for the future, or if we are to pull ourselves together after a massive nuclear attack and prepare to support any kind of war, we will be faced with circumstances under which our control of the environment will be in many cases very greatly reduced. Therefore the threat of infectious disease, such as I have noted above, may be vastly greater under these projected circumstances that it would appear to be if one merely looked around the world today."[19]

Arguments for WRAIR's expanded program also stressed that "the importance of getting competent personnel into the field, working on diseases of major importance in their natural environment must be strongly emphasized if we are to improve our preparedness to deal with these diseases in various parts of the world."[20] Regardless of the source of disease (natural or manufactured), the military felt it was their duty to develop and stockpile vaccines to ensure operational effectiveness or to stabilize populations in the event of an attack with a weapon of mass destruction.

The military expanded their biological warfare research and development efforts in the AFEB as well, for a similar set of reasons. At a 1959 AFEB meeting, General Hays (Surgeon General of the Army) observed, "there has been in the last two years with the Army Medical Service rather a shift-over in the picture of BW [biological warfare]. I can remember just a few years ago when most of our people took the attitude that nothing had been proved in this field, and therefore, there was nothing to it. I think that the opinion of our people has changed, and that we all feel that BW exists as a potential weapon, and that we must very actively pursue research in this field."[21]

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[18] Ibid.
[19] Memo to the Director of WRAIR, "Program for Expanded Research on Infectious Disease" (July 14, 1959). NA: RG 112, E. 1035, B. 90.
[20] Ibid.
[21] Minutes, spring meeting of the Armed Forces Epidemiology Board, (May 18-20, 1959). WR.

This increased focus on biodefense and vaccine development was reflected in part in the growing budgetary allocations for the Army Medical R&D Command. After hovering between $10.1 and $10.5 million for the first half of the 1950's, the command enjoyed successive budget increases since 1956 (Table 1). More tellingly, military commitment to biodefense research and vaccine development produced a high number of vaccine candidates for diseases affecting individuals outside of the United States. The success of these military-led research initiatives reflected in the number of investigational new drug applications (IND's) filed for biodefense vaccines during the 1960's (see Table 2, Chapter 5).

Table 1: Army Medical R&D Command Funding in Millions [22]

FY	51	7.0	FY	57	11.2
	52	10.1		58	12.4
	53	10.2		59	12.5
	54	10.1		60	13.2
	55	10.2		61*	19.5
	56	10.5		62*	20.3
				63*	21.3

* Pentagon approved prospective requested funds

U.S. "occupation" of contested Cold War territories also had positive, if unintended, consequences for international public health. As part of WRAIR's expanded program in vaccine development, WRAIR and the AFEB enhanced their epidemiological and clinical competencies by expanding their network of international laboratories and field stations. The military's international presence in countries such as Thailand and Malaysia directed the attention of modern military medicine towards tropical diseases that were of little commercial interest to U.S. pharmaceutical firms. During this period, they made significant contributions to the improvement of the Japanese encephalitis, typhoid, and cholera vaccines and made important investments in malaria research (see Chapter 1, Table 4).

The SGO was not merely interested in expanding military research and improving force protection through biodefense. They were keenly aware that a strong international presence would permit them to use modern medicine in general, and vaccines in particular, as a political

instrument of the Cold War. For example, a SGO memo stated that military medical presence overseas "establishes warm personal and professional ties with key individuals and the populations generally of countries in so-called "underdeveloped" regions—greatly enhancing the prestige of the U.S. among nations of the world."[23]

Another report on the commitment of public health teams to Vietnam explained that "the training of medical sub-professional personnel -- medics, nurses, laboratory technicians, and teachers drawn from the people of a national minority -- can lead to further acceptance of Western ideas and ideals. Subsequently, the minority group may be led to a wish to provide its own military contribution to the Central Government as a response to a feeling of conciliation and concern on the part of the government, demonstrated through introduction of modern medicine and education."[24]

A 1961 polio epidemic in Kyushu Japan incited a political skirmish, which made it clear that the U.S. and Russia were consciously employing vaccines as a tool to win the hearts and minds of individuals in contested regions. It was reported that "the Russians have offered the Sabin vaccine for inoculations to the Japanese and naturally, they feel they cannot refuse this offer from a political standpoint. A polio inoculation program has never been established in Okinawa because they have a natural program of immunization. Okinawa is a U.S. occupied and administered territory and it is believed (in order to avert adverse publicity) that these children should be inoculated quietly and quickly although preventative medicine people realize it is unnecessary. However, the Russians would enjoy using this as a means for their propaganda."[25]

WRAIR's breed of "science integrators"

The Army Medical Research and Development Command and its network of laboratories were not merely expanding in size; the quality of research was improving as well. In particular, infectious disease research at WRAIR was developing a reputation in the postwar period on a par with university-based research. According to Maurice Hilleman, noted industrial vaccine research scientist and former member of WRAIR's Department of Respiratory Diseases from 1948 to 1956, WRAIR had become the "epicenter for infectious disease research in the world."[26]

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[22] Ibid.
[23] Minutes, from the Surgeon General's Early Morning Meetings, (July 1, 1960). NA: RG 112, E. 1014, B. 9.
[24] L. Friedman, "American Medicine as a Military-Political Weapon," *Army R & D Command Annual Report* (November 26, 1965). NA: RG 112, E. 1012.
[25] Minutes from the Surgeon General's Early Morning Meetings (July 21, 1961). NA: RG 112, E. 1019.
[26] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

Similarly, referring to both WRAIR and Fort Detrick, another vaccine research scientist asserts that the "military was a center of excellence for infectious disease research."[27]

Whereas the military performed virtually no organized in-house medical research prior to World War II, WRAIR now offered a viable career option for young scientists graduating in the late 1940's and 1950's. A report from the Army Medical Service R&D program noted that "prior to World War II, medical research was rarely a full time duty assignment for medical officers and still more rarely a career. Much of the research was done on an individual basis and on individual initiative."[28] After the war, however, military research labs boasted state-of-the-art facilities and starting salaries competitive with university and industry laboratories.[29] WRAIR, Dr. Hilleman explained, "was where all the bright young doctors graduating from medical school would go. If you were about to be drafted and a professor had someone with tremendous aptitude, it would have been a waste to send them out to an aid station--so they were referred to the Walter Reed research program. They would do research in the field and had a base at Walter Reed. They were so good that for a time, the heads of many Infectious Disease and Pediatrics departments had been at Walter Reed. They were an illustrious set of alumni."[30] Dr. Hilleman goes on to note that "this practice [of filtering talent through Walter Reed] continued right up to Korea. This was a great way to evade service in a productive manner. They would get all the best men."[31]

Military research labs offered exceptional training opportunities for scientists interested in vaccine development. Another former staff member recalled that at WRAIR, "I learned every aspect of vaccine development. I never could have done that anywhere else because I would have been pigeonholed as a development guy or a research guy or a manufacturing guy . . . it was unique training."[32] Whereas academic research scientists were often interested only in the fundamental aspects of scientific problems, military research scientists were trained to work through the practical implications of their results to facilitate industrial applications of their research. A WRAIR manual from 1957 outlined research objectives for their programs and explicitly identified the need "to develop the production processes required to translate laboratory scale results for large scale production by industry."[33] To this end, WRAIR offered training

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[27] James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.
[28] Army Medical Service Research and Development Program, fiscal years 1952-1969. NA: RG 112, E. 1013.
[29] Final Report on Review of Medical and Biological Programs within the Department of Defense, Institute of Defense Analysis (August 1962): B-3. NA: RG 319, E. 181, B. 1.
[30] Dr. Maurice Hilleman, interview by author, June 22, 2000.
[31] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.
[32] James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.
[33] WRAIR, fiscal year 1957. NA: RG 112, E. 1035, B 42.

fellowships in which they would send their scientists to industrial labs to learn large-scale production techniques for biological products. [34]

Postwar military research programs at WRAIR spawned a breed of vaccine research scientists that fit the definition of what Bush referred to as "science integrators:" scientists whose skills permitted them to bridge the gap between basic and applied science for vaccine development.[35] Dr. Hilleman notes that WRAIR scientists "would be trained to go to the field and come back to the laboratories." [36] Splitting one's time in this way was, in his opinion, the best way for scientists to learn how to bridge the gap between basic and applied research that frustrates a number of vaccine development efforts.[37] At WRAIR, there was no formal division of labor as one might find in a pharmaceutical company, nor was there the strict departmental specialization one might find in academia.

Researchers were involved in every step of the vaccine development process ranging from epidemiological fieldwork, to lab work of isolating antigens and manipulating them to produce pilot lots of vaccine, to clinical work to demonstrate safety and immunogenicity of vaccines. Another member of WRAIR observed that "U.S. Army scientists, as opposed to university scientists, are particularly strong at bringing a vaccine through the whole development spectrum . . . They had expertise at each stage. The military has unique assets/needs that are not driven by a fiscal bottom line but by the need to generate a product."[38]

As a group, this breed of WRAIR-trained "science integrators" formed a bridge between postwar military and industrial cultures for vaccine development. As WRAIR scientists gained a reputation within industry as a valuable research partners, industry began to seek WRAIR scientists for both collaboration and employment. In 1957, for example, the SGO reported that the "Department of the Army received a letter from the Pfizer Drug Company asking for five retired doctors who might be interested in some interesting and lucrative positions with their

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[34] E. W. Grogan, "Report of Temporary Duty Travel," WRAIR Disposition Form (March, 3, 1959). NA: RG 112, E. 1004, B. 85.

[35] In this speech, Bush refers more generally to the dangers of overspecialization in scientific disciplines and the importance of identifying and promoting scientists that have the capability to integrate findings from a wide range of disciplines. He states, "I should be inclined to establish a Nobel Prize for the integrator and interpreter of science who can, in these days serve his fellows far more than the individual who merely adds one morsel to the growing, and often indigestible, pile of accumulated factual knowledge." V. Bush, "Science in Medicine and Related Fields," remarks of V. Bush at the 23rd Annual Scientific Assembly of the Medical Society of D.C., Oct. 1, 1952. LC: Vannevar Bush Papers, Container 134.

[36] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

[37] M. Hilleman, "The business of science and the science of business in the quest for an AIDS vaccine," *Vaccine* 17 (1999) p. 1215.

[38] Col. Patrick Kelley, Director DOD-GEIS, WRAIR, interview by author, Silver Spring, MD, April 14, 2000.

company."[39] In the same year that Pfizer was plumbing the ranks of WRAIR for new hires, Merck and Company lured away Dr. Maurice Hilleman, one of WRAIR's top vaccine research scientists. As case studies of the influenza and meningitis vaccines demonstrate later in this chapter, this migration of talent from WRAIR into industry strengthened military-industrial networks and fostered a culture of collaboration for vaccine development in the postwar era.

The interdependence of military-industrial networks grew stronger with the onset of the Korean War as well. This relationship was strengthened somewhat by the "postwar consensus" that federal investments in military R&D are also investments in the economy and the human condition described previously.[40] Evidence for this point of view can be found in the comments of Colonel Tom Whayne of the AMS. Reflecting on the legacy of World War II R&D programs, he asserts, "In accordance with our democratic traditions, a small nucleus of Regular Army specialists has combined with the civil medical profession to forge vast and effective organizations in time of war. In peace, an increased sharing of responsibility has eliminated barriers between military and civilian medicine and has fostered the fundamental concept that government agencies represent the will of the people. Proof of the validity of these principles lies in the steady reduction in disease morbidity and fatality of the injured."[41]

More directly however, military-industrial interdependence was strengthened by renewed production demands wrought by another war. Commercial houses formed familiar contractual relationships with the government to supply the military with yellow fever, Japanese encephalitis, typhus, influenza, tetanus, and smallpox vaccines, but the military was anxious for industry to assume a number of new contracts as well. Although several AMS and PHS labs had assumed manufacturing responsibilities to supplement industry's efforts to meet supply requirements during World War II, they were anxious to relieve themselves of these duties and to reclaim time and lab space for research. In the years after World War II, there was a deliberate effort by the government to shift all military vaccine manufacturing needs into the private sector. For example, in 1948, Dr. Parker, Director of the PHS Rocky Mountain Laboratory, questioned the policy of his lab to produce and stockpile Rocky Mountain spotted fever and yellow fever vaccines. He also questioned the entire role of the PHS in vaccine production and suggested turning over manufacturing responsibilities to industry. He cautioned that this would not be easy: "I have been talking recently with Dr. Harold Cox of Lederle Laboratories . . . Certainly there is

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[39] Minutes from the Surgeon General's Early Morning Meetings, (May 10, 1957). NA: RG 112, E. 1014, B. 6.

[40] B. Smith, *American Science Policy since World War II* (Washington, D.C.: The Brookings Institution, 1990).

little actual desire on the part of the Lederle Laboratories to take over, due apparently to the fact that there would be little in it for them financially."[42]

Nonetheless, it appears that Dr. Parker succeeded in his efforts. In September of 1948, his laboratory ceased routine production of Rocky Mountain spotted fever vaccine, turning the responsibility over to both Lederle and Sharp & Dohme laboratories. The military continued to rely on commercial biological houses to assist with biological warfare research and development programs during this period as well. According to the Secretary of War, it was "directed that steps be taken to continue a reasonable research and development program during the postwar period. In this connection, the chief of CWS should determine the practicability of utilizing commercial concerns for biological research and development to the maximum practicable extent."[43]

The Korean War and industry investments in vaccine R&D

Assuming additional manufacturing responsibilities from the military solved some immediate problems facing industry. It permitted industry to re-utilize excess manufacturing capacity left in the wake of World War II. Additional orders also relieved industry of some excess stocks and boosted demand. Additional orders did not, however, improve the profitability of companies. An influx of government contracts connected with the onset of Korean War caused sales at the National Drug Company to hit an all time high of $2 million in 1951.[44] Yet net earnings were dropping due to hidden costs in filling high volume government contracts; National found itself consistently expanding their facilities and building new dedicated facilities to meet the high volume demands of these contracts.

By 1953, there was evidence that National was struggling for ways to compensate for low returns to vaccine development. In a message to stockholders, the president of National Drug wrote, "it becomes more apparent each year that in order to maintain a successful competitive position in the pharmaceutical and biological markets, the company must rely on a creative and aggressive research department."[45]

Other pharmaceutical companies were coming to similar conclusions. One year earlier, after a strategic planning exercise, Merck concluded that their business would have to be based on a

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[41] Col. T. Whayne and Col. J. McNich, "Fifty Years of Medical Progress," *New England Journal of Medicine* 244 (1951): 592-601.
[42] Dr. Parker to Dr. Dyer, Director of NIH, July 15, 1948, NA: RG 443, Decimal File # 0470.
[43] Memo to the Chief of Staff from the Secretary of War, "Research and Development in Biological Warfare," contained in Final Report of the USBW Committee (September 13, 1945). NA: RG 165, E. 488, B. 182.
[44] J. Widmer, *The Spirit of Swiftwater* (Swiftwater, PA: Connaught Laboratories, 1997), 44.

constant stream of product innovations: "The advent of really important new products can prevent the company from being drawn into a situation where it is merely competitive in the manufacture of conventional things, a role for which it is not adapted."[46] In an effort to diversify research opportunities and boost the number of new product introductions, in 1953 Merck merged with Sharp and Dohme, a neighboring company that had demonstrated vaccine research and development capabilities during World War II.[47]

The precise manner in which the federal government would support biomedical research in general and vaccine research in particular had not been resolved before hostilities began in 1950. Whereas industry had achieved high rates of innovation in the 1940's from participating in World War II vaccine development programs, organizations for biomedical research such as OSRD's CMR were not available to the vaccine industry during the Korean War.[48] Without the CMR and WRS to focus research objectives for new vaccine development during the Korean War, industry directors began to search for ways to maintain high rates of innovation achieved during World War II. In doing so, they, like WRAIR during this period, began to invest more heavily in their own research and development capabilities. Prior to World War II, companies rarely set aside their own money for research endeavors, but by the 1950's, they had begun to make unprecedented investments in their in-house research capabilities. For example, between 1930 and 1952, the research staff of the vaccine manufacturer Sharp and Dohme grew from 3 to more than 200, and research expenses increased 863.6 percent.[49] Merck Company was unusual among other firms in the industry in that they had begun to invest their own money into research and development projects as early as 1933. Even so, research expenses at Merck increased 638.7 percent during this period.[50]

As companies began to invest in in-house research and development, several began to draw on relationships forged through collaborative research conducted during the war and to apply lessons they had learned from their participation in World War II vaccine development programs to their

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[45] Ibid., 45.
[46] V. Bush, *Memorandum on Planning Activities of Merck and Company* (Dec. 8, 1952). LC: Vannevar Bush Papers, Container 72.
[47] Sharp and Dohme also provided Merck with developed sales and distribution channels that permitted them to market their own products directly.
[48] The WRS was subsumed into the CWS (renamed the Army Chemical Corps after the war) and the CMR dissolved along with OSRD after the war. Only the AEB retained a research arm. This organization was renamed the Armed Forces Epidemiology Board (AFEB) in 1949 when it became responsible for Navy and Airforce research activities as well.
[49] Statistics taken from L. Galambos and J. Sewell, *Networks of Innovation* (Cambridge: Cambridge University Press, 1995), 38.
[50] Ibid.

own operations. The manner in which the experiences of World War II shaped the ideologies and practices of the vaccine industry is most evident in the postwar activities of Merck and Company.

II. Case Study: Merck and Company

Personal relationships and scientific networks

Referring to the expanding role of the federal government in the support of science after the war, Vannevar Bush remarked that "science has moved out of the wings and into the center of the stage."[51] His comments might equally have applied to the transformations taking place in boardrooms and industrial research laboratories around the country. There were few postwar companies in which science and the lessons of World War II research and development programs figured so prominently as at Merck and Company.

The first step in raising the scientific stature of Merck was to attract prominent scientists onto the board, a task made easier by George Merck's participation in wartime R&D programs. Serving as director of the WRS, George W. Merck came into contact with the top research scientists and scientific administrators of his day. In particular, he met and developed respect for Vannevar Bush (Director of OSRD), John T. Conner (general counsel for OSRD), Edward Reynolds (brigadier general, SGO, in charge of medical supplies), and deepened his relationship with Dr. Alfred Newton Richards (Director of CMR). After the war, out of personal friendship and a desire to replicate some of OSRD's research and development success within his own company, George Merck persuaded each of these men to join his company.

Although George Merck had a long-standing belief in the value of scientific research in industrial settings, the practice of inviting noted scientists onto the board of directors was new and prior to the war Merck's board members had consisted primarily of bankers and lawyers. Yet Merck's instincts proved correct; Bush, Richards, and Reynolds provided valuable advice and direction for the company as board members and, by 1955, Conner had been elected President and CEO of the company.

By encouraging most of the top management of OSRD to join his company, Merck imported and reinforced a number of wartime skills and lessons for the effective management of large scale R&D. One such lesson concerned the political value of "science." As the director of OSRD, Bush would often emphasize the more fundamental aspects of OSRD's research agenda to reduce the perception that OSRD's interests could conflict with those of industrial organizations.[52] In the

[51] V. Bush, "The Scientist and His Government" (1946). LC: Vannevar Bush Papers, Container 139.
[52] D. Mindell, *Feedback, Control, and Computing before Cybernetics*, unpublished manuscript.

industrial context, both Bush and Merck would continue to use science to their political advantage. Although investments in scientific research served a valuable practical purpose - facilitating efforts to attract talent and to gain access to new findings in academia - they served a political purpose as well. Raising the profile of scientific research enabled Merck and Company to shed the prewar "snake-oil salesman" reputation of the pharmaceutical industry, detract from negative portrayals of their profit motives, and emphasize their role in providing a valuable service to humanity.[53]

According to a Harvard Business School case study, "the emphasis placed on bringing noted scientists to the Merck board stemmed not only from the increasingly research-oriented nature of the work in which the company was engaged, but also from beliefs and values held by the president as an individual. Mr. G. W. Merck wanted the company to build a high reputation for the quality of its research."[54]

To this end, Dr. Alfred Newton Richards was the first of this elite group of scientists that was elected to the board, joining Merck's directorship in 1948. Richards was an emeritus professor of pharmacology at the University of Pennsylvania, president of the National Academy of Sciences (1947-1950) and former director of the CMR. Soon after electing Richards, Merck extended an offer to Vannevar Bush as well. Merck conveyed his offer through Richards, who had worked closely with Bush on medical issues within OSRD. Bush's amusing response conveys the sense of collegiality the characterized the relationships among several former OSRD alumni. He writes, "the idea, I believe, is that you and I would keep George Merck in line, that is, we would see to it that he didn't make too much money or get in jail or anything like that, but on the contrary that he put out a lot of stuff that would cure people's ills. Between your knowledge of George and my knowledge of chemistry I think we could do it and it certainly would be a grand thing for people that had things the matter with them."[55] Of course, the last time that Bush and Richards had worked with Merck, it had been in the context of biowarfare research, not the noble advancement of human health.

The irony of this situation was not lost on Bush as he launched a riff on medical ethics: "I don't suppose we would get into a lot of medical ethics; I'm sure I couldn't take that. I've had measles and flu and lot of things that ordinary people have, but I've never had ethics, and I know

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[53] There are indications that the industry was already making efforts to improve its reputation for sloppy science before the war. John Swann's history of the pharmaceutical industry relates that, by the 1930's, a the efforts of a handful of companies, Merck included, to hire a small staff of in-house researchers were improving their reputation among academic scientists. J. Swann, *Academic Scientists and the Pharmaceutical Industry* (Baltimore: Johns Hopkins University Press, 1988).

[54] Harvard Business School Case Study, "Merck & Co., Inc.," (1960). MA.

[55] V. Bush, letter to A. N. Richards (May 23, 1949). LC: Vannevar Bush Papers, Container 97.

medical ethics doubles people all up sometimes. You have to look out for these places were they get all hot and bothered about curing folk's diseases for them, there are likely to be a lot of wild germs around that they are practicing on, and one of them might get in your mucous membrane or your tibia or someplace where germs multiply and give you ethics. I've heard that when people get a real dose of medical ethics they actually go nuts; I don't mean they bite the furniture or assault the keepers, but they get irrational and their logic becomes screwy. I'm not too logical anyway when it comes to theories of human relations and highfalutin social schemes, and I'm sure I couldn't stand an attack of medical ethics. If you think there's any danger of infection we ought to quit right here."[56]

At the time that Bush was considering this offer, the pharmaceutical industry suffered a reputation for crude and sloppy science that had been only partially repaired by wartime successes in the development of penicillin. He alludes to this reputation and in mock despair, he cries, "I'd have to teach you a lot of chemistry, and maybe physiology or something. I don't know how you expect to run George's shop for him unless you get into those things. He makes a lot of queer chemical substances, and people eat them, and that's dangerous unless you know what the things are and what they are likely to do to people's innards. Now I understand George himself doesn't know what some of the chemicals are that he makes, just gives them high sounding names, and can't really tell you what their formulas are, and maybe that's all right, for I understand he tries them out on his lawyers before he sells any, and of course he can't get into very serious trouble that way. But somebody in the outfit ought to study a lot of chemistry, and I'm not too sure how good a pupil you are."[57] Joking aside, Bush would soon prove instrumental in Merck's efforts to recruit serious scientists and to move the industry away from random empiric testing to more rational forms of drug discovery.

Investing in research and "scientific stature"

Merck was well aware that Bush's presence on the board would offer support for his long-held views on the value of scientific research in industrial settings. According to Max Tishler, former president of Merck's research labs, George Merck "wanted scientists on an equal footing with scientists in academia. And he preached that and encouraged us to publish and encourage us to go to meetings. . . . By the time I came to Merck, Merck already had been an attractive place for chemists with PhD's to join because they saw publications from there. That attracted me also."[58]

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[56] Ibid.
[57] Ibid.
[58] Max Tishler, interviewed by Leon Gortler (July 13, 1988). MA.

Bush played an active role in encouraging, not just the top management of Merck, but the entire industry to support scientific research in pharmaceuticals. At an industry-wide conference he explains, "Its presence in the latter [industrial laboratories] is often highly advantageous, for it tends to lift the tone of the whole effort, and it helps in recruiting if there are nationally known scientists in the organization. Encouraging the freedom of association with scientific societies and of publication . . . renders an industrial laboratory attractive to creative minds."[59]

With Bush on the board and Merck at the helm, Merck and Company made scientific research a fundamental part of the business strategy after the Korean War. A 1955 Arthur D. Little report attests to Merck's extraordinary focus on scientific research: "Research management now has the full support of the company officials, the directorate, and the importance of research to the company's future progress is probably more generally accepted in Merck than in virtually any other company in the process industries."[60]

Competing on the basis of research and development was still a relatively unconventional business practice at the time, however. Implying that these investments in basic research were made at the expense of meeting more practical research objectives, the Arthur D. Little report went on to criticize the company for "overemphasis on work which develops and demonstrates the scientific stature of the organization."[61] These comments, predictably, roused whole-hearted disagreement from Bush. He urged patience in the boardroom and explained that, 'in the business of research, one does not pull a rabbit out of the hat every five minutes.' He went on to remind them that "since the war there have been two very large rabbits, namely cortone and B12 . . .every one of them came out of the situation in which we were not only carrying out fundamental research, if you please research of scientific stature, but also because we were thoroughly in contact with others that were doing the same thing in academic circles, and because we were thoroughly alert to the trends in medicine . . . I hope we will not be so short-sighted as to lose our touch with 'development of scientific stature.'"[62]

George Merck was well aware that Bush's presence on the board would signal to his customers, the medical profession, potential employees, and investors that his company adhered to the highest standards of scientific and administrative practice. Bush was, however, as one reviewer put it, "much more than 'wonderful window dressing' . . . He is a skilled

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[59] V. Bush, "Science and Business," remarks delivered at the 10th Annual Rutgers Business Conference. MA.
[60] A. D. Little, "Diversification Opportunities," report to Merck and Company (March 25, 1955). LC: Vannevar Bush Papers, Container 75.
[61] Ibid.
[62] V. Bush, letter to Henry Johnstone, Sr. VP and member of the board (April 1, 1955). LC: Vannevar Bush Papers, Container 75.

administrator."[63] Bush's views on how the chief executive of a pharmaceutical firm should administer his duties bore little difference from his philosophy as the director of OSRD, and thus he advocated a modified form of dictatorship for the efficient administration of targeted research.

Bush's top-down administrative style was modified by his belief that, within certain limits, scientists should be permitted to govern themselves. Although he believed it necessary to have someone at the top to integrate findings from a range of research projects within the company and to outline targets for research teams, he maintained that "to tell a fundamental scientist what to work on, or how to go about it, is just about as futile and disastrous as to try to tell your wife what to cook and how to cook it. The progress of a fundamental research laboratory depends merely upon the caliber of the men and women in it, and the extent to which they like one another and collaborate."[64]

Bush also believed that the proper relationship between the CEO and his management committee of Vice Presidents was not unlike that between a project manager and his scientists. He explained that "every member freely expresses his opinion, but the president decides. Such a relationship can be compared to a general in the field supported by his staff."[65] Bush referred to this practice of encouraging open debate both up and down the chain of command without compromising the autonomy of the ultimate decision-makers as "giving a man his head." He argued that "this is more than a matter of scientific freedom, important though that principle is . . . it is entirely possible to give a man his head and yet to specify by agreement with him his objectives."[66] In this manner, Bush helped Merck to strike a productive balance between a dictatorship and anarchy among the upper managers at Merck.

Finally, the directors of OSRD, CMR and the WRS had discovered that access to the expert advice of scientific advisory committees was indispensable to the effective evaluation of projects and grant contracts. The process for evaluating the feasibility of new ventures in the context of wartime research organizations was not dramatically different from the process of assessing new R&D opportunities in the industrial context. Bush, like Merck, had come to depend on outside expert advice to make these assessments and thus continued the practice at Merck. As Chairman the Board, Bush preached the value of seeking outside advice to check one's judgement and to add perspective on the feasibility and advisability of all project decisions, and he encouraged subsequent CEOs to continue the tradition. One former CEO, Dr. Antonie Knoppers, maintains

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[63] P. Stryker, "Tricky Work, Being Board Chairman," *Fortune* (May 1960).
[64] V. Bush, "Science and Business," remarks delivered at the 10th Annual Rutgers Business Conference. MA.
[65] Harvard Business School Case Study, "Merck & Co., Inc.," (1960). MA.

that this was one of the most distinguishing features of managerial practice at Merck: "Outside advice played a role in Merck. We were never in-bred, and we always had information from the top people from the outside."[67] This inclination to constantly check internal company judgements against outside perceptions and expert advice came naturally for the former directors of OSRD, CMR, and WRS. This inclination was also, Dr. Knoppers argued, at the source of Merck's continued success as a leading research and development company.

Patriotic industrialists and the decision to invest in vaccines

Merck and Company acquired a vaccine division as part of a general diversification strategy when they merged with Sharp and Dohme in 1953. In 1957, however, Merck and Company decided to amplify their investments in vaccine research by building a new virus and cell biology division. Vannevar Bush is widely credited with the decision to boost Merck's investments in vaccine research. According to Hilleman, "he conceived of the ultimate importance of viruses to science and health and requested that Dr. Max Tishler, then President of the Merck Research Laboratories, establish a major research program in virology at Merck."[68]

Though it is clear that Merck and Company wished to become a competitor in the vaccine development field, the question of why they wanted to remains unanswered. Historically, vaccine development had not been profitable. Unlike companies such as National Drug, which had the majority of their resources tied up in vaccine development, Merck had made limited investments prior to 1957 and had a number of alternative investment opportunities in their pharmaceutical divisions. Though there are records of Bush's suggestion, he leaves no outline for his rationale and we can only surmise what may have prompted his decision.

Part of the motivation may have stemmed from the technological opportunities afforded by improvements to cell culture techniques in the mid-1950's. Refinements to tissue culture techniques permitted the development of the polio vaccines of 1955 and made it easier for companies to contemplate cost-effective large-scale production of a wider variety of virus vaccines.[69] Merck likely felt the pressure to build new competencies in this field, since these

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[66] V. Bush, letter to Karl Compton, "Comments on the Subject of Organization for Research," (October 24, 1946). LC: Vannevar Bush Papers, Container 138.

[67] Antonie Knoppers, Vice Chairman of the Board, President, and CEO of Merck and Company (1952-1975), interview by author, NY, New York, July 11, 2000.

[68] M. Hilleman, "Personal Historical Chronicle of Six Decades of Basic and Applied Research in Virology, Immunology, and Vaccinology," *Immunological Reviews* 170 (1999): 7-27.

[69] J. Enders, T. Weller and F. Robbins, "Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Embryonic Tissues," *Science* 109 (1949): 85-87.
Building on the tissue culture techniques developed by Goodpasture in the 1930's, the Enders group developed a method for growing viruses in cell cultures. Previously, researchers relied on infected animal

techniques were being widely adopted throughout the industry for the production of the newly developed polio vaccine. An internal report from this period warned, "if Merck wishes to be a major factor in the field, it seems inevitable that an adequate unit sufficiently versatile to be modified for newer procedures and newer vaccines must be made available before the next major discovery is announced."[70]

Though the introduction of new tissue culture techniques offered some promise for the field, these techniques were relatively new, and the opportunities for the wider application of them were unclear. More than 40 years later, Dr. Hilleman contended that Merck had taken a tremendous risk in boosting their investments in vaccine research. "It is to the credit of the company that it initiated and funded a biological enterprise at a time when the data base was limited, applicable precedents were lacking, scientists with interest and relevant experience were few in number, and there was little means for obtaining patent protection for discoveries in biology that had been achieved at great cost from pioneering research and development."[71]

Another motivation may have stemmed from a sense of social obligation to the military and to the nation. One cannot imagine that at the height of the Cold War Bush, Merck, and Richards, could have been blind to the national security importance of vaccines or insensitive to what they perceived to be their patriotic duty to supply civilian and military populations with adequate defenses. According to one historian, there was a looming sense during the postwar period that "breakthroughs in chemical or biological warfare might at any time create an end run around the atomic balance of terror."[72] During this period for example, Merck had been involved actively in the development of chemical and biological defenses for the military in the form of nerve gas antidotes and the first anthrax vaccine.

Bush's presence on the board ensured that Merck continued to focus on research for national defense and continued to collaborate with military research organizations. Speaking before the entire industry, he urged all executives to consider their duty to accept government contracts. Bush explained, "there is a genuine need, from a patriotic standpoint, for industry to collaborate in the research effort essential to national defense."[73] Bush was also, however, a strong advocate of free markets; he provided the industry with guidelines to ensure that military-industrial

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organs and tissues to culture viruses, which made it difficult to grow large quantities of virus for vaccine production.

[70] Internal report, Tissue Culture Department, "Permanent Quarters for Poliomyelitis Virus Vaccine" (May 12, 1955). LC: Vannevar Bush Papers, Container 75.

[71] M. Hilleman, "Personal Historical Chronicle of Six Decades of Basic and Applied Research in Virology, Immunology, and Vaccinology," *Immunological Reviews* 170 (1999): 7-27.

[72] W. McNeill, *Pursuit of Power* (Chicago: University of Chicago Press, 1982), 373.

[73] V. Bush, "Science and Business," remarks delivered at the 10th Annual Rutgers Business Conference. MA.

collaboration would continue to offer productive advantages to both parties. He warned companies not to accept contracts blindly, however, and informed them of their responsibility to demand a true partnership that would ensure that military-industrial ventures were productive, "The judgement as to the justification for carrying on the program, the estimate of the value of the potential results, cannot just be left to some military committee in Washington. Unless the company is admitted initially into confidence and given the opportunity to form its own judgement as to values, unless the technical staff can genuinely collaborate with the military in formulation the program, it had better leave it alone."[74] These guidelines were relatively easy to follow during the postwar era when military-industrial relations were characterized by a high level of mutual respect and trust.

After the war, George Merck addressed the George Westinghouse Centennial Forum in Pittsburgh on the "peacetime implications of biological warfare." It is clear from this speech that national security and public health were clearly linked in his mind; he envisioned an activist role for both the industrial and academic sector, arguing for their continued investment in research to control disease. He warned that "those responsible for our defenses and preparedness in this upset world are alert; they have their programs ready. But they need support -- support from scientists, academic and industrial, which should be given generously and in full measure -- and it should not wait for an emergency call of patriotism."[75]

The threat of biological warfare weighed heavily on Bush's mind as well. He wrote, "I am personally somewhat terrified by what may happen on this thing in the postwar world. It is new. But there may be a time when it would be possible to build up by this [biological] means the kind of sudden and devastating attack that would be overwhelming, and the next dictator somewhere who has ideas of conquering the world may see this as a means."[76] Bush worked with Conant to devise measures to control the threat from biological warfare after the war. In a memo to the President, they suggested an arms control scheme by which the biological weapons could come under international control – preferably under an international body such as the United Nations.[77]

However, in Bush's view, companies, as well as individuals, had a social responsibility to protect the public. He wrote, "the management of a company and the directors, have a four-way responsibility: to their stockholders, to the public they serve, to their labor force, and to their government. Fortunately there is growing in the country a management group with a distinctly

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[74] Ibid.
[75] G. W. Merck, "Peacetime Implications of Biological Warfare," *The Merck Report* (July, 1946). MA.
[76] G. P. Zachary, quoted in, *Endless Frontier* (New York: Free Press, 1997), 238.
[77] V. Bush and J. Conant, letter to H. Stimson, Oct. 27, 1944, quoted in G. P. Zachary, *Endless Frontier* (New York: Free Press, 1997), 238.

professional outlook and a sense of social responsibility of a high order . . ."[78] It is possible that Bush believed that Merck had a social responsibility to fill, if not a debt to pay, and that investing in vaccine research was one form of payment.

Maurice Hilleman and the reorganization of postwar vaccine research at Merck

Per Frolich, when he was still at Merck, refers to a letter in which Bush prodded him to expand their efforts in the biological sciences. He replied, "I have by no means forgotten that you want to talk to me about matters regarding research organization. A point, which has come up more recently, is your suggestion that we attempt somehow or other to enlist participation in our research efforts of some of the most creative minds in the biological field. I think there is a real need to do something along that line and also to supplement it with some strictly exploratory research projects in our own laboratories. As I see it, this would serve the dual purpose of opening up new fields and of developing men who can think independently of the 'team'. I have talked to Dr. Major about this and hope there will be an opportunity soon to discuss it with you and Dr. A.N. Richards."[79]

The ensuing discussion initiated the search for a new person to head the proposed virus and cell biology division. Bush had remarked in his autobiography, "all my life I have mixed with all sorts of men. The ones I like best to be with are military men and research men."[80] In particular, Bush developed a hearty appreciation for those capable of independent thought and frank expression. All of these characteristics presented themselves in the person of Maurice Hilleman, and he proved an irresistible choice.

Max Tishler, the head Merck's laboratories, recruited Hilleman from WRAIR where he had established a reputation as a talented virologist for his work on influenza and adenoviruses. Hilleman fit Bush's prescription for a new scientific director exactly. He was brilliant, motivated and independent. Although he functioned well at WRAIR, where he was permitted to direct his own activities, it was clear that he would not fit neatly into Merck's pre-existing organization for vaccine research. Nonetheless, Bush convinced Merck and others on the board of his belief that "the primary need is to find the really great research scientists with an intense interest in parts of the problem and see to it that they have every possible support as they work, on their own ideas and in their own manner, without administrative interference or control of any sort."[81] Bush's

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[78] V. Bush, "Of What Use is a Board of Directors?" MA.
[79] P. Frolich, letter to V. Bush, Jan. 9, 1952. LC: Vannevar Bush Papers, Container 72.
[80] V. Bush, *Pieces of the Action* (New York: William Morrow and Company, 1970) 209.
[81] V. Bush, remarks delivered at the 23rd Annual Scientific Assembly of the Medical Society of the District of Columbia, October 1, 1952. LC: Vannevar Bush Papers, Container 134.

conviction bore fruit as Maurice Hilleman proceeded to put Merck at the frontlines of vaccine innovation by introducing the first effective measles, mumps, rubella, meningitis, hepatitis B, and varicella vaccines to the market.[82]

Bush did not have to warn upper management against the dangers of subjecting scientific directors to bureaucratic control. Hilleman quite simply would not allow it. Recalling his early introduction to corporate culture, Hilleman explains, "At Merck I was like a big wart on an elephant's butt."[83] He refused to go to meetings that concerned anything outside his research. When confronted by one of his superiors about his unorthodox approach to administrative duties, Hilleman informed him, with characteristic tact, "If I wanted an administrative job, I would be your boss by now."[84] Fortunately for Hilleman, Bush and other members of the board understood that it was necessary to grant more freedoms within the pre-existing bureaucracy to retain talented scientists such as Hilleman. In a manner that was reminiscent of the way Bush permitted scientists to organize research projects under OSRD, Hilleman was granted central authority and near total independence to run his department as he saw fit.

Hilleman began to model a research organization after the one that had served him so well at WRAIR, where all aspects of the vaccine development process were integrated. While developing the first adenovirus vaccine at WRAIR, Hilleman recalls being "involved in every step in the process. I went on epidemiological trips at the drop of a hat. I always had a bag packed and ready to go by plane or train or whatever it required. If there was a respiratory disease that looked interesting, I would go out there and take a look, collect the specimen, see the patient."[85] Hilleman first isolated the virus from military personnel and published the results in 1954.[86] John Enders, who would later receive the Nobel Prize for refining tissue culture

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[82] While Hilleman was the director of Merck's Virus Cell and Biology Division from 1958 to 1984, his division introduced 41 licensed vaccine products to the market. According to a 1998 issue of the *Nature Medicine Vaccine Supplement*, Dr. Hilleman is "recognized as having developed more vaccines than any other person." (May, 1998, p. 507). He is the recipient of a number of distinctive honors including the Lasker Medical Research Award and the National Medal of Science. He serves on a number of advisory boards including NIH's Office of AIDS Research Program Evaluation, and the National Vaccine Advisory Committee of the National Vaccine Program. He continues to serve Merck and Company as a senior advisor.

[83] Dr. Maurice Hilleman, interviewed by author, West Point, PA, May 8, 2000.

[84] Ibid.

[85] Ibid.
Prior to the development of an adenovirus vaccine, Acute Respiratory Disease (ARD) affected between 6-17% of the military population per week. ARD disproportionately affects new military recruits, sometimes with up to 80% of new recruits becoming infected with the virus and many requiring hospitalization within the first three weeks of training.

[86] M. Hilleman and J. Werner, "Recovery of New Agents from Patients with Acute Respiratory Illness," *Proceedings of the Society of Experimental Biological Medicine* 85 (1954): 183-188. Similar observations where being made in other locations at this time. Rowe and Huebner detected a transmissible cytopathogenic agent in surgically removed tonsil and adenoidal tissue cultures of children. (R. Huebner et

techniques to grow viruses, suggested the name "adenoviruses" for this new group of upper respiratory viruses.[87]

Several years later, Hilleman and his associates on the Commission on Acute Respiratory Diseases of the Armed Forces Epidemiology Board (AFEB) traced a causal relationship between the presence of adenoviruses and acute respiratory disease among the military recruits.[88] Hilleman found that this constant perseveration between the field and the lab facilitated vaccine development, because it forged links in the chain of specialized epidemiological and technical knowledge required to develop an effective vaccine. He was a "science integrator" in the WRAIR tradition and, as such, he offered an answer to many of the technology and information transfer problems that frustrated Merck and Company during the war.[89]

In an effort to recreate the conditions that would permit him to bridge all aspects of the vaccine development process, Hilleman created "cross-over" teams at Merck that integrated the expertise of members from different departments. These teams, he explained, were designed to "permit knowledge to be passed as necessary from the immunology to the chemistry to the physiology department, etc."[90] Unlike other companies at the time, "we did field investigations, epidemiology, from clinic to clinic, isolated viruses to attenuate. We had the complete spectrum."[91]

As was the case with World War II vaccine development programs, this form of research required a high level of coordination from the top in order to integrate work streams from a wide range of departments. Hilleman explains, "As committee head, I was the main coordinator and link in the chain . . .. I did all the field trials, I was involved in every step and every decision . . . It was directed coordination."[92] Like Bush, Hilleman recognized the importance of "giving a man his head," and he would delegate responsibility to individual team directors. However, he had a tendency to manage vaccine development projects with unrelenting degree of control and focus. In Hilleman's experience, "researchers like to deviate – chasing every which thing that comes their way. I could walk out of the lab for one week- I'd come back and I'd already find these bastards working on something else. When you're gone three weeks, you hardly know the

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al., "Adenoidal-Pharyngeal Conjuctival Agents," *New England Journal of Medicine* 251 (1954): 1077-1087).

[87] J. Enders et al., "Adenoviruses: Group Name Proposed for New Respiratory Tract Viruses," *Science* 124 (1954): 199-120.

[88] M. Hilleman and R. Butler, "Appraisal of Occurrence of Adenovirus Caused Respiratory Illness in Military Populations," *American Journal of Hygiene* 66 (1954): 29-51.

[89] See Chapter Two, footnote 66.

[90] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

[91] Ibid.

[92] Ibid.

laboratory anymore. You need to crack the whip."[93] Hilleman was intimately involved in the daily operations of each of his teams, a practice that, he argued, permitted quick decision-making and enabled efficient operations. He concludes " That system worked. Everybody was happy. They were overjoyed to be productive. They could see these vaccines coming out."[94]

As with all dictatorships, the quality of governance is a function of the energy and intelligence of the individual, and Hilleman was a brilliant force of nature. His research teams were efficient and productive and, from the time of his arrival in 1958, Merck's Virus and Cell Biology Division put forty-one vaccine products on the market. Six of them (the meningitis, measles, mumps, rubella, hepatitis B, and varicella vaccines) were entirely new to the market.[95] Referring to Hilleman's productivity and contributions to the field, one vaccine research scientist explained that, "he was the granddaddy of them all."[96]

III. Case Study: Development of the Meningitis and Influenza Vaccines

This examination of the ideology and practices that dominated Merck and Company during the postwar era demonstrates that high rates of vaccine innovation during this period were due in part to a belief in the value of scientific research, as sense of social obligation, and the direct application of management strategies learned in the context of World War II vaccine development programs and military research labs. However, a closer investigation of the developmental history of particular vaccines during this period reveals that a network of informal collaborative relationships between military research institutes and industrial labs facilitated innovation during this period as well.

The community of skilled vaccine research scientists was small, and it was not unusual for military and industrial lab directors to know one another from a prior stint at WRAIR. Common training and mutual respect between WRAIR and industrial scientists bred a culture in which the two groups readily agreed to collaborate on projects and to share information, biological samples, and laboratory equipment. A sense of indebtedness and duty to the military further encouraged collaboration, as industry felt compelled to accept vaccine development projects for the military even when commercial prospects for a vaccine were poor. These characteristics of the postwar culture for vaccine development are illustrated in the developmental history of the meningitis and influenza vaccines.

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[93] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.
[94] Ibid.
[95] Licensure Dates for Products Developed by Virus and Cell Biology Research, (1996). MA.
[96] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.

Early work on a meningitis vaccine was initiated by the military in the early 1960's. The military had routinely used sulfa drugs to control meningitis outbreaks within their ranks since World War II. According to James Simmons, Chief of Preventative Medicine Service, the prophylactic use of Sulfadaizine within the armed forces dramatically reduced the incidence of meningitis during World War II. He reported that "the case fatality rate [from meningitis] which was 38 percent in the previous war has been less than 5 percent."[97] By the early 1960's, however, military personnel were becoming infected with strains of *Neisseria meningitis* that were resistant to sulfadaizine.

Recruitment camps in particular began to suffer from these outbreaks of bacterial meningitis. Occasionally, with no other recourse, the military would be forced to close down camps to stem outbreaks. After one particularly severe outbreak among recruits in 1963, the Armed Forces Epidemiology Board initiated studies within military populations to determine which strains of the bacterium predominated.[98] Within a year, the Army had set up a new research unit at WRAIR to study the problems of vaccine development as well.

This new unit was headed by Malcolm Artenstein, a career military physician specializing in infectious disease. During this time, the Army was able to call up draft-eligible research scientists. Taking advantage of the draft, Dr. Artenstein handpicked a recent graduate from NYU medical school, Emil Gotschlich, to help him develop a meningitis vaccine. Together, Artenstein and Gotschlich decided to revisit research performed by Dr. Elvin Kabat of Columbia University in the 1940's before the widespread availability of antibiotics made the search for bacterial vaccines seem redundant.

Kabat had identified immunogenic properties of bacterial polysaccharide capsules, suggesting that it might be possible to induce active immunity against meningococcal meningitis with a polysaccharide vaccine. Building on this research, Artenstein and Gotschlich--along with Dr. Irving Goldschneider, another recent draftee--began to isolate and identify polysaccharides present in the capsules of *N. meningitis.* Their research demonstrated that these polysaccharides could generate antibodies to meningococcal types A and C, strains that were most commonly found in U.S. recruitment camps. By 1969, this team had developed pilot lots of this vaccine and began small-scale testing on Army recruits for safety and efficacy.[99]

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[97] Brig. General James Simmons, Chief of the Preventative Medicine Service, OSG, U.S. Army, statement for presentation, December 14, 1944, before the Senate Sub-Committee on Wartime Health and Education, under the Chairmanship of Senator Claude Pepper. NA: RG 165, E. 488, B. 183.
[98] N. Vedros et al., "Studies on Immunity in Meningococcal Meningitis," *Military Medicine* 131, no. 11 (1966): 1413-1417.
[99] W. Bell and D. Silber, "Meningococcal Meningitis: Past and Present Concepts" *Military Medicine* 136, no. 7 (1971): 601-11; M. Artenstein et al., "Immunoprophylaxis of Meningococcal Infection," *Military*

Once the WRAIR team demonstrated the feasibility of a meningitis vaccine, the Army began to solicit offers from companies to accept contracts to manufacture the vaccine on a larger scale. The contract had first gone to Squibb and Sons but, according to Hilleman, Squibb could not figure out how to obtain high yields of polysaccharides and, after working unsuccessfully for two years to scale up production of the vaccine, the company had given up. At this point, military officials contacted Max Tishler at Merck, which had developed a reputation as a company that could solve problems and get products to market. According to Hilleman, the military often came to Merck with their requests because "Merck was the basic research DO company."[100]

When Tishler approached Hilleman with the military's request, he sent the scientist into a tailspin. Hilleman explains, "At the time that I came to Merck, I didn't want anything to do with bacteria." He recalls, "Army officers talked to Max Tishler, trying to get him to take the contract. Max then came to me and I said, 'Meningicoccus? Christ! That's a bacterium isn't it? I don't know anything about bacteria. I've just heard of them.'"[101] Hilleman was making tremendous progress with viral vaccines, having just developed the measles, mumps, and rubella vaccines, and he was anxious to continue working on new viral diseases. Yet his sense of loyalty and indebtedness to the military ran deep. Though he knew little about bacterial diseases and the sporadic nature of the disease did not promise a steady revenue stream from the vaccine, Hilleman felt obliged to comply with their request. "I thought, oh my god, this would be a real disloyalty to the military so I said, oh, ok, I'll take it over."[102]

Before Hilleman accepted the military contract to develop a new meningitis vaccine, two scientists the National Drug Company in Swiftwater, Pennsylvania, had also started to work on this project informally. This work was headed up by Dr. James Sorrentino who, like Hilleman, had learned the principles of vaccine research and development at WRAIR and had recently transitioned into a job in industry. From 1960 to1967, Dr. Sorrentino had been a research scientist in WRAIR's biologic group under Dr. Joseph Lowenthal.[103] Sorrentino's training and experiences were not unlike those of Dr. Hilleman who had been director of WRAIR's virus and respiratory disease division in the 1950's. Sorrentino explained, "I learned every aspect of

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Medicine 139, no. 2 (1972): 91-5; E. Gotschlich et al., "Human Immunity to the Meningococcus III: Preparation and Immunochemical Properties of the group A, Group B, and Group C Meningococcal Polysaccharides," *Journal of Experimental Medicine* 129 (1969): 1349-65.

[100] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

[101] Ibid.

[102] Ibid.

[103] Dr. Sorrentino joined the National Drug Company in 1967 as the Assistant Manager of Viral Products. He was promoted to Director of Manufacturing and Development in the early 1970's. In 1974, he left to join Richardson-Merrell where he eventually became the Director of Research at Richardson-Vicks for

vaccine development. I never could have done that anywhere else because I would have been pigeonholed as a development guy, or a research guy or a manufacturing guy. I learned the animal part of evaluation of vaccines in terms of efficacy and safety. I learned the manufacturing aspects of vaccine development, the research aspects of what comes before and after vaccines are developed, and it was unique training."[104]

Based on his experiences at WRAIR, Sorrentino came to industry with product development and project management techniques that resembled those of Dr. Hilleman. He was frustrated to find that, in industry, "everyone was a specialist. They didn't know what went before or after their piece of it. You get bias by the researcher and the manufacturer. They have their own agendas and it gets in the way of smooth development of the drug."[105] In an effort to overcome these departmental separations, Sorrentino forged an alliance and a friendship with Dr. Donald Metzgar who had joined National a year earlier after spending five years as a virologist at Merck.[106]

Metzgar had been hired as a senior virologist and Sorrentino had been hired to manage vaccine development and manufacturing operations. Within months of Sorrentino's arrival, the two were sharing offices and, to a certain extent, a budget. In this manner, they were able to coordinate work along the research, development and manufacturing areas of the vaccine development process. Sorrentino recalled, "we had those three aspects and so the only thing we had left to control was quality control; so we did it by brute force."[107]

Their first project was the development of a highly purified influenza vaccine. Prior to the development of this new vaccine, which was licensed by National in 1970, influenza vaccines were not widely used. Sorrentino recalls that "heretofore, you had a flu vaccine that took your arm off."[108] Influenza vaccines at that time were still being purified with a Sharples centrifuge according to methods developed under CMR contracts in World War II. Summarizing what had been state of the art for influenza vaccine production, Sorrentino explained that, "all they did was

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over the counter respiratory medicine. Dr. Sorrentino is currently the Managing Director of Healthcare Products Development Inc. in Norwalk, CT.

[104] Dr. James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.

[105] Ibid.

[106] Dr. Donald Metzgar joined the National Drug Company as a senior virologist in 1966. He became the director of Biological Research and Manufacturing in the mid-1970's and was appointed Vice President of Operations in 1978. He retired in 1994 after serving as Senior Vice President of Connaught Laboratories in 1994. (Connaught merged with the former National Drug Company in 1987). Dr. Metzgar continues to serve on a number of national advisory committees including the most recent IOM committee to assess the safety of the anthrax vaccine.

[107] Dr. James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.

[108] Ibid.

spin down the egg material, took the sludge, re-hydrated it, diluted it, put a preservative in it, and shot it into your arm."[109]

While working on the Eastern Equine Encephalitis vaccine at WRAIR, Sorrentino had been introduced to new density gradient techniques that could be used to separate and identify immunoglobulins by size. It occurred to Sorrentino that he might use these techniques to further purify influenza vaccines if he could find a way to get the virus to band according to its density gradient, thereby reducing the reactogenicity and increasing the acceptance of the vaccine. Dr. Charlie Riemer at Eli Lilly had recently published a paper in which his team had adapted the use of an ultracentrifuge, originally developed by the Atomic Energy Commission for gaseous diffusion enrichment of uranium, to purify viral materials in this manner.[110] Inspired by this, Sorrentino set to work devising his own methods for separating virus material out from the allantoic fluid of developing chick embryos in which it was cultivated.

National did not have the sort of ultracentrifuge that would permit him to perform his initial experiments, and they were unwilling to invest in Sorrentino's unproven idea. Undeterred, Sorrentino tapped into his network of military research scientists and went to see Norman Anderson, then the director of the Molecular Anatomy Program (MAN) at Oak Ridge National labs, who had also adapted the use of an ultracentrifuge to work with biological agents. He would fly down to Tennessee with his influenza samples in the seat next to him, run them through the government's centrifuge and peer at the results through the government's electron microscope. As he recalled it, Norman Anderson just "opened his lab to me . . . I would go out and seek help from the government and the program at Oak Ridge and get ultimate collaboration."[111] The process worked, National invested in the new technologies and facilities required to manufacture the vaccine, and, as Sorrentino recalled, "we ended up forcing the entire industry to purify their product."[112]

Soon after developing his purified influenza vaccine, Sorrentino was restless for a new project and anxious to try his purification techniques on a new vaccine. "I knew that meningitis was one of those things on the burner that needed to be done."[113] He recalled that Dr. Emil Gotschlich had just been brought into the biologics research group at WRAIR and had started work on a meningococcal vaccine at the time that he left for National. He called Dr. Sanford Berman,

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[109] Ibid.
[110] According to Dr. Metzgar, Lilly abandoned the project because, unlike National, they did not have the automated egg-handling equipment that Sorrentino had recently developed to be able to supply the high volume of material required for zonal centrifugation.
[111] Dr. James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.
[112] Ibid.
[113] Ibid.

another former colleague at WRAIR, to check on the status of the project. Berman relayed that WRAIR had taken the development as far as they could, but that the vaccine required further purification and that thus far, no one had managed to produce it commercially. Sorrentino agreed to try immediately. He had no problems getting National to agree with his decision. He recalls, "after I gave them flu, I could come to them with anything. I was like Maurice Hilleman to National Drug."[114]

At this time, military-industrial collaboration was characterized by a sense of informal collegiality and trust and was still relatively unfettered by intellectual property or liability concerns. When National agreed to develop the military's meningitis vaccine, Dr. Sorrentino does not recall that any contracts, licenses, or patents changed hands. According to Dr. Sorrentino "it was free-exchange. I didn't sign a single paper."[115] Metzgar recalled the simplicity of the arrangement with amusement and chagrin: "Jim brought back this bottle of paste [WRAIR's seed stock of *Nisseria meningitis*]. We had no authorization and no budget."[116]

Undeterred by the lack formal support from the National Drug Company, Sorrentino and Metzgar set to work on the vaccine. Familiarity with personnel in the biological research division of WRAIR significantly facilitated efforts to develop the military's vaccine. They soon discovered, however, that technology transfer, even under the most favorable conditions, is rarely straightforward. Artenstein and Gotschlich had published their work on the vaccine but, as Sorrentino notes, "like everything in the literature, when you start trying to follow what they say in the literature, it is not exactly reproducible."[117] Whenever he ran into a roadblock, he merely had to "pick up the phone for Joe Lowenthal and say, 'hey Joe, I've had a problem with this step.'"[118] Similarly, he had full access to Emil Gotschlich who also helped him on several occasions. Nevertheless, Sorrentino and Metzgar found that it took months merely to adapt what Artenstein's group had done at WRAIR to what National was able to do in their own labs.

Next, Sorrentino and Metzgar were confronted with the problem of scaling up pilot lots. Sorrentino explains that "It's good for the manufacturer to know what the developer does but there are a lot of things you have to change when you start scaling up. A lot of things that aren't as efficient and that aren't as sensitive; yields are different. So there have to be a lot of changes that are made in the process."[119] One such change consisted of learning how to grow large amounts of *Nisseria meningitis* in large fermenters. Metzgar related that *Nisseria meningitis* was

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[114] Ibid.
[115] Ibid.
[116] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[117] Dr. James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.
[118] Ibid.

a fussy organism and that growth rates were highly sensitive to media construction, temperature, and other environmental conditions . . . "as a matter of fact, we are still working on the yields of that product."[120] Using density gradient technologies, they then devised methods for separating the polysaccharide capsules from the bacterial cells and distinguishing among them by size. Applying what Sorrentino had learned with viral particles proved more difficult with larger polysaccharide molecules. He recalled that this particular problem stumped them for about a year until they devised a way to exclude molecular sizes on columns according to molecular weight with the aid of gel permeation chromatography. With this technology, Sorrentino and Metzgar were able to select the larger molecules, which elicit better antibody responses for their vaccine. Once they had cleared this hurdle, they were poised to manufacture a large quantity of vaccines for clinical trials.

Proving efficacy presented another problem. Sorrentino recalled that meningitis generally attacked two in every 15,000 people in the U.S. at that time. To do an efficacy trial of any statistical significance would require immunizing hundreds of thousands of subjects. Therefore, with the cooperation of a South African health minister, National began to conduct clinical trials in an area where the disease was both endemic and epidemic. "If you go down in the gold mines 2,000 feet, it is an ideal environment for transmitting. We went from a very low rate to 15/1,000 people that come down with meningitis in the mines."[121]

Meanwhile, the Army was anxious to provide adequate efficacy data to NIH's Bureau of Biologics (BOB) to get the vaccine licensed as soon as possible. To this end, with BOB as a mediator, they arranged a means by which efficacy data from Merck's and National's clinical trials could be pooled to reduce the time required for clinical testing by half.[122] Though this sort of data sharing arrangement would be considered unusual today, Sorrentino explained that, "it was something that happened back then because we were very collaborative."[123] Metzgar further attested to the collegial atmosphere surrounding the project, explaining that "Jim had come from Walter Reed and knew the people there and I came from Merck. I knew who the players were, who I could pick up the phone and call if I had a problem with something."[124]

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[119] Ibid.
[120] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[121] Ibid.
[122] Sorrentino was under the impression that Merck and National shared more than efficacy data under this arrangement. He believed that "there was a problem with polysaccharide size. And, what I've been told is that we had purified polysaccharide that was appropriately sized and Merck was having trouble so that data was shared so everybody could produce the appropriate amount of polysaccharide with the appropriate size."
[123] Dr. James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.
[124] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.

The meningitis vaccines were a tremendous technological and clinical success. They offered safe and effective protection against a deadly and previously unpreventable disease. Subsequent tests revealed that Merck's vaccine would be also effective in the most vulnerable age category – very young children.[125] Furthermore, there was strong demand for the vaccine. In a manner that was foreseeable, however, the highest demand for the vaccine came from countries such as Brazil and Africa that could not afford the vaccine at full price. Industry sold the vaccine in the US to a small travelers market and through low margin military contracts. The rest was donated to countries that suffered a high incidence of the disease.

While National continued to manufacture the meningitis vaccine, despite the technical success, clinical effectiveness, and medical need for the vaccine, Merck eventually decided that meningitis outbreaks were too few and far between in U.S. populations, Merck's primary market, to justify further investments in producing the vaccine.[126] As with the pneumococcal vaccine during World War II, military contracts to develop new vaccines put industry on the "bleeding edge" of vaccine development. Military protection needs were once again too far ahead of U.S. civilian needs to ensure the commercial success of the vaccine. Yet, as recent epidemics of meningitis on college campuses have shown, the military was an accurate though premature canary for what would ultimately become a more general public health threat. Metzgar notes that National, which continued to manufacture the vaccine, has noticed that demand for the vaccine has gone up in recent years. He attributes this trend to overcrowded dormitories, explaining that "colleges and universities are different now. When I went to Purdue, there were 12,000 students on the whole campus. Now there are 64,000 and they are cramped in small spaces and it looks more like the military."[127]

Merck's decision to discontinue production of the meningitis vaccine in the 1990's reflects a growing divide between the principles that guided research and development decisions in the post World War II period and those that would guide them in the years following the Vietnam War. Neither Merck nor National made a business decision when they decided to develop a meningitis vaccine in the early 1970's. Rather, their decision to go ahead with the project reflected the duty-driven spirit of vaccine development in the postwar era. Industry directors believed that they had just as great a duty to the public and to the government as to its customers and stockholders, and that the military in particular deserved generous support.[128] As the case of the development of the

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[125] *JAMA* 238, no. 17 (1977): 1804; *Pediatrics* 60, no. 5 (1977): 673-80.
[126] Merck discontinued production of the meningitis vaccine in 1995.
[127] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[128] V. Bush, "Of What Use is a Board of Directors?"; and G. W. Merck, "Peacetime Implications of Biological Warfare," *The Merck Report* (July, 1946). MA.

meningitis and influenza vaccine demonstrate, directors shared this sentiment with WRAIR alumni within their company who were equally driven by a sense of obligation to the military.

IV. Exchange Relationships in the Postwar Culture for Military-Industrial Vaccine Development

The meningitis and influenza vaccine development case emphasizes a characteristic of the postwar industrial culture for vaccine development that was that was also visible in the earlier examination of Merck: the role of "gift" exchanges in military-industrial relations.

The experience of having worked closely with the military under the threat of war conditioned industry attitudes towards vaccine development projects in the postwar era even after the immediate threat of war had diminished and the commercial rewards for investments in vaccine development remained low. In this context, vaccines were regarded as an instrument of public health and national security. In other words, they often carried the social and economic status of a public good or a "gift," and were therefore not subject to normal pricing practices in the pharmaceutical industry. Evidence for this can be found in both the actions and comments of members of the vaccine industry at this time. For example, Bush and Merck accepted military contracts on principle, and urged the rest of the pharmaceutical industry to do the same, arguing that "there is a genuine need, from a patriotic standpoint, for industry to collaborate in the research effort essential to national defense."[129] Similarly, Hilleman accepted the Army's meningitis contract, not because he thought a meningitis vaccine would be profitable, and not because he had a scientific interest in bacterial polysaccharide vaccines, but because a failure to accept the contract "would be a real disloyalty to the military."[130] Dr. Sorrentino described National's attitude towards providing vaccines for the military in a similar vein: "it may sound syrupy, but they [National] really believed that they had something special and if they could give it to the government, they would. No matter how little money they made, they felt that if the government needed it, they had to respond to that. They were always working around the clock. I can't tell you how many times I saw those old army trucks pulling to the back of those bays to pick up a supply."[131]

These cases offer some evidence that companies such as Merck and National's vaccine divisions were operating according to the principles of what anthropologists call a "gift regime"

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[129] V. Bush, "Science and Business," remarks delivered at the 10th Annual Rutgers Business Conference. MA.
[130] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.
[131] James Sorrentino, interview by author, Norwalk, CT, May 25, 2001.

in the postwar era. [132] Economic anthropologists commonly distinguish between gift and commodity exchanges as a way to track the shifting social and moral identity of objects as they are exchanged within a variety of cultural contexts.[133] Whereas commodity exchanges exact a price, gift exchanges are personal and exact a sense of social debt. The former can operate in a market of arms-length transactions, whereas the latter are based on shared experiences and intermingling personal histories of the sort that administrators and scientists developed from working together in World War II vaccine development programs or later at WRAIR.

"Gift" and "commodity" distinctions are particularly useful in the examination of military-industrial relations for vaccine development because they provide a framework in which to understand transformations to the state of military-industrial relations in the 1970's. Specifically, the postwar culture, which supported military-industrial collaboration through participation in low margin military contracts gave way, by the mid-1970's, to a regime in which economic concerns prevailed. For example, a member of Merck's manufacturing team in the 1970's recalled that the perception that vaccines were a public good or a gift confounded the profit objectives of private industry. He explained, "it was hard to make money in vaccines because people resent paying a large amount for a vaccine. They've got the idea that a couple of dollars is all you should pay. Well, it's an extremely complex production process with a lot of inventory storage considerations and quality control testing. It is always something you look at and say, you've got to find some way to make a profit if you're going to provide this."[134]

These comments reflect a growing tension between the dueling identities of commercially produced vaccines. By the mid-1970's, as the memory and experiences of World War II began to recede into the past, many of the conditions that had once fostered military-industrial collaboration began to deteriorate, gift regimes gave way to commodity regimes, and rates of vaccine innovation began to suffer as a result.

V. Conclusions

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[132] M. Mauss, *The Gift: Forms and Functions of Exchange in Archaic Societies* (New York: Free Press, 1954).
Warwick Anderson applied the distinction between gift and exchange regimes to medical research in a talk titled "Exchange Regimes in Late Colonial Science" at Harvard University, November 12, 1999.

[133] For a review of the literature of economic anthropology as applied to modern scientific exchange relationships, see: W. Anderson, "The Possession of Kuru: Medical Science and Biocolonial Exchange," *Society for Comparative Study of Society and History* 10 (2000): 713-744.

[134] Robert Hendrickson, oral history interview by Jeffrey Sturchio and Louis Galambos, December 20, 1991 and April 13, 1992. MA.

A strong culture of military-industrial collaboration continued to fuel vaccine innovation during the postwar period. This culture was sustained by a number of friendships, ideologies, and R&D practices that migrated out of OSRD and WRAIR and into industry.

The personal connections that sustained this culture were particularly evident at Merck and Company where a number of OSRD members, including Vannevar Bush and Alfred Newton Richards, followed George Merck into the pharmaceutical industry. Personal connections to military research labs were reinforced as Merck continued to hire vaccine research scientists from WRAIR. Industry connections to military research were not limited to Merck; as WRAIR developed a reputation as a "center of excellence" for infectious disease research, a number of firms within the vaccine industry began to seek collaborative partners and new hires at WRAIR.

A number of ideological principles sustained this culture, as well. The shared experience of developing vaccines during World War II created a postwar culture in which military and industrial planners and research scientists regarded vaccines as an essential instrument of national security as well as public health. The military-industrial culture that supported this conception of vaccines had a tendency to engage in "gift" exchange relationships. In other words, industry investments in vaccine research during this period often stemmed from a sense of personal and social obligation rather than from a straightforward rational calculation of costs and returns. Industrial leaders that had participated in World War II R&D programs demonstrated an ideological predisposition to support scientific research in industrial settings and to accept military contracts for the national good. Early Cold War anxieties reinforced this predisposition, driving DOD investments in vaccine research and encouraging companies such as Merck to invest in vaccine development and to accept military contracts despite economic disincentives.

Finally, the migration of talent from WRAIR into industry during the postwar period further reinforced this culture, as it increased the number of personal ties between individuals in military and industrial institutions, while it also imported the R&D practices of "science integrators" such as Maurice Hilleman and James Sorrentino. As the development of the meningitis and influenza vaccine demonstrates, their interdisciplinary tactics, combined with a sense of personal obligation and loyalty to colleagues at WRAIR had a significant and positive influence on industrial vaccine innovation patterns throughout the postwar period.

Chapter Four: Decline of the Postwar Culture of Military-Industrial Collaboration

By the late 1970's the rate of vaccine innovation was trending downward (Figure 1, Chapter 1). Moreover, with fewer vaccine product introductions in industry pipelines, levels of innovation showed no immediate signs of recovery. Lending support to this observation, Maurice Hilleman explained, "much of the pioneering for vaccines had been completed by 1984 . . . this was true for the entire industry."[1] He concedes that "two to three vaccines were finished after this period but that was just due to a time-lag in the engineering and scale-up."[2] There was mounting evidence that levels of supply were on the wane as well. From 1968 to 1977, more than half of the vaccine producers in the United States ceased production and the total number of biological products on the market fell from 385 in 1968 to 150 in 1979.[3]

By the mid-1980's, however, economic incentives and technological opportunities were improving due to industry consolidation and advances in genetic engineering. Further, firms began to build capabilities that would enable them to exploit these opportunities. Thus, all of the conditions for technological innovation that are traditionally recognized by historians of industrial innovation had been met. Why then did vaccine innovation rates continue to fall? A close examination of military-industrial relations during the period offers some insight.

I. Diminishing industry commitment

During the postwar period, pharmaceutical directors had been content to maintain vaccine divisions as a public service and continued to collaborate with the military even after the threat of a world war diminished and the commercial rewards for investments in vaccine development were low. By 1979, however, the Office of Technology Assessment (OTA) observed a distinct shift in industry attitudes towards vaccine development.[4] They reported that "the apparently diminishing commitment -- and possibly capacity -- of the American pharmaceutical industry to research, develop, and produce vaccines,

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[1] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

[2] Hilleman refers here to a varicella vaccine (licensed in 1995) and a protein coupled pneumococcal vaccine licensed by Lederle in 2000. He discounts the rotavirus vaccine developed by Wyeth for it was taken off the market within weeks of its introduction when it was discovered that the vaccine caused bowel obstruction in infants. He also discounts Lederle's Lyme Disease vaccine, explaining that individuals taking the vaccine lose immunity after a year and that the vaccine is ineffective for individuals under the age of 15. "This is a non-vaccine if you ask me." (Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000).

[3] Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985) 46; Office of Technology Assessment, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979).

[4] See Chapter One for background information on the 1979 OTA study.

however, may be reaching levels of real concern."[5] In particular, they noted that the number of licensed vaccine manufacturers had dropped from 37 in 1967 to 18 in 1979 and that only 8 of these remaining companies were actively producing vaccines for the U.S. market.[6] Industry, government and academic observers of these events generally credited the swine flu affair of 1976 with setting this wave of consolidation into motion.[7]

Swine flu affair

In January of 1976, an Army recruit at Fort Dix, New Jersey died of an upper respiratory ailment after an overnight hike. Army epidemiologists isolated an unusual strain of the influenza virus that was usually only found in pig populations. This "swine flu" had not been encountered in human population for the past 50 years. Furthermore, both antigenic proteins on the surface of the virus were significantly different from any known viral antigens circulating through the population at that time, an indication that there would be no residual immunity to the swine flu from previous flu infections. This antigenic shift alarmed epidemiologists, because it suggested that the swine flu had the potential to cause a pandemic on a scale comparable to the Spanish Influenza pandemic of 1918. After a series of urgent meetings and heated debates, the federal government decided to proceed with a nationwide program to develop the swine flu vaccine and to vaccinate the entire U.S. population before flu season returned in the fall and winter of 1976-77.[8]

Under the threat of a public health emergency, vaccine producers agreed to assist the government with the large-scale immunization campaign, launching programs to produce record quantities of vaccine on short notice and for no profit.[9] Swine flu manufacturers (Parke Davis, Merrell National, Wyeth, and Merck) proceeded with trepidation, however, demanding liability protection from vaccine-related injury claims. The swine flu vaccine, no different than other vaccines, was guaranteed to produce adverse reactions in a small but certain percentage of the population. But because the swine flu vaccine was

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[5] Office of Technology Assessment, *A Review of Selected Federal Vaccine and Immunization Policies* (Washington, D.C., 1979), 27.

[6] Ibid., 27.; By 1989, the number of large vaccine manufacturers would be reduced to four.

[7] Office of Technology Assessment, *A Review of Selected Federal Vaccine and Immunization Policies* (Washington, D. C., 1979); Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985).

[8] For an account of the circumstances and personalities surrounding the decision to proceed with a federal swine flu immunization program, see R. Neustadt and H. Fineberg, *The Epidemic That Never Was: Policy Making and the Swine Flu Affair* (Toronto: Vintage Books, 1983).

[9] Initially, "companies committed their manpower, plants and working capital to the operation before pinning down profit and loss factors." ("Vaccine Plan: Produce Now, Dicker Later," *Chemical Week* (April 14, 1976).) Months later, Congress passed legislation that offered companies liability protection on the condition that no profits were made on swine flu vaccines sold to the government. Despite the no-profit clause, companies upheld their agreement to produce the vaccine. (R. Neustadt and H. Fineberg, *The Epidemic That Never Was: Policy Making and the Swine Flu Affair* (Toronto: Vintage Books, 1983), 89.

going to be administered to the entire population, the overall number of adverse reactions was bound to be higher than normal.

In June of 1976, the director of the American Insurance Association informed David Sencer (director, CDC) Harry Meyer (director, BOB), and W. Delano Meriwether (director, National Influenza Immunization Program) that the industry would not provide coverage for swine flu producers and that any pre-existing coverage would be terminated June 30.[10] Manufacturers held that, without government-sponsored liability protection, they could not shoulder the risk of participating in the immunization program.[11] Faced with the impending collapse of the immunization program, President Ford urged Congress to draft legislation that would allow the government to provide liability protection, and enable the program to proceed. Due to the efforts of Congressman Paul Rogers, who believed that the nation was facing a catastrophe analogous to the 1918 pandemic, and with the help of Ford's request for a no-amendment rule, the bill passed through Congress in August and immunizations began in October.[12]

The feared epidemic never emerged but, within months of the first vaccinations, the swine flu vaccine became associated with Guillain-Barre Syndrome, a disease affecting the peripheral nervous system. Due to the indemnification bill passed by Congress, industry did not suffer directly from product liability suits filed against the swine flu vaccine. There was, however, a great deal of publicity about the hypothesized adverse effects of the vaccine; this publicity raised public awareness of the risks associated with vaccination itself and subsequently encouraged an avalanche of product liability suits for other vaccines not protected by the indemnification act.[13] Merck recorded annual increases in the number of vaccine-related lawsuits from 15 filed in 1979, reaching a total of 47 in 1986.[14] National (recently acquired by Connaught) also felt the sting of what they called "a national crisis of product liability." They reported that a total of $5 billion in claims had been filed with $3 billion in lawsuits filed against manufacturers of the combined diphtheria, tetanus, pertussis vaccine (DTP) in 1985 alone.[15]

The growing risk of product liability suits strained an industry that was already struggling with low margins. One historian relates that "senior managers of Merrell-National were spending more than half of their time on a business segment that only amounted to about 5% of their revenues."[16] Frustrated by the growing cost and low returns to vaccine development, manufacturers began to reconsider their

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[10] Ibid., 70.
[11] "Snag in Flu Vaccine," *Business Week* (June 28, 1976); "Troubles Plague Flu Vaccine," *Industrial Edition* (June 7, 1976).
[12] R. Neustadt and H. Fineberg, *The Epidemic That Never Was: Policy Making and the Swine Flu Affair* (Toronto: Vintage Books, 1983), 86.
[13] E. Kitch, "Vaccines and Product Liability: A Case of Contagious Litigation," *Regulation* (May/June, 1985).
[14] L. Galambos and J. Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995).
[15] Internal Memo, David William, VP and General Manager, Connaught Laboratories, Swiftwater, PA (1985). AP.
[16] J. Widmer, *The Spirit of Swiftwater*, (Swiftwater: Connaught Laboratories, 1997), 61.

commitment to the vaccine business. Merrell National (then owner of the National Drug Company) decided, along with half of the industry, to divest its vaccine division.[17] Of the companies that remained in the business, many, such as Merck, stopped manufacturing DTP and influenza vaccines altogether and pulled back on other vaccine research and development investments.

This chain of events is consistent with the interpretation that poor economic incentives accounted for declining rates of innovation and supply in the 1970's. In other words, the economic strain posed by the risk product liability suits forced industry to make difficult choices between R&D initiatives and new vaccine projects often lost out to higher margin pharmaceutical ventures. Did the swine flu affair merely tip the balance on a rational calculation of the economic costs and risks of vaccine development?

Before accepting this interpretation in its entirety, it is important to consider that product liability had already become an issue for the industry by the early 1960's, as courts began awarding large sums to individuals claiming vaccine injuries.[18] Further, there is evidence to suggest that economic disincentives for vaccine development were present well before 1976. An article published in *Industrial Edition* during the 1970's noted that liability represented only one of many factors contributing to low margins in the industry. "Others include big capital investment requirements, complicated manufacturing processes, burdensome licensing procedures, a static market for established vaccines, and, until recently, an overabundance of competition," all of which had been dominant characteristics of the vaccine market for years.[19] Further, in noting Merrell National's industry exit, the article observed that "in more than 10 years, Merrell National, one of the nation's largest pharmaceutical companies, is reported to have failed to turn a profit in vaccines."[20] Merrell National was, at that time, the parent company to National Drug, which had recently made large investments in the successful development of a new meningitis and influenza vaccine. The fact that their vaccine division had not been profitable for years did not discourage the company from engaging in ambitious vaccine development projects in the early 1970's. Merrell National had simply funded vaccine development with profits from their other product lines, a practice they could well afford to continue. Why should poor economic incentives in the vaccine market represent an obstacle now? And, to consider a much larger question: were poor economic incentives entirely to blame for industry consolidation and falling rates of innovation in the late 1970's or were other forces at work?

Public relations

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[17] The Canadian firm, Connaught, eventually acquired National Drug's laboratories in Swiftwater, PA after Merrell-National donated the company to the Salk Institute in 1978.

[18] R. Neustadt and H. Fineberg, *The Epidemic That Never Was: Policy Making and the Swine Flu Affair* (Toronto: Vintage Books, 1983), 71.

[19] "A Risky Exodus From Vaccines," *Industrial Edition* (April 10, 1978).

The costs of the swine flu affair were not merely financial. The experience undercut a long-held belief within the vaccine industry that the public relations benefits reaped from responding to large government contract requests often outweighed the accompanying financial costs. This viewpoint dates back at least as far as the 1940's and figured into company decisions to manufacture vaccines for the military during World War II. Industry's participation in the federal swine flu campaign was motivated by a similar attitude; however, participation became a thankless endeavor that contributed to a fundamental shift in industry attitudes toward vaccine development in the late 1970's.[21]

When the federal government announced its intention to vaccinate the entire U.S. population against swine flu, Robert Hendrickson, who was director of Merck's manufacturing at the time, recalls, "suddenly we got hit with this tremendous requirement for millions of doses—in a very short time span. So we geared up like mad to try to do this thing."[22] Hendrickson went on to explain that the development and scale-up of the vaccine for high-volume production was an extraordinary accomplishment undertaken for no profit. Yet, he remarked, "it ended up engendering nothing but bad will despite a really massive effort to try to do something for the benefit of the country . . . We got nothing but criticism from the whole program because, as it ended up, the vaccine wasn't needed . . . You start out with something which is being done as a goodwill gesture for the benefit of mankind, and like many things that happen in the industry, it gets turned against you because of suspicion that you did something wrong, that you put out a harmful product."[23]

As the perceived public relations benefits of filling low margin government contract requests evaporated, a number of firms began to reevaluate their participation in the vaccine business on the basis of profit potential alone. Given the ever growing number of product liability suits for alleged vaccine-related injuries, many companies decided to divest their vaccine divisions and to focus on more profitable product lines in the pharmaceutical industry. Merrell National, Eli Lilly, Pfizer, Parke Davis, and Dow Chemical were among the large U.S. firms to exit the business. By 1985, only Merck, Wyeth, Lederle, and National (which was now a part of Connaught) remained.[24]

New Profits

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[20] Ibid.

[21] Merck conducted a study on the vaccine industry in the 1970s that lent support to the theory that industry involvement in the vaccine business was often motivated by factors other than the bottom line. They concluded that "the reasons [that companies stayed in the vaccine business] are mostly NOT of the 'rational strictly business' type. The major one for many is political." (L. Galambos and J. Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995),148.

[22] Robert Hendrickson, oral history interview by Jeffry Sturchio and Louis Galambos (December 20, 1991 and April 13, 1992). MA.

[23] Ibid.

Following a decade of large-scale industry consolidation, economic prospects for the remaining players had begun to improve considerably. By 1985, Merck held 60% of the U.S. market for vaccines, Lederle 18%, Connaught 14 % and Wyeth 8%.[25] Further, each company held quasi-monopolies over individual vaccine product lines, giving these firms the freedom to raise prices. Reflecting on business in the 1980's, Dr. Metzgar recalled, "ironically, Connaught [formerly National Drug] began to make money when litigation became so prevalent."[26] He explained that the company "started to charge money to cover self-insurance needs. And raised prices. There was a period of time when we didn't sell anything -- almost drove ourselves out of the market. Eventually, other companies began to look at what we were doing and followed suit."[27] Dr. Metzgar's comments resonated in a statement by Dr. Lance Gordon, a vaccine research scientist at Connaught Labs, Squibb, and later at North American Vaccine. He explained that "when I entered commercial vaccine development in 1980 the aggregate U.S. market for the core pediatric vaccine, DTP, was approximately $6 million, a market that was shared by nine manufacturers . . . [after funding established for the vaccine compensation Act of 1986], sales of the DTP vaccine in the U.S. had grown to almost $300 million . . . the larger sales were due almost entirely to product liability price increases."[28]

These individual accounts of industry pricing behavior are supported by empirical data. According to a study of the industry, from 1980 to 1995, vaccine prices rose at a greater rate than the consumer price index or the producer price index.[29] However, Dr. Gordon's assertion that prices were raised solely in response to product liability costs is not consistent with Dr. Metzgar's admission that price hikes were a source of profitability for his company. Another study of the industry attributes prices hikes, in part to the rising cost of R&D and product liability, but it concludes that a large portion of the price hikes are consistent with monopoly pricing behavior and reflect the growing market power of remaining vaccine producers.[30]

Thus, it appears that as prices continued to rise during the 1980's and 1990's, industry profits grew as well. Companies do not provide information on R&D costs for individual products or divisions for competitive reasons and thus it is difficult to obtain accurate data on profitability trends for vaccine

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[24] Consolidation continued over the years. Wyeth and Lederle were merged and held as a division under American Home Products, and Connaught was absorbed in the French manufacturer, Aventis-Pasteur.
[25] J. Clark and R. Ghislain, "Commercial Aspects of the Vaccine Industry," eds. G. Woodrow and M. Levine, in *New Generation Vaccines* (New York: Marcel Dekker, Inc., 1990).
[26] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[27] Ibid.
[28] Prepared statement of Dr. Lance Gordon before the House Committee on Commerce, June 15, 1995.
[29] R. Arnould and L. DeBrock, "The Application of Economic Theory to the Vaccine Market," ed. M. Pauly, in *Supplying Vaccine: An Economic Analysis of Critical Issues* (Amsterdam: IOS Press, 1996), 103.
[30] Background paper, M. Sing, and M. Willian, presented at *A Study of the Economic Underpinnings of Vaccine Supply*. Sponsored by the National Vaccine Program Office and the CDC on November 12, 1993 in Washington, D.C.

divisions. However, it is reasonable to expect that vaccine margins improved considerably, especially after the 1986 passage of the Vaccine Compensation Act. In an effort to stem price hikes and to prevent more manufacturers from exiting the industry, Congress passed this act to relieve manufacturers of liability for non-negligent vaccine-related injuries sustained in compulsory immunization programs.[31] This program has successfully limited the number of vaccine liability lawsuits for industry. Compared to the 255 DTP suits filed in 1986, only four were filed in 1997.[32] While reducing the lion's share of product liability costs for industry, the Act has not, however, stemmed the tide of rising vaccine prices.

New Strategies

As profits rose, industry began to develop a new attitude towards vaccine development. Douglas MacMaster, President of Merck in the mid-1980's, warned Congress that his company was changing its strategy towards vaccines, indicating that, in the future, Merck would treat vaccines like any other high-margin business opportunity: "the vaccine business is a high technology business, not a commodity business, and profitability is not determined by a sales minus costs basis. Profitability is determined by assessing our total business situation, looking at the elements affecting our total business including cost of promotion, capital expenditures, production costs, costs of raw material and the cost of research and development."[33] MacMaster hinted that barring a public health emergency, private industry was less likely to grant favors to the government. Rather, Merck's continued involvement in the vaccine business would be contingent on profits. In a carefully worded statement, he explains, "Merck has a long standing commitment to vaccine research. We believe it is a matter of public trust to remain in the marketplace as long as possible. Nevertheless, the extent to which we are able to allocate resources to the development of new vaccines is certain to turn in part on the profitability of such products."[34] The tone of these statements differs significantly from the strong sense of duty and obligation that permeated Merck, Bush, and Hilleman's comments regarding their commitment to vaccine development.

Higher financial returns to vaccine investments did not translate into higher rates of innovation. No longer willing to regard their vaccine divisions as a public service, industry was less likely to invest in aging production facilities that were producing low margin items, more likely to terminate production of low margin items, and less likely to accept low margin military contracts. For example, following the

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[31] This program put a surcharge on vaccine sales to create a federal fund from which individuals could be compensated.

[32] R. Rader, *Biopharma: Biopharmaceutical Products in the U. S. Market* (Rockville: Biotechnology Information Institute, 2001).

[33] "Hearing on Funding of the National Vaccine Injury Compensation Program," summary testimony of Douglas MacMaster, President Merck, Sharp and Dohme Division before the Subcommittee on select revenue measures, Ways and Means Committee, U. S. House of Representatives, March 5, 1986.

[34] Ibid.

swine flu affair, Merck stopped manufacturing influenza and DTP vaccines. Eventually, they ceased producing their meningitis vaccine as well. Reflecting on Merck's diminished commitment to vaccines in 1970's and '80's, Dr. Gordon Douglas, President of Merck Vaccines, stated, "I think it's fair to say that during the '70's and '80's Merck under-invested in vaccines, in the manufacturing and research as well as sales and marketing."[35]

Frank Ecock, Vice President of manufacturing (1958-1991), relates that the vaccine business in the mid seventies "wasn't real profitable and we got into some fusses about facilities."[36] While Merck's new hepatitis vaccine was under development, Ecock wanted to build new manufacturing facilities. Merck Senior Vice Presidents overruled Ecock's suggestions, though, opting to refurbish an existing building. Wrote Ecock, "I felt we were throwing our money in a rat hole . . .it was not a good decision . . . because we're now archaic in our facilities. . . . I don't think we put the resources in there that we should have because we knew Heptavax [Merck's first Hepatitis B vaccine, licensed 1981] was coming."[37]

Indeed, it appears that these under-investments continue to trouble industry today. In addition to slowing rates of innovation, industry has been unable to produce sufficient amounts of already-licensed vaccines.[38] In particular, it appears that Merck's earlier under-investments in hepatitis (A and B) vaccine manufacturing facilities may be causing problems for the firm currently, as the FDA cited "numerous deficiencies" with the their manufacturing facilities, requiring Merck to recall dozens of lots of its hepatitis A vaccine in February of 2002.[39]

The manner in which National Drug (now a division of Connaught) chose its next vaccine development project illustrates a new emphasis on market-driven vaccine development and investment decisions. In contrast to the way in which National decided to work on the influenza and meningitis vaccines in the early 1970's, their subsequent decision to develop a *Haemophilus influenzae B* (HIB) vaccine was made strictly on the merits of market potential. Looking for a way to expand the market for National's new meningitis vaccine, Doug Reynolds, marketing director at National, commissioned Rutgers University to conduct a survey asking physicians whether they would routinely administer meningococcal meningitis vaccines in their office practice. Dr. Metzgar recalled that the results indicated they would not, but that they would be interested in a potential vaccine to prevent HIB infections (another

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[35] "An Ounce of Prevention is Worth a lot to the Bottom Line," *Merck World* (February 8, 1996). MA.
[36] Frank Ecock, oral history interview, conducted by Jeffry Sturchio and Louis Galambos, (October, 1991 and November, 1991). MA.
[37] Frank Ecock, oral history interview by Jeffry Sturchio and Louis Galambos, (October 11, 1991 and November 4, 1991). MA.
[38] Examples include: R. Pear, "Juvenile Vaccine Problems Worry Officials and Doctors," *The New York Times*, December 2, 2001; "Children's Vaccine in Short Supply," *Associated Press*, January 3, 2002; G. Harris, "CDC Warns Vaccine Supply in Jeopardy," *The Wall Street Journal*, February 11, 2002.
[39] G. Harris, "CDC Warns Vaccine Supply in Jeopardy," *The Wall Street Journal*, February 11, 2002.

source of meningitis) in young children.[40] Based on this survey, National promptly dropped all military contracts pertaining to the development of a vaccine against group B meningococcal meningitis and started working with the National Institutes of Health (NIH) to develop HIB vaccines.

Once vaccine divisions began to yield profits, upper managers began to manage the activities of vaccine divisions more closely, an event which, ironically, may have indirectly inhibited innovation by limiting informal opportunities for military-industrial collaboration. Dr. Metzgar recalled that "prior to that time [that vaccines became profitable], vaccines were a sideline. They were not market-driven research investment decisions."[41] He explained that "corporate willingness to collaborate relaxes when the product potential for a reasonable profit does not exist. This mentality of small revenue and community service prevailed when vaccines were a boutique enterprise whereas now vaccines are a mainstream revenue producer for manufacturers that are still in business."[42] Comparing the collaborative atmosphere in which the meningitis vaccine was developed to subsequent development projects at National, Dr. Sorrentino echoed Metzgar's remarks, stating, "it is my understanding that no one collaborates anymore."[43] More significantly, Metzgar observed that "most productive collaboration happened when the vaccine business was less than 5% of the revenues of National Drug."[44] Once industry directors began to evaluate vaccine development projects on their commercial merits alone, they became less willing to accept low margin military contracts or to permit their scientists to pursue their own projects and to rely on personal networks of informal collaborative partnerships. Since collaborative partnerships were most often formed with former colleagues at WRAIR, industry began to deprive itself of the one product development partner that, since the 1940s, had directed it toward the highest number of new vaccine products.

Industry's diminished commitment to vaccine development in general, and military collaboration in particular, was also a response to transformations in public attitudes. Higher numbers of vaccine liability lawsuits were partly a response to the events surrounding the swine flu affair. They also, however, reflected deeper transformations in social attitudes about vaccines. By 1980, a combination of vaccination and sanitation had brought the U.S. incidence of infectious disease to an all-time low.[45] In the absence of salient reminders of the threat from infectious disease, individuals became more concerned about the risk of adverse effects from a vaccine than about the risk of contracting the disease itself. Dr.

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[40] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[41] Ibid.
[42] Ibid.
[43] Dr. James Sorrentino, interview by author, Norwalk, CT, May 21, 2001.
[44] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[45] D. Gordon, D. Noah and G. Fidas, *The Global Infectious Disease Threat and Its Implications for the United States*, National Intelligence Estimate, CIA, January 2000: 99-17D, Figure 17: Trends in Infectious Disease Mortality Rates in the United States.

Metzgar explained that any vaccine will elicit a reaction in less than one percent of the population. "It's the less than one percent reactions that bring it to the attention to people. And kids we've raised in recent years want protection from everything. I think it's a symptom of the times. When I grew up, there were no vaccines. There was polio running rampant and people can't relate to that any better than they can relate to World War II."[46]

The unpopularity of the Vietnam War was also a contributing factor. Military institutions lost credibility over the course of the Vietnam War. Reports and images of military use of napalm and Agent Orange in Vietnam corrupted the World War II notion that military-funded research and development deserved the unquestioning support of public tax dollars. It was no longer as accepted, as it may have been in 1951, that "government agencies represent the will of the people."[47] This was true of both civilian and military agencies and, as was the case with the swine flu program, associating one's firm with the war effort ceased to guarantee public relations benefits. Maintaining public trust was (and is) critical to the pharmaceutical and vaccine industries and thus they became less motivated to seek an overt association with military medicine. Increasingly, industry would refuse new military contracts and fail to renew old ones.[48] These developments contributed to looser ties with military research programs at WRAIR and USAMRIID during this period. This trend also deprived industry of the advantages of collaborating with a lead-user of vaccines for it limited their opportunities to test and develop viable vaccine candidates coming out of military research programs.

Vaccines: from gifts to commodities

The military-industrial culture for vaccine development suffered from a problem that was related to, yet more fundamental than, public relations strategies in the vaccine industry. As the Cold War began to lose intensity after the Vietnam War and as the incidence of infectious disease reached a record low in 1980, national security and public health threats became less salient, thereby permitting economic concerns to take center stage. These transformations created a new political and social landscape in the 1970's which, as Bruce Smith has observed, was no longer characterized by "patriotism and broad public support, deference to executive leadership, and the subordination of partial interest to the larger national interest."[49] The military-industrial culture for vaccine development was born out of a sense of patriotism in World War II and was predicated on the conception of vaccines as a "gift," a public good, and as

[46] Dr. Donald Metzgar, interview by author, Aventis-Pasteur, Swiftwater, PA, June 21, 2001.
[47] Col. Tom Whayne and Col. Joseph McNich, "Fifty Years of Medical Progress," *New England Journal of Medicine* 244 (1951): 592-601.
[48] Between the 1980s and 1990s Greer Labs terminated production of the plague vaccine, Wyeth terminated production of the adenovirus, cholera, and smallpox vaccines, and Michigan Biologic Products Institute ceased producing the anthrax vaccine.
[49] B. Smith, *American Science Policy Since World War II* (Washington, D.C.: The Brookings Institution, 1990), 72.

instruments of national security and public health. This perception was easily sustained in the early stages of the Cold War and permitted industry to overlook some financial disincentives to collaborating with the military on commercially unsuccessful yet socially beneficial vaccines. However, as industry began to subordinate national interests to their own particular economic interests in the late 1970's, vaccines began to assume a different identity within the industry. The transformation of the perception of vaccines as a gift to a commodity represented a significant disruption to the culture that supported military-industrial collaboration in the postwar era. Industry was not entirely responsible for dismantling the postwar military-industrial culture of collaboration; the political and social transformations of the 1970's also encouraged the military to withdraw their commitment to vaccine development.

II. Diminishing government commitment

Military, executive, and congressional commitment to military medical research and development began to slacken in the 1970's. In particular, in what marked an abrupt change from the government's postwar commitment to expanded vaccine development programs at WRAIR and at Fort Detrick (now the U.S. Army Medical Research Institute for Infectious Diseases or USAMRIID), military-sponsored vaccine research was either terminated or compromised for a host of political, strategic, and economic reasons.

Declining strategic interest in biological weapons research

By the 1970's, as the U.S. began to pull out of Vietnam and other contested Cold War territories, the Department of Defense (DOD's) commitment to early Cold War strategies that relied on biological measures (such as vaccination campaigns and international epidemiology) to conduct diplomacy and ensure security began to slacken. The DOD began to cut back on investments in its international laboratory network and, according to one report, "epidemiological surveillance in these countries slowed to a crawl."[50] In 1979, Congress proposed handing DOD's international laboratories over to civilian contractors, if not eliminating them entirely.

A series of strategic considerations led the DOD to reduce their commitments to biological warfare (BW) research as well. A recent study notes that "the perception of senior decision makers that biological weapons lacked value as a deterrent was one of the factors leading to the 1969 decision by President Richard Nixon to abandon the offensive program."[51] The study goes on to explain that as a deterrent, the

[50] T. Woodward, *The Armed Forces Epidemiology Board: Its First 50 Years* (Falls Church, VA: Office of the Surgeon General, Department of the Army, 1990).
[51] G. Koblentz, "Biological Warfare and International Security," (unpublished manuscript: Department of Political Science, MIT, 2002).

DOD believed that biological weapons were redundant to nuclear weapons and had limited retaliatory value due to their delayed effects. After a decade of heightened attention and investment in BW research, investigators rediscovered what had become apparent to World War II biodefense scientists: that offensive measures were far easier to devise than defensive measures. Whereas offensive weapons could be formulated in two to three years, effective countermeasures (usually vaccines) took anywhere from seven to ten years to develop. Indeed, some scientists, most notably Harvard Biologist Mathew Meselson, were concerned that the program was merely generating knowledge and weapons that could be used against the U.S.. Paradoxically then, the decision to dismantle offensive biological warfare programs in 1969 did not reflect a perception that the threat from biological weapons had diminished. To the contrary, the perception was that biological weapons were a highly effective offensive instrument *and* they had little value as a deterrent.

Nixon's decision did not prohibit the DOD from continuing to invest in research to defend against biological attacks (a field that includes vaccine research), but it did limit progress in this field. Echoing the words of scientists working for the War Research Service during World War II, General William Creasy, head of the U.S. Army Chemical Corps, attempted to disabuse Congress of the notion that defensive research could be pursued in isolation of offensive research in 1971.[52] He testified that "you cannot know how to defend against something unless you can visualize various methods which can be used against you, so you can be living in a fool's paradise if you do not have a vigorous munitions and dissemination-type program."[53] Given the interdependence of offensive and defensive biological weapons research, the abolition of the former was felt by the latter, and biodefense research began to lose momentum in the post-Vietnam War era.

Declining political interest in military vaccine research

A number of political factors also caused military vaccine research initiative to lose momentum in the late 1960's and early 1970's. Specifically, political support for non-targeted DOD R&D initiatives began to erode. This development was related to a larger political movement that signified a disruption of the assumptions that sustained federal support for scientific research in the postwar era.

For example, during the Vietnam War, several politicians began to question Vannevar Bush-inspired notions that federal investments in research and development served the national and the public interest. According to Daniel Kevles, during the 1970's "science" became guilty by association with the Vietnam War, and politicians were moved to reduce federal investments in DOD R&D initiatives. As the war

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[52] See Chapter 2, Footnote 40.

[53] General Creasy, congressional testimony, recorded in SIPRI, *The Prevention of CBW*, eds. Alqvist and Wiksell, in *The Problem of Chemical and Biological Warfare vol. V.* (1971), 278.

escalated, he argued, "critics turned to searing attacks on science for its close identification with the military, including its advisory relationships to the armed services and DOD's salient presence in academia and training."[54] Kevles continued that "by the late 1960's, the dissidents had produced a coalition that brought a halt to the geometrical growth rate in federal science (while the federal budget had risen eleven-fold since 1940, the R&D budget had exploded some 200-fold)."[55] These attempts were fairly successful, he concludes, since, "by the mid 1970's, the federal R&D budget, then about $19 billion, had fallen in constant dollars about 20% below what it had been in 1967."[56]

The Mansfield Amendment, part of the military procurement and research authorization bill of November 1969, reflected the growing sentiment that curbs should be placed on federal R&D expenditures. The Mansfield Amendment prohibited the DOD from financing research not directly related to a military function or operation. Though the language of this amendment was modified a year later to permit appropriations for a wider range of research activities, it signified a congressional predisposition to roll back DOD support for non-weapons related research. Due in part to this movement, military medical research budgets were squeezed for many years following the Vietnam War.

Some budget cuts were felt as early as 1969. An October Armed Forces Epidemiology Board (AFEB) meeting was consumed with "problems that all [Army Medical R&D Command] departments are going through regarding considerable budget cuts."[57] One board member suggested that AFEB board members "take advantage of channels open to the Board and its members to add weight to the need for continuing research in medicine."[58] All agreed, though none knew how to follow-up on his suggestion. As the U.S. began to lose the Vietnam War militarily, politically, the AFEB discovered that traditional justifications for military medical research were no longer available. One participant noted, "a few years ago, Vietnam was a good word. Now with the de-escalation over there, what is the objective?"[59] No immediate answers were forthcoming and military medical research programs would continue to fall into desuetude over the next two decades.

In 1971, the DOD announced that it would conduct a management survey of AFEB operations. Rising oil prices, industrial competition from other countries, and the unprecedented phenomenon of stagflation staggered the U.S. economy, and the AFEB was one of many government organizations undergoing budgetary review in the early 1970's. General Jennings explained to AFEB board members that the DOD planned to conduct a management survey of the AFEB. The survey, they were told, was "aimed at

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[54] D. Kevles, "Principles and Politics in Federal R&D Policy, 1945-1990: An Appreciation of the Bush Report" preface to V. Bush, *Science—The Endless Frontier* (Washington, D.C.: National Science Foundation, 1990).
[55] Ibid.
[56] Ibid.
[57] Minutes, meeting of the Armed Forces Epidemiology Board, (October 24, 1969). WR.
[58] Ibid.
[59] Ibid.

achieving similar improvements in economy, efficiency and productiveness. . . we are in a period of shrinking resources, a situation which makes it absolutely imperative that we make every effort to manage our resources with the greatest effectiveness and efficiency."[60] Predictably, the survey generated justifications for significant budget cuts within the AFEB.

Budget cuts within the Military Medical R&D Command dovetailed with shifting research priorities. For example, Colonel Greenberg from the Preventative Medicine Division of the Army reported that "at the present, all of the infectious diseases are in competition with environmental pollution. Federal legislation and congressional interest now requires us to give a lot of attention to this."[61] Taken together, these trends left military support for infectious disease research in a precarious position for the first time since World War II.

The AFEB was also a victim of a new movement within Congress during the 1970's to eliminate potential conflicts of interest for individuals responsible for dispersing government funds. The management survey concluded that "the present system violates the spirit, indeed if not the letter of the law. It is improper to hold a government contract and be an official member of the review group that technically approves one's research proposal even if the advisor leaves the conference room during the discussion."[62] As a result of this report, the board and its commissions were deprived of their research function and were reduced to an advisory role for medical problems in the military.

In response to DOD's decision to abolish the board's research arm it was noted at the annual AFEB meeting in the following year that "with the demise of the Commission as we've had it in the past, we are really faced with a paradox. The field state of the art is getting to the point where I think rapid and important advances could be made on a modern biological basis. Never before have we had the tools that we have right now. At the same time, we are losing the one major organization in this country that has held the field together and has provided the major stimulus for all of this."[63]

Institutional and professional reasons for decline in military vaccine research

Vaccine research began to suffer at WRAIR during this period as well, but the reasons had less to do with budget cuts than a series of institutional and professional factors. Chief among these was the fact that the end of the draft cut off the flow of talent from graduate schools to WRAIR. An internal Army report from 1974 stated that "filling the junior staff positions, although adequate at the moment, is seriously threatened by the end of the draft. Already inadequate, however, is the number of 3-year men

[60] Minutes, annual meeting of the Armed Forces Epidemiology Board, (May 1971). WR.
[61] Ibid.
[62] T. Woodward, *The Armed Forces Epidemiology Board: Its First 50 Years* (Falls Church, VA: Office of the Surgeon General, Department of the Army, 1990), 124.

who elect to stay in the service. The reasons for this defection . . . include the competition offered by civilian opportunities and the uncertainties of a military medical career with no assurance to a young researcher that he will continue to hold research-oriented positions."[64]

Without the draft, WRAIR lost an important recruiting tool at a time when a number of scientists and physicians were beginning to question the inherent attraction of a career in military medicine. An independent review of DOD medical research programs conducted in the 1960's foresaw many of the professional and personnel problems that would contribute to the exodus of talent from military research institutes after the Vietnam War. The report identified the salary structure for senior scientists as a major source of the problem. "Fixed by statute, it cannot compete with industrial salary structures."[65] The report noted that the excellent facilities and competitive salaries of government labs were able to seduce talented scientists early in their training, but that poor long-term professional opportunities within the military made it difficult to retain good scientists. In particular, " when [a scientist] reaches the level of senior investigator, a reverse process takes place. At this level, government salaries and other benefits are below those of universities and industry. Consequently the government is deprived largely of the peak productivity of a professionally mature scientist. This in turn makes it more difficult to hold the younger scientists as there are so few outstanding men left to attract them."[66] As a consequence of this negative dynamic, the report observed that "during the past seven years, a staff of investigators, once recognized as one of the strongest of its kind in the world, has been literally decimated by resignations."[67] Dr. Maurice Hilleman and Dr. James Sorrentino were among those who resigned from WRAIR for industry positions. During the postwar era, however, their move to industry only served to reinforce the informal networks of military-industrial collaboration for vaccine development because the draft, coupled with WRAIR's reputation as a center of excellence for infectious disease research, continued to attract top students from graduate schools. However, by the 1970's, the end of the Vietnam War and budget cuts made it more difficult for WRAIR to attract top students and to offer competitive salaries. In this new environment, part of the dynamic that sustained WRAIR's reputation as a center of excellence and as an attractive place for scientists to do research began to lose force.

Another reason for WRAIR's decline during this period can be traced to commonly observed characteristics of military organizations in times of peace. Political scientist, Barry Posen has observed that, in the absence of a war, military organizations tend to behave in a manner consistent with general

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[63] Dr. Wisseman, Commission on Rickettsial Diseases, minutes of the annual spring meeting of the Armed Forces Epidemiology Board, (1972). WR.
[64] F. Ingelfinger, visit to WRAIR (July 30, 1974). WR.
[65] Institute of Defense Analysis, final report on Review of Medical and Biological Programs within the Department of Defense, (August, 1962), 69. NA: RG 319, E. 181, B. 1.
[66] Ibid.
[67] Ibid., L-1.

theories of organizational behavior.[68] In particular, organizational theory predicts that, over time, organizations will develop an array of standard operating procedures and routines that become hard-wired with use. Eventually, these routines begin to lose relevance as the environmental conditions to which they were adapted change. Similarly, Posen argues that military organizations guard their independence and are fearful that outside authority "will upset the delicate balance of internal structure and routine" and that this tendency thwarts the ability of military organizations to innovate, or to form adaptive responses to new environmental conditions.[69]

Thus, the fate of military research organizations following the Vietnam War was almost predictable. Vannevar Bush observed that in times of peace the military "suffers from a disease that permeates all governmental, that is, politically controlled organizations -- the daft belief that if one does nothing one does not make mistakes, and the drab system of seniority and promotion will proceed on in its deadening way."[70] Bush was hopeful, however that "the obstructionism of military systems, as it existed for a thousand years, ended with the last Great War. It is far more possible today to maintain a productive collaboration between military men on the one hand and civilian scientist and engineers on the other than it ever was before."[71]

There was ample evidence, however, that by the end of the Vietnam War, the military was suffering a relapse of the creeping obstructionism and rigidity that had characterized it before World War II. The Military Medical Research and Development Command, which directed the activities of WRAIR and USAMRIID, began to embrace an ever-growing repertoire of standard operating procedures to direct research, development and procurement procedures. This development began to restrict the scientific freedom of individual scientists at WRAIR and to impede effective military-industrial cooperation for vaccine development.

Dr. Thomas Monath, former chief of virology at USAMRIID, noted that, during his tenure at USAMRIID (1989-1992), the bureaucracy of military medical research had grown considerably, with both productive and non-productive effects.[72] "On the one hand, there is so much scientific review, institutional review and infrastructure to help you out. They can back you up with a clinical lab; you could easily put your hands on the necessary expertise, etc. Yet the system was complicated and it was difficult to order supplies, and the bureaucracy was so large that there were a lot of junior irrelevant

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[68] B. Posen, *The Sources of Military Doctrine* (Ithaca: Cornell University Press, 1984).
[69] Ibid., 45.
[70] V. Bush, *Pieces of the Action* (New York: William and Morrow Company, 1970).
[71] Ibid.
[72] Dr. Thomas spent the early part of his career as the CDC director of vector borne diseases at Fort Collins (1973-1988). He joined USAMRIID in 1989, and eventually became the Chief of the Virology Division. He left the military in 1992 to become the Chief Scientific Advisor, Oravax (now Acambis).

people to get in your way."[73] Frustrated by an ever-growing array of bureaucratic obstacles, Monath, like many other talented vaccine research scientists during the post Vietnam War period, left the military for industry in search a more straightforward approach to vaccine development.[74]

Military procurement practices and the fate of the adenovirus vaccine

Bureaucratic rigidity began to reduce the effectiveness of DOD vaccine development and procurement practices during this period as well, a development, which served to further drive the wedge between military-industrial partnerships. DOD's efforts to develop and procure adenovirus vaccines after Vietnam illustrate the point. Adenoviruses are one of the largest sources of upper respiratory diseases. They are often suffered by military recruits in training barracks, and the military has had a longstanding interest in developing a means for their control. The adenovirus vaccine, developed by WRAIR and once manufactured by Wyeth, consists of live adenovirus in pill form. When swallowed, it infects recruits by an alternate route and causes them to develop immunity to the more serious respiratory form of the disease. Although the adenovirus vaccine is widely regarded as extremely effective and important among military medical doctors, it has received inconsistent and insufficient support from DOD procurement officers.

In the early 1970's, the military asked Wyeth to accept contracts to manufacture their new live-oral adenovirus vaccine for the military use. Dr. Ben Rubin from Wyeth Laboratories warned members of the AFEB that, in the absence of adequate and sustained DOD funding, additional research on the late-stage development of adenovirus vaccines had come to a stop within his laboratory.[75] He explained that much research, requiring long-term, consistent funding, was needed before the live-oral vaccine could be scaled-up for production. Colonel Buescher, member of the AFEB, revealed that, despite their desire for the vaccine, inflexible military funding practices made it difficult for the military to accommodate Wyeth. Speaking to other members of the AFEB, he explained that "because it takes so much time to get from there to here, this is not compatible with military funding."[76] Colonel Buescher's comments highlight Monath's observation that the Army suffered from the conception that "the process of product [vaccine] development was a mild modification of how the army develops a new tank . . . getting to that last step

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[73] Institute of Defense Analysis, Final Report on Review of Medical and Biological Programs within the Department of Defense (August 1962), L-1. NA: RG 319, E. 181, B. 1.

[74] Monath observed that although, by moving to a small biotechnology company, he was able to eliminate the frustrations of working within a large bureaucracy, he lost many of its advantages as well; "There is much less infrastructure in industry—particularly in a small company. It is much more free wheeling and it is much harder to know where to go to get information or tap expertise on any range of problems that may arise." (Dr. Thomas Monath, Chief Scientific Advisor, Oravax (now Acambis), interview by author, Cambridge, MA, September 18, 2000.)

[75] Minutes, annual spring meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.

[76] Dr. Denny, comments, minutes, spring meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.

with products was exceedingly difficult because the tank mentality doesn't apply to pharmaceuticals very well. So there are a lot of people who get involved at the end stage here who really don't know what they are doing."[77]

Dr. Rubin had reportedly concluded his meeting with the DOD with the following comment: "Let's make it perfectly clear. Wyeth is going to get out of the business, and furthermore, most of the other companies that are producing vaccines are going to get out of the business too, and it's probably going to be a lot sooner than you think."[78] Thus, the military had been well warned by their industrial partners that its inflexible contracting practices and low levels of support were unsatisfactory and those contracted were eager to be released from previous manufacturing agreements.

Despite this warning, the DOD failed to make the appropriate adjustments. For example, in the mid-1980's, when the manufacturing facilities for the vaccine needed to be renovated, Wyeth asked the government if they would assist with the cost of the renovations- estimated at $5 million. The government refused. According to Dr. Monath, "at the time, the JPO [Joint Program Office] probably just didn't have the extra money needed. There was no way to advance the funds and so they couldn't negotiate."[79] He explained that Wyeth threw up their hands and countered, "we're not making any money from it, it is just a service."[80] And so Wyeth ceased producing the vaccine and the military stopped vaccinating troops in 1995. Monath explained that, "we're now having epidemics in recruits of adenovirus types 5 and 7 again, as well type 3. And there has been no manufacturer. The Army has been unable to find a manufacturer because the market is so small. So it's a real embarrassment. Now it will cost them $50 million at least to reconstitute this thing. You could have done it for $5 million 5 years ago- just absolute crass stupidity."[81]

Thus, in a manner reminiscent of pre-World War II military organizations, obstructionism and rigidity crept back into the system in the 1970's. As the adenovirus vaccine procurement debacle demonstrates, these tendencies contributed to the deterioration of the military-industrial culture of collaboration.

III. The rise of NIH

As military medical research labs began to lose talent, funding, and prestige during the post-Vietnam period, the NIH began to gain in all three areas. As Victoria Harden noted in her history of NIH,

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[77] Dr. Thomas Monath, Chief Scientific Advisor, Oravax (now Acambis), interview by author, Cambridge, MA, September 18, 2000.
[78] Minutes, spring meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.
[79] Dr. Thomas Monath, Chief Scientific Advisor, Oravax (now Acambis), interview by author, Cambridge, MA, September 18, 2000.
[80] Ibid.
[81] Ibid.

Congress became increasingly fond of measures to support health-related research in the civilian sector, and by the mid-1950's NIH appropriations grew by 25 percent per year. [82] Federal funding for biomedical research became increasingly plentiful during this period, and NIH support for academic research continued to grow in the midst of the government wide budget cuts of the 1970's, initiating a trend that persisted throughout the 1980's and 1990's.[83]

However, just as higher profits did not translate into higher rates of innovation for industry, this boom in federal support for biomedical research did not facilitate vaccine development efforts either. In the 1950's, Vannevar Bush warned: "There are dangers in the magnitude and intensity of the present research programs . . . For one thing, there is danger of over-extension and consequent support of the mediocre and the inconsequential . . . Another danger of government support and great expansion in research is that of regimentation and bureaucratic control."[84] In particular, Bush was concerned that excessive funding would encourage overspecialization, leading to the construction of a scientific "Tower of Babel" that would frustrate efforts to integrate findings and coordinate research programs. This warning foresaw many of the problems that beset NIH-funded vaccine development after the Vietnam War.

By the post-Vietnam era, Bush's concern that excessive funding could frustrate integrative research efforts proved to be prescient. This was particularly true for vaccine development, an inherently interdisciplinary endeavor. Vaccine research scientists, or vaccinologists, need to be able to integrate findings from disease pathogenesis, immunology, virology, molecular biology, and structural biology. They also need to know how to design and interpret clinical trials. Hilleman noted that, by the 1980's, integrated research was becoming increasingly difficult. Referring in particular to the mountain of data coming out of the National Institute of Allergy and Infectious Disease (NIAID's) independent investigator-initiated research program, Hilleman warned that "the most insidious problem we face in research today is the gross inundation by technical information that I like to refer to as information pollution. Information pollution is that ubiquitous miasma of information and misinformation, of fact and of fancy, of unrefined data and of general hogwash."[85]

As an antidote to the problems of overspecialization and regimentation, Bush offered: "I should be inclined to establish a Nobel Prize for the integrator and interpreter of science, who can in these days often serve his fellow far more than the individual who merely adds one morsel to the growing, and often

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[82] V. Harden, *Inventing the NIH* (Baltimore: Johns Hopkins University Press, 1986), 182.
[83] National Science Foundation, *Science and Engineering Indicators, 2000*, Appendix Table 6-8, "Federal Obligation for Academic R & D, By Agency: 1970-99," A-393.
[84] Remarks of V. Bush, President of the Carnegie Institution of Washington at the 23rd Annual Scientific Assembly of the Medical Society of the District of Columbia, (October 1, 1952). MA
[85] M. Hilleman, "Some Thoughts on Industrial Research in the Health Sciences" Industrial Research Institute, Cincinnati OH, (October 20, 1975). MA.

indigestible, pile of accumulated factual knowledge."[86] Indeed, Bush suggested just the sort of "science integrator" that his company had found in Maurice Hilleman.

Asked why Merck had not produced more than two new vaccines in the past decade (Hepatitis A and Varicella), Dr. Hilleman replied, "I believe it is because Hilleman is not there anymore."[87] Beneath the self-effacing humor, he made a valid point. Hilleman brought WRAIR-style "bench-to-batch" scientific management to industrial research at Merck. His unique training in all aspects of vaccine development gave him the expertise to mediate and interpret incongruous results for his scientists, engineers, and clinicians as the vaccine underwent transitions from test tubes, to fermentation tanks, to field tests. Other integrators, such as Dr. Sorrentino, who brought WRAIR-style research strategies to industrial vaccine development, met with similar success at National Drug.

After Vietnam, however, as WRAIR began to lose talented researchers and funding, the "science integrators" began to disappear. As the pool of talented researchers at WRAIR dwindled, industry began turning to NIH and academia for new hires and collaborative partners. However, both NIH and academia bred scientific specialists without the interdisciplinary training necessary to usher a vaccine through the development process. For example, after Hilleman retired in 1984, Merck hired his replacement, Dr. Edward Scolnick, from the genetics division of the National Cancer Institute. Under Scolnick's leadership, Hilleman observed, Merck's vaccine division reverted to more a more bureaucratized form of scientific management with greater separation by specialization. Reflecting on his days as the director of Merck's vaccine division, Hilleman exclaimed: "We did everything. . . We did field investigations, epidemiology, from clinic to clinic, isolated viruses to attenuate. We had the complete spectrum. Other companies had separation. No broad spectrum. Now there is separation even at Merck."[88]

Hilleman took a dim view of this development. In his experience, separation limits productive learning opportunities and lengthens development times: "I've found it to be of extreme importance and help to have a concentrated program of very great breadth, covering a diversity of diseases and extending from the laboratory bench through the clinic. By this I mean a program ranging from discovery of the cause of disease and the assessment of its importance through the development of means for control and the proof of safety and efficacy of the method in large-scale clinical studies in man. This provides for self-catalyzing spill-over from one study to another and encourages progress toward the target objective

[86] V. Bush, President of the Carnegie Institution of Washington, remarks, 23rd Annual Scientific Assembly of the Medical Society of the District of Columbia, (October 1, 1952). MA
[87] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.
[88] Ibid.

without the disruptions imposed by passing the successive stages of development from one research group or department to another."[89]

As military-industrial partnerships strained under a series of public relations, economic, political, and bureaucratic frustrations, industry leaders in vaccine development such as Wyeth, Merck, and National began to rely more heavily on NIH to assist in early-stage vaccine development. However, a number of industrial vaccine scientists have observed that NIH has not been able to bring vaccines to the point of feasibility as well as the military did. Dr. Metzgar noted that the "military was best suited to basic research. They have access to areas of epidemiology that academia and industry do not have. They are on the front lines and therefore are better suited for isolation and early R&D."[90] Moreover, he noted that the military was also well positioned for clinical trials through their network of overseas laboratories, where a variety of diseases are endemic and trials can be conducted quickly and efficiently. NIH researchers, on the other hand, did not have these advantages and they often failed to demonstrate the feasibility of new vaccine candidates to industry's satisfaction. Thus it appears that military labs may have filled a critical gap between basic and applied development activities by bringing vaccines to the point where industry could make a reasonable bet that their efforts to develop that technology would result in a safe and effective vaccine.

Industry's reliance on the NIH as a vaccine development partner grew stronger as advances in molecular biology and genetic engineering in the late 1970's became increasingly relevant to vaccine development. By 1982, the NIH was the unquestioned leader in the field of molecular biology having spent an estimated $380 million on research in this field.[91]

The prospect of being able to engineer antigens in isolation from their pathogen represented a significant opportunity for industry to develop vaccines with fewer side effects. The relative predictability and specificity afforded by recombinant techniques was particularly attractive for vaccine producers operating in the litigious climate of the 1980's. Faced with this new technological opportunity, firms began to invest in developing their own in-house capabilities in the fields of molecular biology and genetic engineering. According to one study of the biotechnology industry, between 1980 and 1983, the pharmaceutical industry directed over $150 million into scientific research institutions in an effort to form linkages with academia that would enable them to build capabilities in biotechnology.[92] As evidence of the pharmaceutical industry's growing capabilities in the field of biotechnology, another study observed that the number of publicly traded U.S. firms developing biotechnology-based drugs rose from 45 to 113

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[89] M. Hilleman, "Some Thoughts on Industrial Research in the Health Sciences," Industrial Research Institute, Cincinnati OH, (October 20, 1975). MA.
[90] Dr. Donald Metzgar, interview by author, Swiftwater, PA, June 21, 2001.
[91] Office of Technology Assessment, *Commercial Biotechnology: An International Assessment*, Washington, D.C., U.S. Government Printing Office, 1984.

between 1989 and 1996. Similarly, the number of biotechnology-based drugs under development rose from 80 to 284 during this same period.[93] Although there is no specific data on vaccine industry investments in biotechnology during this period, one study notes that overall levels of R&D devoted to vaccine development within the pharmaceutical industry increased from 2 percent in the early 1980's to an average of 4 percent during the 1990's.[94] The study attributes higher R&D investments to heightened interest in bioengineer vaccines. However, overall vaccine-related investments in biotechnology were likely higher than these figures indicate given that these numbers do not include biotechnology firms that were not members of the Pharmaceutical Research and Manufacturers Association.

Program for Accelerated Development of New Vaccines

As industry began to invest in biotechnology and as the NIH was becoming the unquestioned forerunner of federally sponsored research in molecular biology, industry interest was further deflected away from the military and towards the NIH as a source for new hires and collaborative partners. In 1980, NIH's National Institute for Allergies and Infectious Diseases (NIAID), in contrast to the military, called attention to itself as a center for "next-generation" vaccine research by initiating the Program for Accelerated Development of New Vaccines to apply recombinant technologies to vaccine development. According to a report of the program, "the incentive for an expanded effort lay in new knowledge and processes emerging from recombinant DNA and hybridoma technologies and in the better understanding of the workings of the immune system."[95] The idea was to select high priority vaccines and target research objectives to accelerate their development. By 1986, however, the program had assisted in the development of only one vaccine containing antigens derived from recombinant DNA expressed in yeast cells (hepatitis B).

Dr. William Jordan, Director of the Microbiology and Infectious Diseases Program of NIAID, acknowledged that progress in the development of genetically engineered vaccines was not proceeding as quickly as had been expected. He reported that "the NIAID initiated its program and the IOM made its reports with the expectation that the application of new advances in molecular genetics, recombinant technology, hybridoma immunology, and antigen synthesis would make possible the preparation of polypeptides and the chemical synthesis of oligopeptide epitopes, as purified antigens, appropriate for the

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[92] L. Orsenigo, *The Emergence of Biotechnology* (New York: St. Martin's Press, 1989), 78.
[93] Pharmaceutical Research and Manufacturer's Association, "1996 Survey: 284 Biotechnology Products Testing" (Washington, D. C.: website www.phrma.org/charts/biochart/htm.)
[94] H. Grabowski, and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997) p. 10.
[95] National Institute of Allergy and Infectious Diseases, *Accelerated Development of New Vaccines 1986 Progress Report.* WR.

induction of the humoral and/or cellular immune responses that afford protection against infection and disease. . . Although encouraging progress has been made, it has not been as rapid as anticipated."[96]

Jordan catalogued a number of scientific setbacks, noting that synthetic oligopeptides were not as antigenic as hoped and it was discovered that they must be potentiated through presentation in micelles, liposomes, or through the use of aluminum adjuvants. Similarly, polysaccharides must be coupled with proteins to be immunogenic in young children. And finally, he noted that investigators have had difficulty demonstrating the safety of antigens produced in continuous mammalian cell lines.[97]

The problems facing NIAID's vaccine development programs were, from Dr. Jordan's point of view, entirely scientific in nature. A number of military and industrial vaccine research scientists familiar with of NIAID's vaccine development program did, however, notice a few organizational and managerial characteristics of the program to suggest otherwise. Colin MacLeod, member of the AFEB since World War II, compared the organization and efficacy of AFEB commissions for vaccine development (as they once functioned before being dismantled in 1973) against the value of NIH study sections. He explained that AFEB commissions were made up of experts in a well-defined disease oriented area who devised targeted research programs in collaboration with medical departments of the military services. NIH study sections, on the other hand, "are not goal-oriented and usually do not have any responsibility for the development of a program . . . They are passive, judicious bodies whose function is to review applications sent to them."[98]

Hilleman is also critical of the ability of NIH to lead vaccine-development initiatives. Regarding NIH contract research programs, Hilleman exclaimed, "these are little cottage industries, aren't they? And they are different disciplines, different programs. Now, in these little cottage industries, you can't bring central focus. . . All of these independent diddleworks never get coordinated to provide solutions."[99] To get effective and efficient vaccine development, Hilleman argues, it is imperative to let scientists form committees of their own and decide among themselves how to target research: "they each undertake what they do and there's a big pot of money in the center and they give grants to other people for what they can't do."[100]

In this manner, Hilleman described precisely the same arrangement that worked so well to develop vaccines through OSRD and the AEB during World War II. His description is also characteristic of the organization of the National Foundation for Infantile Paralysis (NFIP), the private organization that funded and organized research on the polio vaccine in the 1940's and 1950's. In each of these cases,

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[96] Ibid.
[97] Ibid.
[98] C. MacLeod, address, at the 30th anniversary meeting of the Armed Forces Epidemiology Board, Washington, D.C., (February 18, 1971). WR.
[99] Dr. Maurice Hilleman, interview by author, West Point, PA, May 8, 2000.

expert committees and/or individuals were given sufficient funding and ultimate authority to guide the project from the field, to the laboratory, through large-scale production, and back to the field for clinical trials.

NIH programs are, however, not designed to conduct targeted research in the manner that World War II vaccine development programs and that the NFIP had been. NIH programs encourage individual scientists to pursue many lines of inquiry simultaneously. This independent investigator-initiated peer-reviewed grant system offers an effective way to generate a large quantity of scientific knowledge and publications. However, by design, and in contrast to World War II vaccine development programs, the NIH does not offer an oversight body to integrate findings or to bring research projects in line with a cohesive vaccine development plan. This organization works well when nothing more than undirected research and publications are requested of the NIH, but it falters when the government requests tangible results as did in the late 1980's and the early 1990's when the organization was called upon to produce a vaccine to prevent AIDS.

AIDS vaccine development program

In 1984, Dr. Robert Gallo announced that he, along with his colleagues at the National Cancer Institute (NCI), had identified the virus that causes AIDS. Jon Cohen, in his study of the U.S. effort to develop an AIDS vaccine, observed that, from this moment forward, the "NIH positioned itself as the center of the AIDS vaccine universes."[101] By 1987, Cohen noted that the center of gravity for the AIDS vaccine research initiative had shifted to the National Institute for Allergy and Infectious Diseases (NIAID) under Dr. Antony Fauchi with a budget of $261 million. By 1999 the budget would grow to $1.8 billion, but the program still had not produced a viable vaccine candidate to prevent AIDS.[102]

The organization of the NIH-sponsored AIDS vaccine development program stands in direct contrast to these historically successful integrated research programs. Hilleman has argued that NIH's "fractured organization, centered on individual investigator-initiated RO1 grants, allowed it for too long a time to pursue a subunit envelope vaccine against AIDS as a continuing paradigm to the highly effective subunit hepatitis B vaccine of 1981 and 1986 that can prevent infection by antibodies alone."[103] Had there been more oversight over the entire AIDS vaccine research program, he argued, efforts would have been sooner redirected towards an examination of cell-mediated immune responses. Instead, NIH-funded

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[100] Ibid.
[101] J. Cohen, *Shots in the Dark* (New York: W. W. Norton and Company, 2001), 71.
[102] Ibid., 320.
[103] M. Hilleman, "The Frustrating Journey toward an AIDS Vaccine," (unpublished draft). MA.

scientists engaged in an "oft excessive and redundant emphasis on facilitating mechanism for vaccine [delivery]."[104]

Citing the voluminous data coming out of NIAID's AIDS research program, Hilleman suggests that additional money and research are unlikely to yield a vaccine, but that a reorganization of the research program itself may. He blames the NIH grant system for encouraging scientists to pursue "what is the more doable at the expense of what is more urgently needed (. . .) the total of basic knowledge in AIDS, particularly its immunology and molecular biology, is overabundant and is highly complex (. . .) the more fundamental problem for achieving an AIDS vaccine may lie with organizational structure and management than in attaining the needed science itself. Pursuit of an AIDS vaccine could be benefited greatly by a determination of what areas of missing information are important and how these needs could be organized into defined areas of emphasis for investigation by separate team efforts."[105]

Hilleman may have been one of the earliest and more vociferous opponents of the NIH program but he was not the only one. Jon Cohen related that Hilleman's call for a more targeted approach to vaccine research, while abhorrent to some basic research scientists, began to hold sway with others. He notes that in 1996, a committee of 100 scientists and activists, with a "list of participants that read like a Who's Who in academic AIDS research" issued a report on the state of vaccine research at NIH after a year-long study.[106] In what amounted to more than a treatise on the relative merit of targeted verses non-target approaches, the report stated unequivocally that the "HIV vaccine research and development is in crisis" and that "the entire AIDS vaccine research effort at NIH should be restructured."[107] In what was known as the Levine report, the committee argued that "the NIH must be prepared to go beyond its traditional role, for the discovery and development of a vaccine demands more than just the acquisition of fundamental knowledge; it requires that the information be applied and resultant vaccine strategies appropriately evaluated."[108] To accomplish this, they posed a number of recommendations that resembled Hilleman's. Namely, they recommended the formation of an interdisciplinary study section for vaccine research that would set priorities to direct research objectives. This report lent support to the recommendations of the Presidential Advisory council on HIV/AIDS (PACHA) which, in turn, led to

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[104] M. Hilleman, "Personal Historical Chronicle of Six Decades of Basic and Applied Research in Virology, Immunology, and Vaccinology," *Immunological Reviews* 170 (1999): 7-27.
[105] M. Hilleman, "The Business of Science and Science of Business in the Quest of an AIDS Vaccine," *Vaccine* 17 (1999): 1211-1222.
[106] The Levine Committee represented in inter-institutional "working group" or advisory committee assigned by the NIH's Office of AIDS Research in 1995 to review the organization and function of NIH's AIDS vaccine research projects.
[107] J. Cohen, *Shots in the Dark* (New York: W. W. Norton and Company, 2001), 282.
[108] Ibid., 283.

Clinton's 1997 call for a reorganization of the AIDS vaccine research effort and the establishment of a new AIDS Vaccine Research Center at NIH.[109]

Both Hilleman, and later, the Levine Committee, advocated an OSRD-style top-down coordination and integration of research objectives. This method for applying basic research findings to the development of a vaccine worked well in the context of World War II vaccine development programs as well as in postwar industrial labs. During World War II, the CMR and AFEB integrated disparate efforts under expert committees. During the postwar era, industry and military cooperated with one another to bridge the gap between early and late stage vaccine development. Successful vaccine development programs did more than integrate research findings, however. In each case, there was a mechanism by which research on vaccine candidates was married with pilot production facilities, testing facilities, and large-scale manufacturing expertise.

Herein lie some valuable clues for how one might restructure vaccine research programs to generate high rates of innovation and sufficient levels of supply. Impending transformations of the organization of AIDS vaccine research at NIH may offer a guidepost for other disease-specific vaccine efforts. However, a fundamental reorganization of the post-Vietnam system for vaccine development is unlikely in lieu of a compelling and urgent historical circumstance akin to World War II to overcome economic, political, and institutional opposition to the types of proposals that might work. As the following chapter demonstrates, the airliner and anthrax attacks of 2001 represent one such historical circumstance, presenting both greater challenges and opportunities for the future of vaccine development.

IV. Conclusions

In the wake of the swine flu affair of 1976, the conventional explanation for falling rates of innovation gained credence as a rash of product liability suits through the late 1970's raised the cost and risk of vaccine development and discouraged industry investment. However, the vaccine industry had suffered adverse product liability judgments since the early 1960's, and low margins had been a consistent characteristic of the market since the 1940's. Why did firms begin to pull out of the vaccine business when they did?

On closer inspection, it becomes clear that larger political and social transformations that took place during the post-Vietnam period disrupted the military-industrial culture of collaboration, allowing economic concerns to assume a more central position in industrial vaccine development decisions with predictable consequences. Chief among these transformations was the waning salience of national

[109] Commencement address, President at Morgan State University, The White House, Office of the Press Secretary, (May 19, 1997).

security and public health threats as the Cold War began to lose intensity and as the incidence of infectious disease in U.S. reached a record low. As urgency dissipated, so too did a sense of patriotic obligation within the vaccine industry, the general public, and Congress. Further, the unpopularity and sense of failure surrounding the Vietnam War made close association with the military uncomfortable for industry and encouraged Congress to question the DOD's discretionary use of public funds for research and development. These trends, coupled with problems internal to military medical research institutes, such as inflexible promotion and procurement practices as well as the loss of the draft, converged to undermine the military's (and specifically WRAIR's) reputation as a "center of excellence" for infectious disease research.

No longer obligated to assist the military, industry began to invest in vaccines solely on the basis of commercial potential, offering diminished collaboration with the military in the development and improvement of socially beneficial yet commercially unattractive vaccines such as those to prevent meningitis, malaria, and tuberculosis.

The growing interest within industry to develop bioengineered vaccines further disrupted the postwar military-industrial culture of collaboration by deflecting industry attention toward academia and the NIH for collaborative partners and new hires. In contrast to WRAIR's "science integrators," university and NIH scientists have not been adept at helping industry to bridge the gap between early and late stage vaccine development processes, nor have they been able to provide insight on development needs based on user application of these vaccines. These difficulties are visible in the NIH's attempt to develop an AIDS vaccine since 1984.

Thus, even as economic and technological opportunities for vaccine development improved by the 1980's and as industry began to re-invest in in-house R&D, the social and political transformations of the 1970's and 1980's disrupted the postwar culture of military-industrial collaboration and innovation rates continued to fall.

Chapter Five: The Return of Urgency

By the 1990's, innovation rates reached their lowest level since the 1940's, yet there is some reason to believe that this trend may improve. In the 1990's, the federal government began to redirect its attention to the problems of vaccine innovation and supply for the purposes of national defense. Well before the terrorist attacks in the fall of 2001 raised the profile of bioterrorism, defense planners began taking note of a growing list of biological threats to national security and began to develop an appreciation for the destabilizing effects of natural and manufactured disease. The airliner and anthrax attacks of 2001 have further mobilized both the federal government and the pharmaceutical industry with a renewed sense of urgency and have generated a spirit of cooperation that is reminiscent of industry-government relations on the eve of World War II.

Can this same combination of urgency, patriotism, and opportunism rejuvenate vaccine innovation today? Despite many parallels, the social, political, legal, economic, and scientific landscape for vaccine development has been redrawn since the 1970's in ways that could make it difficult to recreate the successes of government vaccine development programs in the 1940's. Drawing on lessons from the history of vaccine development, I examine the opportunities and challenges that today's "war on terrorism" presents in the efforts to improve vaccine innovation and supply.

I. Disease threats in the 1990's

Manufactured disease threats

At the close of World War II, George Merck warned, "in whatever deliberations that take place concerning the implementation of a lasting peace in the world, the potentialities of biological warfare cannot be safely ignored."[1] Similarly, Leroy Fothergill, Technical Director of the Special Projects Division of the Chemical Warfare Service during World War II warned that, though biological weapons have not been a major factor in World War II, they have "received serious consideration on the part of all the combatants in this war. . . In the coming peace, severe restrictions will undoubtedly be imposed on the enemy nations with respect to armament and heavy industry. This may force them to explore more subtle methods of warfare. It would not be difficult to prostitute facilities in the medical and biological fields for the purposes of developing

biological warfare."[2] These comments appear prophetic today, since biological weapons have proven themselves to be a threat to civilization regardless of the geopolitical arrangement. Known as the "poor man's nuclear bomb," biological weapons offer a relatively inexpensive and surreptitious method of inflicting mass casualties. Given the difficulties of policing their proliferation in the global community and of tracing their source once deployed, biological weapons will continue to remain attractive to any individual, group, or nation with a desire to inflict harm and to avoid detection.

A series of events in the 1990's raised awareness of the growing threat of biological attacks on U.S. soil. In 1992, Ken Alibek, a former Soviet Union bioweapons scientist, defected to the U.S. and provided intelligence officials with hair-raising accounts of the advanced development and proliferation of biological weapons. Alibek, a former senior deputy director of the USSR biological weapons program, revealed that the former Soviet Union had been operating an offensive biological weapons program since 1973, the size of which dwarfed the U.S. biological weapons program at its height.[3] He explained that the real threat to U.S. security came, however, when Yeltsin dismantled this program in 1992, leaving large numbers of bioweapons scientists unemployed. A 1997 visit to Vektor (in Koltsovo, Novosibirsk), one of Russia's largest bioweapons labs, revealed that what was once a high security compound containing 30 buildings and nearly 4,000 employees had been reduced to "a half-empty facility protected by a handful of guards who had not been paid for months."[4] This former fortress is home to what is supposed to be the only store of the smallpox virus outside of the CDC. The 1997 discovery led experts to fear that samples of the virus may have escaped along with well-trained bioweapons scientists to other countries, thereby eroding technical barriers for other nations and terrorist organizations with an interest in these weapons.

In 1995, the Aum Shinrikiyo sarin gas attack in a Tokyo subway, and the Oklahoma City bombing a month later, alerted the Clinton Administration to terrorist group activities and their interest in weapons of mass destruction. Furthermore, in 1995, UNSCOM confirmed that Iraq had

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[1] G. W. Merck, special consultant to biological warfare to the Secretary of War, "Activities of the U.S. in the Field of Biological Warfare," (October 31, 1945). NA: RG 165, E. 488, B. 182.

[2] L. Fothergill, letter to Chief of the Special Projects Division, Chemical Warfare Service, "A Proposal for an American Plan for Postwar Research and Development of Biological Warfare," (August 2, 1945). NA: RG 165, E. 488, B. 186

[3] When these programs were at their height, the USSR employed 65,000 personnel whereas the U.S. employed under 6,000; the USSR operated 60 facilities whereas the U.S. operated 3; the USSR had standardized 52 agents whereas the U.S. standardized 11; and the USSR produced 5,000 tons of anthrax annually whereas the U.S. produced only 9 tons. (G. Koblentz, "Proliferation of Biological Weapons," MIT BW Workshop, May 7, 2001).

[4] Personal communication between DA Henderson and P. Jahrling, recorded in D. Henderson, "Bioterrorism as a Public Health Threat" *Emerging Infectious Diseases*, 4 (3) 1998.

produced and filled anthrax and botulinum toxin in bombs, rockets, and airplane spray tanks in the Gulf War.

A number of empirical studies in the 1990's attempted to assess the threat of bioterrorism and revealed the dove-tailing of two unsettling trends (1) the proliferation of bioweapons materials and expertise and (2) the increased propensity of terrorist groups to inflict indiscriminate mass casualties. Evidence of the proliferation of bioweapons materials and expertise has been supported by a number of studies. In 1972, the CIA and DOD confirmed that four countries possessed offensive biological weapons (BW) programs. By 2001, a Stimson Center Report confirmed that the number had grown to twelve, noting that China, Egypt, India, Iran, Iraq, Israel, Libya, North Korea, Pakistan, Russia, Syria, and Taiwan possessed biowarfare capabilities and that at least five of these countries were cross-listed as state-sponsors of terrorism.[5] Other assessments have been even higher. George Tenet, Director of the CIA, informed Congress in 1997 that at least 20 (out of a possible 30) countries with mature biological weapons programs had successfully produced these weapons.[6] The Chemical and Biological Weapons Nonproliferation Project at the Monterey Institute's Center for Nonproliferation Studies maintains a database of publicly-known attempts to acquire or use chemical, biological, radiological, or nuclear materials.[7] In 1999, the database indicated the following: (1) that terrorist incidents have been on the rise since 1985, and the highest peaks of activity are associated with the use of chemical and biological agents in 1995 and 1998; (2) that preferred targets have changed over time, with an increased emphasis on civilian populations; and (3), that the use of biologic agents tends to be associated with furthering nationalist or separatist objectives: a desire to retaliate; exacting revenge; and/or fulfilling apocalyptic prophecies, and evidence of all three of these motivations have increased since 1990.

These findings highlight the emergence of a new breed of terrorist that is prone to indiscriminate violence. According to one characterization, this new breed is "less interested in promoting a political cause and more focused on the retribution or eradication of what he defines as evil . . . For such people, weapons of mass destruction, if available, are a more efficient means

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[5]A. Smithson, "Ataxia; the Chemical and Biological Terrorism Threat and the U.S. Response" *Stimson Center Report*, no. 35, ch. 2, (2001); U.S. Dept. of State, *Patterns of Global Terrorism 1999* (Washington, D.C.: U.S. Government Printing Office, April 2000).
Biological warfare capabilities exist primarily in the form of biological seed cultures and weapons expertise.

[6] U.S. Congress. Senate. George Tenant speaking for the Select Committee on Intelligence. *Hearing on Current and Projected National Security Threats to the United States*. 105th Cong., 1st sess., February 5, 1997.

[7] J. Tucker, "Historical Trends Related to Bioterrorism: An Empirical Analysis," *Emerging Infectious Diseases* 5 (1999): 4.

to their ends."[8] This new breed increasingly includes religious groups, racist and anti-government groups, as well as millenarian cults. Databases that track the composition and activities of these groups reveal that in 1968, of the 11 known international terrorists groups, none were religiously motivated, whereas in 1995, 42% of the 52 known groups were. These databases also revealed a link between religious motivations and higher levels of violence. Religious groups, for example, were responsible for only 25% of the terrorist acts committed in 1995, yet they were responsible for 58% of the fatalities.[9] One member of Hezbollah provided a succinct explanation for this phenomenon: " We are not fighting so that the enemy recognizes us and offers us something. We are fighting to wipe out the enemy."[10] And increasingly, the enemy has become the U.S. According the RAND-St. Andrews database and State Department records of terrorist activities, U.S. citizens and facilities are the target of choice among international terrorist groups.[11]

Furthermore, there is evidence that proliferation has not been limited to state sponsored programs. The Japanese cult, Aum Shinrikyo, offers a good example. Investigations into the activities of the cult have revealed an extensive interest in and development of biological agents and a willingness to use them on civilian populations.[12] The cult has reportedly attempted nine biological attacks, including attacks on U.S. naval bases, Narita airport, the Imperial Palace, and the Japanese Diet, using with trucks and aircraft fitted with spray tanks filled with anthrax and botulinum toxin. In 1992, cult members also allegedly traveled to Zaire to obtain Ebola samples.[13]

Natural disease threats

Renewed attention to the national security implications of naturally occurring infectious diseases is another hallmark of the present era. For example, the National Security Council classified AIDS as a security threat in April of 2000, prompting the Clinton Administration to request $250 million to fight the disease overseas. Recognizing the indirect, yet equally destructive and destabilizing effects of a naturally occurring disease, the Clinton Administration placed AIDS alongside security threats such as weaponized biological agents and other chemical and nuclear weapons of mass destruction.

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[8] J. Nye and R. J. Woolsey, "Heed the Nuclear, Biological, and Chemical Terrorist Threat," *International Herald Tribune*, June 5, 1997.
[9] B. Hoffman, "Terrorism and WMD: Some preliminary Hypotheses," *Nonproliferation Review* 4 (1997): 3.
[10] C. Mercier, "Terrorists, WMD, and the U.S. Army Reserve" *Parameters*, no. 27 (1997): 98-118.
[11] U.S. Dept. of State, *Patterns of Global Terrorism 1999* (Washington, D.C.: U.S. Government Printing Office, April 2000).
[12] J. Stern, *The Ultimate Terrorist* (Cambridge: Harvard University Press, 1999), 64.
[13] Ibid., 65.

The administration's decision to formally classify an infectious disease as a national security threat came in the wake of number of reports issued in the 1990's regarding the growing threat from emerging and re-emerging infectious diseases.[14] After decades of watching disease rates fall, experts noted that the death rate from infectious disease has been on the rise since 1980. Even if one excludes HIV/AIDS cases, the death rate from infectious disease rose by 22 percent in the U.S. between 1980 and 1992.[15] Another report estimated that the "annual infectious disease related deaths in the United States have nearly doubled to some 170,000 annually after reaching an historic low in 1980."[16] Furthermore, the report concluded that this trend is likely to continue: "infectious diseases are a leading cause of death, accounting for a quarter to a third of an estimated 54 million deaths worldwide in 1998. . . As a major hub of global travel, immigration, and commerce with wide-ranging interests and a large civilian and military presence overseas, the United States and its equities abroad will remain at risk from infectious diseases."[17] Similarly, a 1992 report by the Institute of Medicine identified eight major factors that contribute to the introduction and spread of infectious disease and concluded that each one of these contributing factors is trending upwards.[18]

In addition to the problems of emerging infectious diseases, the Institute of Medicine estimates that twenty known diseases (such as tuberculosis, malaria, and cholera) have re-emerged or have spread to new geographic areas since 1973.[19] In most cases, these diseases have re-emerged in more virulent and drug-resistant forms. For example, by the 1960's, the U.S. wiped out all cases of malaria. However, increasing rates of immigration and international travel have reintroduced

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[14] Examples include: Institute of Medicine, *Emerging Infections: Microbial Threats to Health in the U.S.*, eds. J. Lederberg, R. Shope, and S. Oaks, (Washington, D.C.: National Academy Press, 1992); Committee on International Science, Engineering, and Technology, *Infectious Disease—A Global Health Threat* (Washington, D.C.: National Science and Technology Council, 1995); D. Gordon, D. Noah, and G. Fidas, "The Global Infectious Disease Threat and Its Implications for the United States," *National Intelligence Estimate* 99-17D (January 2000).

[15] Committee on International Science, Engineering, and Technology, *Infectious Disease—A Global Health Threat* (Washington, D.C.: National Science and Technology Council, 1995).

[16] D. Gordon, D. Noah, and G. Fidas, "The Global Infectious Disease Threat and Its Implications for the United States," *National Intelligence Estimate* 99-17D (January 2000).

[17] Ibid.

[18] Institute of Medicine, *Emerging Infections: Microbial Threats to Health in the U.S.*, eds. J.Lederberg, R. Shope, and S. Oaks, (Washington, D.C.: National Academy Press, 1992).
Factors contributing to the increased incidence of infectious disease include population growth, globalization (immigration, travel and commerce), changing land-use patterns, climate change, and changing health care practices (these include immunosuppressive therapies, more invasive procedures, overuse of antibiotics etc.).

[19] Institute of Medicine, *Emerging Infections: Microbial Threats to Health in the U.S.*, eds. J.Lederberg, R. Shope, and S. Oaks, (Washington, D.C.: National Academy Press, 1992).

the disease, with approximately 1,200 cases being reported to the CDC annually.[20] In the absence of an effective vaccine and in the face of growing drug resistance, the geographic spread of the disease is increasingly difficult to control. According to one estimate, "the first-line drug treatments for malaria are no longer effective in over 80 of the 92 countries where the disease is still a major health problem."[21] Similarly, eighty percent of the *Staphylococcus aureus* isolates in the U.S. have become penicillin-resistant and 32 percent have become methicillin resistant.[22] Further, a recent CDC study estimated a 60-fold increase in high-level penicillin resistance among *Streptococcus pneumoniae* cases in addition to significant levels of multi-drug therapy resistance.

Although naturally emerging infectious diseases do not present an immediate threat to national security, a number of the reports cited reflect an emerging political willingness to examine the national and global security implications of infectious disease. The National Intelligence Estimate offered what is perhaps the starkest formulation of the relationship between disease and national security. Describing the national security significance of AIDS, the report explained that over a quarter of South Africa's population will die from the disease and that this trend is expected to worsen over the next 10 years and to spread to other countries such as South Asia and Russia.[23] The report went on to state that the trend is more than just a public health problem and that rising rates of infection will "challenge democratic development and transitions and possibly contribute to humanitarian emergencies and military conflicts to which the United States may need to respond."[24]

II. Patriotism and its Payoffs

The events of September 11th, followed by the spread of anthrax through the U.S. mail system, have amplified federal attention to the problems of vaccine innovation and supply for the purposes of biodefense. Moreover, hard evidence that terrorists have both the means and the motivation to use biological weapons has introduced an element of urgency that was not present in federal biodefense plans prior to 2001. As Chapter Two demonstrates, a similarly strong sense of urgency permeated World War II vaccine development programs and contributed to their success by creating an environment in which national concerns trumped the economic concerns

[20] D. Gordon, D. Noah, and G. Fidas, "The Global Infectious Disease Threat and Its Implications for the United States," *National Intelligence Estimate* 99-17D (January 2000).
[21] Ibid.
[22] Ibid.
[23] Ibid.
[24] B. Gellman, "AIDS is Declared Threat to Security," *Washington Post*, April 30, 2000.

of individual companies, encouraging whole-hearted industry participation in vaccine development efforts. There is some evidence that history may be repeating itself on this dimension as another salient threat has generated a comparable spirit of cooperation in industry-government relations.

Increased industry interest in biodefense

For the first time since the postwar period, large pharmaceutical manufacturers are responding to government requests to fill contracts for vaccines such as smallpox that currently have no commercial market. Just weeks after the attacks Merck, GlaxoSmithKline, American Home Products, and Baxter International were among a number of companies that submitted formal proposals to produce a smallpox vaccine for the government.[25] Within a month of submitting these proposals, it was announced that Baxter International, in cooperation with Acambis, a British biotech company, was chosen to fill the $428 million contract to produce 155 million doses of smallpox vaccine.

As in the 1940's, these pharmaceutical companies did not compete for the smallpox contract with the expectation that they would receive large financial rewards for doing so. For example, soon after Baxter was awarded the government contract to produce the smallpox vaccine, an analyst at Morgan Stanley Dean Witter warned investors that it would be difficult for Baxter to make money from this contract: "it's a competitive business, and in this sort of bidding situation, there's no way you can make money."[26] In a manner reminiscent of World War II, it appears that these companies were driven by some combination of public relations and public service incentives rather than profits.

The press has been quicker to discern the public relations incentives of industry rather than any genuine motivation to serve the public. In recent years, firms such as Merck and GlaxoSmithKline have been losing public relations battles due to perceived price gouging, efforts to extend patents and thwart generic manufacturers, and a general reluctance to provide affordable AIDS drugs to poor countries. Baxter International, in particular, has reportedly been casting about for a good public relations opportunity, since it was found liable for the deaths of over fifty individuals undergoing treatment with Baxter dialysis machines.[27]

Similarly, Alan Holmer, president of the trade group, Pharmaceutical Research and Manufacturers of America, has seized the moment to restore the reputation of the pharmaceutical industry. Broadcasting the "overwhelming desire" of the pharmaceutical industry to fill

[25] "Drug Firms Consider Smallpox Vaccine," *Associated Press* online, November 1, 2001.
[26] "Vaccines May be Profit Engine for Baxter," *Reuters*, November 29, 2001.

government contracts for the smallpox vaccine, he boasts, "We're Americans first."[28] To support his claim to patriotism, he draws on the historical role of pharmaceutical companies in the development of antibiotics and vaccines during World War II, reminding the public that "American pharmaceutical companies have been there in the past for the country in times of national crisis."[29]

In their efforts to curry public favor, a number of companies have begun to use patriotic rhetoric that is reminiscent of World War II era industrial proclamations of national support that is characteristic of an erstwhile culture of gift relations. Eli Lilly and Company, for example, made a brash show of support in America's new war against terrorism, rushing to the government with a series of proposals to research and develop smallpox prophylactics. According to one report, within days of the announcement that people were being diagnosed with anthrax, Gail Cassell, a Vice President at Lilly, "tore through paperwork that normally would have taken months, put samples of the drugs on a plane and flew them to government laboratories in the Washington area to be tested against smallpox."[30] Should one of Lilly's drugs prove effective, Cassell pledged Lilly's commitment to a crash development program, stating, "we are absolutely willing to do that. I would emphasize that we would do it for the good of the country, not for the good of Lilly."[31]

In another move reminiscent of World War II military-industrial relations, pharmaceutical companies have reportedly offered to lend their own scientists to government laboratories to work on the early stage development of new vaccines and therapeutics in what they describe as a "gift to the nation."[32] Such "gifts" would not go uncompensated, however, given that most of the nation's biodefense expertise resides in military research laboratories such as USAMRIID and WRAIR, and industrial scientists have a great deal to learn about biodefense research from military scientists. Indeed this sort of cross-fertilization of expertise will be as necessary today, as it was in the 1940's, to jump start industrial research and development efforts for the purposes of biodefense.

Although the public relations incentives of the pharmaceutical industry are easy to identify, there is a danger of overlooking elements of what may be a selfless patriotic reaction to a national security crisis. As in the 1940's, genuinely patriotic motives are intermingled with opportunistic

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[27] J. Gillis, "Drugmakers Step Forward in Bioterror Fight," *The Washington Post*, October 31, 2001.
[28] Ibid.
[29] Ibid.
[30] J. Gillis, "Scientists Race for Vaccines: Drug Companies Called Key to Bioterror Fight," *The Washington Post*, November 8, 2001.
[31] Ibid.

ones, and thus it is important not to regard the reintroduction of "gift" rhetoric within the pharmaceutical industry with too much cynicism. Reflecting on the wave of heroic actions and public gifts in the wake of the World Trade Center attacks, Rosalind Williams has written that national disasters have the capacity to evoke "the grandeur latent in individuals and societies."[33] History witnessed a similar outpouring of selfless gestures in the 1940's as industry, academia, and the military banded together under the threat of war, transcending individual agendas to participate in vaccine development programs. It is not unreasonable to expect that the vaccine industry is on the verge of participating in a similar historical moment.

Increased federal interest in biodefense

A heightened sense of urgency has also secured unprecedented levels of funding for biodefense efforts. The Bush Administration budget proposal for Fiscal year 2003 asked for $5.9 billion to counter bioterrorism, nearly a 400% increase over pre-September 11th biodefense spending levels. These dramatic increases stand in direct contrast to efforts to secure funding for biodefense before the events of September 11th. In the absence of a salient threat, it was difficult to garner political support for biodefense proposals and to secure funding for new programs. During his administration, former President Clinton stated that he believed that biological weapons posed the greatest security threat to the U.S..[34] Former Secretary of Defense William Cohen made equally urgent remarks on the subject of biological terrorism, stating on a number of occasions that he believed that it was not a matter of if, but of when. Despite such urgent remarks from the Commander in Chief and the Secretary of Defense, according to one report, "many of Clinton's requests were cut by his own Office of Management and Budget or the Congress which remained skeptical."[35] In the absence of a salient threat and a palpable sense of urgency, Clinton era biodefense plans did not enjoy much support outside of the White House and rarely amounted to more than a series of disjointed, unfunded mandates.

Part of the difficulty lay with the fact that effective biodefense requires investments in preventative health and public health infrastructure, two causes for which it has been historically difficult to garner political support. Lawrence Gostin, professor of law at Georgetown, summarized the problem when he stated, "the fact that public health often polices the commons

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[32] L. Wayne, and M. Petersen, "A Muscular Lobby Tries to Shape Nation's Bioterror Plan," *The New York Times*, November 4, 2001.

[33] R. Williams, remarks at the plenary session, Society for the Social Study of Science, (Cambridge, Massachusetts, November 1, 2001).

[34] J. Miller and W. Broad, "Clinton Describes Terrorist Threat for 21st Century," *The New York Times*, January 22, 1999.

and champions population-based risk reduction through behavior change (e.g., smoking cessation, designated drivers, exercise and diet modification) deprives it of specific beneficiaries who are motivated to form political constituencies. The prevalence of an individualistic, market ideology in political circles makes it difficult even to speak of public health in the vocabulary of contemporary politics."[36]

There is reason to believe that the vocabulary of contemporary politics could change. United by the threat of bioterrorism, vaccine development and infectious disease-based public health initiatives will not need to rely as heavily on special interest groups for political support in the near future. President Bush gave a clear indication of the changing political status of these issues when vaccine research and public health made an unprecedented appearance in a Presidential State of the Union Address. In his address, President Bush assured the nation that "we will develop vaccines to fight anthrax and other deadly diseases."[37] Furthermore, he asserted that "knowledge gained from bioterrorism research will improve public health."[38] Thanks to the efforts of a handful of hijackers and bioterrorist(s), the federal government has become motivated to take action on biodefense issues with alacrity not witnessed since World War II. Carol Heilman, division director at NIH, told reporters in November that, "this has been a shock to so many people. . . . People aren't sleeping anymore. Everybody is working as much as they possibly can. Bureaucracy is not a word that's acceptable anymore."[39]

Thus, a salient threat has united public health and national security in the public mind, inspired industrial cooperation, and rehabilitated the federal government's commitment to vaccine development through unprecedented financial and political support for expanded biodefense initiatives. With so many historical parallels to the conditions that fostered high rates of innovation during the 1940's, can we not expect a full-fledged reprise of the success of World War II vaccine development programs?

III. Barriers to a reprise of World War II vaccine development successes

Lack of trust

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[35] J. Miller, "Bush To Request a Major Increase in Bioterror Funds," *The New York Times*, February 4, 2002.
[36] L. Gostin, "The Law and the Public Health: A Study of Infectious Disease Law in the U.S.," *The Columbia Law Review* 99 (1999): 59.
[37] "President Bush's State of the Union Address to Congress and the Nation" transcript reprinted in *The New York Times*, January 30, 2002.
[38] Ibid.
[39] J. Gillis, "Scientists Race for Vaccines: Drug Companies Called Key to Bioterror Fight," *The Washington Post*, November 8, 2001.

Replicating World War II vaccine development successes will be more difficult today for a number of reasons. The first of these is trust. The culture of military-industrial collaboration that fostered high rates of vaccine innovation was held together by a sense of mutual respect and trust that promoted close collaboration and "gift exchange" relationships between military and industrial research scientists, encouraging the high rates of technology transfer and information sharing essential to effective vaccine development. Trust in the military began to erode during the 1970's as revelations about napalm and Agent Orange use in Vietnam, human radiation experiments, and the unethical use of human subjects for hepatitis B research at the Willowbrook tarnished the reputation of military-sponsored biomedical research. Similarly, the government's trust in the pharmaceutical industry to assist them to develop socially desirable vaccines began to erode as companies exited the business, pulled out of government contracts, or raised their prices.

A persistent lack of trust in military medical initiatives in the 1990's continued to impede biodefense efforts. Controversy raised by the DOD's Anthrax Vaccine Immunization Program (AVIP) offers ample evidence for this claim. In December of 1997, former Secretary of Defense, William Cohen announced the DOD's intent to immunize all service personnel with the anthrax vaccine. Rumors that the vaccine was unsafe began to circulate among service personnel. Since biodefense preventives and therapeutics were already under suspicion for having caused symptoms of the "Gulf War Syndrome," fears ran high among service personnel and a growing number individuals risked their military careers by refusing to comply with the immunization regimen.

Dr. Donald Metzgar, who served on the Institute of Medicine panel that assessed the safety of the anthrax vaccine, believes that the vaccine is no less safe than any other vaccine, causing adverse reactions in less than 1% of the population. He surmised that resistance to the AVIP is a symptom of the times, arguing that younger generations of Americans grew up without vivid reminders of the ravages of disease and therefore undervalue the need for preventative medicine. Adverse reactions from the vaccine, he reasons, were more salient to service personnel than the threat of the disease itself.

Congressman Christopher Shays (R-CT) has indicated that distrust of the military runs deep and may be hard to overcome even in the face of a salient threat. Referring the DOD's anthrax immunization program, Shays exclaims, "we're supposed to trust the military--and I wonder why, based on past experience, whether it was Agent Orange, whether it was people my office has had to help that have been exposed to radiation--we're supposed to trust the military to do the right

thing . . . they have no basis in which to say, trust us, based on past experience."[40] He also proclaimed, "I'm not comfortable with generals practicing medicine, and I'm not comfortable with doctors planning wars, and, frankly, I'm not comfortable with doctors planning war doing medicine."[41]

Congressional rumblings over the price of Bayer's Cipro, the antibiotic initially used to treat anthrax victims, reflected a persistent distrust of large pharmaceutical companies as well. Representative Bernard Sanders (I-VT) gave expression to these sentiments in a recent congressional hearing when he stated, "when you have a national crisis, you do not have to give enormously profitable pharmaceutical companies the price they want. That is why we're here, to protect the American people, and if they want profits rather than serving the people, I think the law is very clear, that we have a right to go outside of that company [to break their patent]."[42] Given that the anthrax sent through the mail was sensitive to an array of antibiotics already available under generic labels, Bayer was not under any particular obligation to lower the price of their drug. Nonetheless, their failure to do so spawned a vitriolic reaction from an untrusting Congress.

Persistent distrust between Congress, the military, and the pharmaceutical industry does not bode well for future biodefense planning because such planning will require the full and open participation of all parties. Under the current system, only pharmaceutical companies possess the large scale manufacturing capabilities required to produce enough vaccine for clinical trials and stockpiling. The military, on the other hand, holds much of the expertise for early stage biodefense vaccine development within military research institutes such as WRAIR and USAMRIID. For instance, every vaccine on the list of current and possible biodefense vaccines (Table 2) has either been developed in military research labs or with the aid of DOD funding. The military also continues to be an indispensable vaccine development partner, because military populations are still the most likely lead-users of biodefense vaccines. As in World War II, military experiences and follow-up research on these vaccines will offer invaluable information on their safety if not their efficacy. In lieu of a new agency to coordinate the development of biodefense vaccines, Congress will have to disperse public funds to the pharmaceutical industry and the military and trust them "to do the right thing."

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[40] Christopher Shays. House Representative, CT. "Defense Vaccines: Force Protection or False Security?" House of Representatives. *Hearing Before the Committee on Government Reform.* 106th Cong., 1st sess., October 12, 1999.
[41] Ibid.

Weakened industrial base

Michael Friedman, a former FDA administrator recently enlisted by the office of homeland defense to coordinate industry biodefense efforts, has remarked, "a lot of people would say we won World War II with the help of a mighty industrial base. In this new war against bioterrorism, the mighty industrial power is the pharmaceutical industry."[43] If the war against bioterrorism was going to rely on antihypertensive and anxiolytic drugs, biodefense planners could rest assured. However, given the current dearth of effective viral therapeutics and the potential limits of biological ones, effective biodefense is still predicated on the availability of a vaccine. Phillip Russell, former commander of the U.S. Army R&D Command and professor of International Health at Johns Hopkins, argues that the success of any U.S. response to the deliberate release of a highly infectious organism will depend on "the rapidity of the public health response, the effectiveness of a vaccination campaign, and, most importantly, the availability of vaccine."[44] The current specificity of vaccines and the potentially wide range of infectious organisms make it impractical to attempt to vaccinate the U.S. population as a first line of defense. However, vaccines are valuable as a second line of defense, to protect surrounding populations from secondary waves of infection, and to protect first responders, health care workers, and laboratory workers at high risk. This is particularly true, for example, in the event of an anthrax attack, since the vaccine (in combination with antibiotics) can be used for post-exposure prophylaxis.

Unfortunately, biodefense planners cannot take immediate comfort in the industrial power of the vaccine industry. As the previous chapter has demonstrated, the industrial base for vaccine development has steadily eroded since the 1970's, leaving vaccine supplies more vulnerable and innovation less likely. Nonetheless, during the 1990's, domestic preparedness planners drew a black box around factors affecting vaccine development, often taking the availability of vaccines for granted. In a pre-September 11 conversation with a current Senior Director for Policy at the Office of Homeland Security, I was informed that vaccine innovation and supply was not problematic: 'we will just stockpile available vaccines,' and 'as new ones become available, we'll stockpile those too.' [45]

Such confidence in U.S. systems of vaccine innovation and supply is misplaced. Tables 1 and 2 demonstrate that new vaccine development has not been able to keep pace with the growing

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[42] B. Sanders, House Government Reform Committee, Veteran's Affairs and International Relations Subcommittee, "Bioterrorism Vaccines," (October 23, 2001).
[43] J. Gillis, "Scientists Race for Vaccines: Drug Companies Called Key to Bioterror Fight," *The Washington Post*, November 8, 2001.
[44] P. Russell, "Vaccines in Civilian Defense Against Bioterrorism," *Emerging Infectious Disease* 5 (1999): 4.
[45] Richard Falkenrath, conversation with author, Harvard Kennedy School of Government, March 13, 2000.

number of emerging and manufactured disease threats. In sum, these tables demonstrate that vaccines have been licensed to address only two out of the nineteen new disease threats identified since 1973. Furthermore, both of these (the rotavirus and the Lyme disease vaccine) have since been pulled from the market. Similarly, only five vaccines have been licensed to protect against a minimum of twenty-one high-risk biological warfare agents identified by the DOD, and manufacturers have ceased producing all but one of these (yellow fever).[46] Although recent steps have been taken to start producing smallpox and anthrax vaccines, currently the nation must rely on a limited and aged stockpile of vaccines.

Table 1:
Development Status of Vaccines and Antibiotics for Emerging and Re-emerging Diseases[47]

Year	Emerging Diseases	Development Status of Vaccine or Antibiotic
1973	Rotavirus	Vaccine licensed in 1998 but recalled in 1999 for causing bowel obstruction in infants
1977	Ebola virus	
1977	*Legionella pneumophila*	Pre-clinical
1980	Human T-lymphotrophic virus I (HTVLI) t-cell lymphoma/leukemia	
1981	*Staphylococcus aureus* – toxin producing (TSS)	Phase II
1982	*Escherichia coli* O157:H7	Phase II
1982	*Borrelia burgdorferi* (Lyme Disease)	Vaccine licensed in 1998. Despite rising incidence of disease, pulled off market 2002 for commercial reasons
1983	HIV	IND
1983	*Helicobacter pylori* (peptic ulcer disease)	Phase I (antibiotics also effective)
1989	Hepatitis C	Pre-clinical
1992	*Vibrio cholerae O139* (new strain associated with epidemic cholera)	Phase III
1993	Hantavirus	Phase II
1994	Cryptosporidium (protozoa- enteric disease)	
1995	*Ehrlichiosis*	
1996	New variant Creutzfeldt-Jakob disease (prion)	
1997	HVn1 (influenza)	
1999	Nipah virus	
Re-emerging		
1986	Dengue	Phase II trials for a live-attenuated monovalent vaccine
2000	West Nile Virus	Pre-clinical
Diseases with increased resistance over the past 10 years:		
	Tuberculosis	BCG vaccine (efficacy 0- 80%)

[46] As of January 31, 2002, the FDA re-licensed Bioport to produce the anthrax vaccine.
[47] "Accelerated Development of Vaccines," (The Jordan Report, www.niaid.gov/publications/pdf/jordan.pdf, 2000); World Health Organization, *World Health Report*, (Geneva, 1999); D. Gordon, D. Noah, and G. Fidas, "The Global Infectious Disease Threat and Its Implications for the United States," *National Intelligence Estimate* 99-17D (January 2000).

		(13% resistant to any drug in the US; 16% resistant to any drug in NYC; 20% multi-drug resistance in Eastern Europe)
	Malaria	Chloroquine resistance: 65% in Kenya; 45% Ghana; 59% Zimbabwe. Mephloquine resistance: 17% Burkina Faso; 45% Thailand SKB has a vaccine in clinical trials, but WHO estimates 15 years away fro effective vaccine
	Staphylococcus aureus	80% penicillin resistant and 32% methicillin resistance in US; 60% multi-drug resistance in Japan Phase II trials of a capsular polysaccharide vaccine
	Streptococcus pneumoniae	Penicillin: 10-35% resistant in US; 20% resistance in Asia, Chile, and Spain; 58% resistance in Hungary Phase III
	Shigella dysenteride	Burundi and Rwanda: 100% multi-drug resistance; Phase II of a polysaccharide protein conjugate vaccine

Table 2: Development Status of Vaccines for Potential BW Agents

Disease	**Vaccine**	**Current Availability**
Anthrax	Bioport	License suspended 2000, reissued 2002
Botulism	DOD pentavalent toxoid for serotypes A-E	IND
Brucellosis		Pre-clinical
Chikungunya		IND (filed 1986)
Cholera	Wyeth-Ayerst	Licensed, ceased manufacture 2000
Dengue		Pre-clinical
Ebola/Marburg	Viral replicon /DNA	Pre-clinical
Glanders		No vaccine
Plauge	Greer inactivated vaccine	Licensed, ceased manufacture
Q-Fever	Inactivated whole cell vaccine	IND (filed 1972)
Ricin		No vaccine
Smallpox	Wyeth calf lymph vaccinia vaccine DOD cell-cultured avirulent vaccinia virus	Licensed, ceased manufacture IND
Staphylococcus Enterotoxin B		Pre-clinical
T-2 Mycotoxins		No vaccine
Tularemia	Live attenuated vaccine	IND (filed 1965)
Viral Encephalitides	VEE- DOD TC-83 live attenuated vaccine VEE- DOD C-84 (formalin inactivated TC-83) EEE- inactivated WEE- inactivated	IND (filed 1975) IND (filed 1965) IND (filed 1967) IND (filed 1984)
Viral Hemorrhagic Fevers	Argentine Hemorrhagic Fever (Junin) BHF Rift Valley Fever: inactivated vaccine Live- attenuated virus	IND (filed 1985) IND IND (filed 1969) IND (filed 1991)
Yellow Fever	Live attenuated virus (Aventis Pasteur)	Licensed

Source: C. Hoke, "Military Infectious Diseases Research Program", presented at a meeting of the IOM Committee on the development of vaccines of military significance, April 3, 2000.

Key:

Pre-clinical	Animal model safety and efficacy testing
IND	Investigational New Drug: FDA grants permission to begin Phase I trials in humans after extensive review of pre-clinical animal data
Phase I	Test vaccine in 20-80 volunteers for evidence of safety and efficacy
Phase II	Test vaccine in 100-200 volunteers for efficacy in proposed use
Phase III	Test vaccine 100's-1,000's to ensure safety and efficacy and to determine optimal dosages for a wider demographic

The economic and ethical barriers to the development of these vaccines are high. The commercial incentive for the pharmaceutical industry to engage in their development and manufacture and the use of these vaccines is low given that biodefense vaccines protect against diseases with low to no natural incidence such as smallpox and the use of these vaccines has heretofore been limited to military settings. Furthermore, proof of efficacy, according to current FDA standards, requires randomized clinical trials with large numbers of human subjects. Performing such trials would require the deliberate exposure of unvaccinated subjects to lethal pathogen. To overcome this ethical obstacle, the FDA has proposed a new ruling that would modify efficacy requirements for biodefense vaccines allowing them to be licensed on the basis of animal studies alone.

Apart from the difficulties of developing new biodefense vaccines, the vaccine industry has struggled in recent years merely to provide adequate supplies of pre-existing vaccines such as anthrax, influenza, DTP, and MMR vaccines. This is due in part to strict regulation, which have made it more difficult for older vaccines, such as the anthrax vaccine, to meet current FDA requirements for Good Manufacturing Practices. However, contraction of the vaccine industry is also to blame.

Although consolidation of the vaccine industry in the 1980's improved profit margins on vaccine production, it produced a number of single source suppliers and rendered the vaccine supply more vulnerable to production problems within individual companies. For example, anytime a pathogen has low yields or a plant experiences problems with a production run, the developer must often start the development process from the beginning. Given the long production runs in vaccine manufacturing (sometimes 7-10 months for a single vaccine), supplies can be disrupted for an entire year before the company is able to grow and purify new antigenic substances. Attesting to the vulnerability of the U.S. vaccine supply, Robert Hendrickson, Merck's Senior Vice President of Manufacturing and Technology (1961-1990) remarked, "It used to bother me that we had the world's supply of all of these vaccines sitting in refrigerators in

the Butler building at West Point. You'd think it would be like Fort Knox because you couldn't replace those inventories overnight."[48]

Since the industry consolidated in the 1980's, supply shortages have been a perennial problem.[49] Most recently, there has been evidence that the problem is growing worse. In February of 2002, the federal Centers for Disease Control and Prevention (CDC) announced that there were temporary shortages of eight out of eleven of the most commonly administered childhood vaccines.[50] The director of the CDC's immunization program has stated that such wide-scale shortages are "unprecedented—posing a threat to the public health that's far more concrete than the fears that led so many to panic about anthrax and smallpox."[51] Given the difficulties of the U.S. vaccine industry in meeting vaccine demands under normal circumstances, it is clear that the industry would be hard pressed to expand production or to boost innovation in the event of any public health or national security emergency.

Lack of governance

The third and largest difference between World War II conditions and the current environment for vaccine development is that there is no programmatic equivalent to the OSRD or the AFEB to coordinate large-scale research and development for the purposes of biodefense.

Prior to September 11th, biodefense efforts proceeded through unfunded mandates or congressional initiatives reflecting a wide range of constituent interests rather than a nationally coordinated program for biodefense.[52] This is symptomatic of what Ashton Carter has recently described as the "governance issue."[53] Since the declaration of America's new war on terrorism, Carter has argued that defense planners can no longer afford to respond to these issues in an ad hoc and piecemeal manner. In particular, Carter has suggested that the U.S. government adopt a "managerial approach (i.e., a framework for bringing responsibility, accountability, and resources

[48] Robert Hendrickson, oral history interviewed by Jeffrey Sturchio and Louis Galambos, (December 20, 1991 and April 13, 1992). MA.
[49] R. Pear, "Juvenile Vaccine Problems Worry Officials and Doctors," *The New York Times*, December 2, 2001.
[50] The federal government is reporting shortages of diphtheria, tetanus, pertussis, and pneumococcal vaccines and limited deliveries of influenza, chicken pox, measles, mumps, rubella, and influenza vaccines for the 2001–2002 winter season.
[51] Editorial, "Averting Vaccine Disaster," *The Washington Post*, February 22, 2002.
[52] For a review of this problem see: G. Koblentz, "Overview of Federal Programs to Enhance Sate and Local Preparedness for Terrorism with Weapons of Mass Destruction," BCSIA discussion paper, 2001–5, John F. Kennedy School of Government, Harvard University, (April, 2001).
[53] A. Carter, "The Architecture of Government in the Face of Terrorism," *International Security* 26, no. 3, (Winter 2001/2).

together in sharp focus) to deliver a key public good - - security in the homeland against catastrophic terrorism."[54]

Currently, responsibility for biodefense is distributed among a wide variety of military and civilian federal agencies as well as state and local government bodies. The formation of the Office of Homeland Security as an umbrella organization offers some hope for a "managerial approach" to the biodefense problem. However, the biodefense component of the Office of Homeland Security was born out of an immediate need to respond to operational issues. For example, Homeland Security officials are occupied with questions such as "what is the chain of command when the CDC, FBI, FEMA, and local first responders arrive on the scene?" "How do we coordinate large immunization and decontamination efforts?" And "how can we prepare regional labs for a surge in diagnostic demands, and hospitals for a surge of patient demands?" Thus far, there has been no evidence of a long-term, large-scale research and development plan for the purposes of biodefense.

In light of these factors, the governance issue looms large for biodefense planners concerned with the research, development, and procurement of vaccines. Members of the industrial and academic community have testified that they have workable vaccine development proposals but that they do not know who to talk to or where to send them. They explain that responsibility for vaccine development is so distributed within the government that the agencies themselves often do not know where to direct these calls.[55] Una Ryan, CEO of Avant Immunotherapeutics, which has licensed a prototype recombinant anthrax vaccine to the DOD, argued that "there needs to be a clearinghouse for information that lets me know exactly which government agencies, offices, and labs are responsible for research, development, procurement, and policy relevant to my products."[56]

Given the protracted and unpredictable nature of the threat from bioterrorism, there will be a long-term demand for a wide range of commercially unattractive vaccines to build and maintain national pharmaceutical stockpiles. Thus far, the federal government has approached this problem as it has in the past, by granting low-margin, short-term contracts to willing industrial partners. In contrast to World War II, in which there was a tacit understanding among vaccine development program participants that all arrangements were temporary, there is no such assurance today and industry may therefore be more reluctant to commit themselves to a large

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[54] Ibid., 9

[55] Testimonies from the House Government Reform Committee, Veteran's Affairs and International Relations Subcommittee, "Bioterrorism Vaccines." (October 23, 2001).

[56] Dr. Una Ryan, testimony before the Subcommittee on Science, Technology, and Space, Senate Committee on Commerce, Science, and Transportation, (February 2, 2002).

number of contracts. Further, history demonstrates that, in the absence of an immediate and salient threat, the pharmaceutical industry will become less willing to accept these low margin government contracts. In other words, although a newfound patriotic spirit in the pharmaceutical industry appears to have renewed a culture of gift relationships, history demonstrates that this is a short-term condition that is unlikely to outlast the enduring threat of bioterrorism. This reality calls for a creative and sustainable solution to the problems of vaccine innovation and supply.

Any plan that is devised, however, will have to be reconciled with a landscape for vaccine development that bears little resemblance to the one that existed in the 1940's. This is due to the fact that much of the expertise required to develop the next generation of bioengineered vaccines often lies outside of the military or pharmaceutical companies and within smaller biotechnology companies or the NIH. Given this distribution of expertise across a wider variety of institutions, targeted vaccine development programs face more potential roadblocks to integrated approaches than were present in the 1940's. Nonetheless, any vaccine development program devised after the genetic engineering revolution not only must seek to improve collaboration between the military and the pharmaceutical industry, but also must find ways to incorporate the contributions of the biotechnology companies and the NIH.

Biotechnology industry: challenges and opportunities

Increasingly, the most promising new biodefense vaccines have been developed in smaller biotechnology companies. Acambis, for example, is producing the first cell-culture version of the smallpox vaccine for the federal government, and Avant Immunotherapeutics recently licensed a prototype for a recombinant anthrax vaccine to the DOD through Dynport, the prime systems contractor for the DOD. These companies have superior experience with an array of genetic engineering techniques for vaccine development that permit them to develop vaccines according to more precise manufacturing practices that are more easily approved by the FDA than older, less standardized techniques. Unlike large pharmaceutical companies, however, these smaller companies do not have the manufacturing expertise or facilities to perform late-stage vaccine development or manufacturing.[57] And, unlike military research laboratories, biotechnology companies neither observe the clinical manifestation of novel diseases nor have access to samples of infected material. Rather, Avant's early stage contributions, for example, are cycled back through Dynport. Dynport must then find another small firm that is willing to develop and manufacture the vaccine using Avant's technology with which they, naturally, are not familiar.

[57] A. Gambardella, *Science and Innovation: The U.S. Pharmaceutical Industry in the 1980s* (Cambridge: Cambridge University Press, 1995), 147.

Any chance for a smooth, integrated development process is therefore thwarted by the dispersion of specialized expertise through myriad biotechnology companies.[58]

The increased participation of the biotechnology industry in vaccine development does not displace the military as a vaccine development partner, but it does suggest a different role for military-led research and development initiatives. For example, these smaller biotechnology companies will still need to collaborate closely with military research scientists who have a superior knowledge of the biological threat agents and access to high security laboratories that permit the safe study of these organisms. However, while smaller biotechnology companies take the lead in the early-stage development of vaccines against biological weapons, the DOD could make relatively stronger contributions to more traditional public health aspects of the biodefense effort. For example, the military has maintained a leading role in international epidemiological surveillance. Recognizing the superior capabilities of the military in this field, the IOM reported in the early 1990's that "the seven overseas medical research laboratories maintained by the U.S. DOD are the most broadly based international facilities of their kind supported by the U.S.. In addition to being well situated to recognize and study emerging disease threats, these facilities are valuable sites for testing new drugs and vaccines, because they are located in areas of the world in which the diseases of interest are endemic."[59]

Increased participation of smaller biotechnology companies creates opportunities to solve the governance issue as well. Rather than thwarting efforts to integrate vaccine research and development, biotechnology companies may offer defense planners a way in which to navigate the troubled military-congressional-industrial relationships of the post-Vietnam era. The biotechnology industry does not suffer from the trust issues that have complicated these relationships in the past. In contrast, biotechnology companies are eager to work with the military, and Congress appears more willing to entrust them with public funds than the pharmaceutical industry. As Una Ryan, CEO of Avant, informed Christopher Shays at a Congressional hearing on vaccines for biodefense, "we are not the pharmaceutical industry.

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[58] Underscoring the dispersion of specialized expertise within the biotechnology industry, a number of studies have noted that, rather than being developed entirely in-house, most bioengineered drugs have been developed through a collection of collaborative R & D contracts and joint ventures between large pharmaceutical companies and smaller biotechnology start-ups. See A. Arora and A. Gambardella, "Complementary and External Linkage: The Strategies of Large Firms in Biotechnology," *Journal of Industrial Economics* 37, no. 4, (1990): 361; G. Pisano, "The Governance of Innovation: Vertical Integration and Collaborative Arrangements in the Biotechnology Industry," *Research Policy* 20 (1991): 237.

[59] Institute of Medicine, *Emerging Infections: Microbial Threats to Health in the U.S.,* eds. J.Lederberg, R. Shope, and S. Oaks, (Washington, D.C.: National Academy Press, 1992), 5.

We're small, we're nimble, we're unencumbered by profits, and we are extremely motivated to help the government."[60]

The willingness of biotechnology companies to work with the government is more than matched by the DOD's desire to work with biotechnology companies. Carl Feldbaum, president of the Biotechnology Industry Organization (BIO) stated that he has sensed "a seismic shift in the Defense Department's interest in what private firms and academic departments are doing."[61] In support of this view, the DOD is planning a joint conference with BIO within the year to coordinate military needs with industry capabilities to provide biomedical therapeutics and vaccines.[62]

The NIH: challenges and opportunities

The Bush administration's budget requests for Fiscal Year 2003 indicate that the NIH is becoming the de facto lead agency to direct civilian biodefense research and development efforts, as it will receive the bulk of federal funding for this purpose. Whereas the NIH had planned to spend $93 million on research related to bioterrorism prior to September 11th, $1.8 billion is now set aside for this purpose, nearly a 2000 % increase.[63] According to Dr. Anthony Fauchi, director of National Institute of Allergy and Infectious Diseases (NIAID), a division of NIH that does vaccine research, this is "the biggest single-year request for any discipline or institute in the history of the NIH."[64] Dr. Fauchi has indicated that he will set aside $441 million for basic research , $592 million for drug and vaccine discovery and development, and another $522 million to build new laboratories that can accommodate dangerous microbes. The rest, he says, will be used to fund drug trials.[65]

However, appropriating large sums of money for biodefense research and development alone does not constitute an effective strategy. As it stands, the federal government is throwing money into a research environment that is fundamentally unsuited to targeted research and development initiatives. The NIH independent investigator initiated grant program was designed to accelerate fundamental research, not to perform the sort of large scale applied R&D required for biodefense.

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[60] Dr. Una Ryan, testimony before House Government Reform Committee, Veteran's Affairs and International Relations Subcommittee, "Bioterrorism Vaccines," (October 23, 2001).
[61] J. Wechsler, "Manufacturers Face Challenges and Regulatory Changes," *Pharmaceutical Technology* (November 2001).
[62] Ibid.
[63] In addition to $1.8 billion, which has been devoted to federal agencies, Bush's budget has reserved an addition $1.6 billion for rebuild state and local health care systems and response capabilities.
[64] J. Miller, "Bush to Request a Major Increase in Bioterror Funds," *The New York Times*, February 4, 2002.
[65] Ibid.

As the NIH AIDS vaccine development program demonstrated in the 1980's and '90's, targeted research fails in the context of NIH because the system requires the initiative for such projects to be generated from the bottom-up. There is no project manager or advisory body at the top to integrate research findings into a coordinated development plan. Furthermore, as demonstrated in the previous chapter, the NIH cannot offer the lead-user advantages to industrial partners that the military can. Nor can they bridge the basic-applied gap as well as their counterparts in military research institutions.

IV. Planning for targeted vaccine research

Twenty-first century biodefense planners may find it useful to recall James Conant's advice on large-scale R&D planning at the close of World War II. As described in Chapter Two, the former Chairman of the National Defense Research Committee within OSRD concluded: "There is only one proven method of assisting the advancement of pure science, - that of picking men of genius, backing them heavily, and leaving them *to direct themselves* [emphasis his]. There is only one proven method of getting results in applied science, -picking men of genius, backing them heavily, and *keeping their aim on the target chosen* [emphasis his]."[66] As Conant suggests, the governance problem for biodefense research is best solved with an organizational structure that is tailored to "applied" or targeted research. This implies a top-down administrative structure with scientifically and technologically competent project managers and administrators whose job it is to winnow through research findings and integrate them into targeted development projects. Conant also noted, in retrospect, that research and development was facilitated by close collaboration with the lead-users of the technology under development: "In the case of OSRD, defining these objectives was possible because of close cooperation and frequent consultation with the "users" – the Army and the Navy."[67]

Hilleman's remarks on the organization of vaccine research are instructive as well. He stated that "I've found it to be of extreme importance and help to have a concentrated program of very great breadth, covering a diversity of diseases and extending from the laboratory bench through the clinic. By this I mean a program ranging from discovery of the cause of disease and the assessment of its importance through the development of means for control and the proof of safety and efficacy of the method in large-scale clinical studies in man. This provides for self-

[66] James Conant, President of Harvard University and then chairman of the National Defense Research Committee, Letter to the Editor of *The New York Times* in response to an unfavorable editorial regarding Bush's proposals in *Science: the Endless Frontier* (August 3, 1945). NA: RG 227, E. 2, B. 1.
[67] Ibid.

catalyzing spill-over from one study to another and encourages progress toward the target objective without the disruptions imposed by passing the successive stages of development from one research group or department to another."[68] Peggy Johnson, former scientific director of the International AIDS Vaccine Initiative and the recently hired scientific director of the AIDS vaccine research effort at NIAID, endorses the sort of empirical, targeted approach recommended by Hilleman. In support of this point, she explained that "a lot of vaccine research does tend to be more empirical . . . It is not asking a key fundamental virology or immunological question."[69]

Taken together, Conant, Hilleman, and Johnson describe the essential characteristics of successful vaccine development programs whether conducted under the auspices of OSRD, within military research labs such as WRAIR or USAMRIID, or in industry or NIH laboratories. These characteristics include 1) top-down control of the product development process, 2) an integrated interdisciplinary development process, and 3) close collaboration with the lead-users to demonstrate efficacy empirically rather than reductively.

A number of experiments and proposals have been launched in recent years to improve vaccine development. One recent experiment, the NIH Vaccine Research Center, possesses some of these characteristics and offers an encouraging template for future vaccine development endeavors. Another plan proposed by the DOD in July 2001, possesses all three characteristics and has the potential ability to address a number of the barriers to present day vaccine development discussed in the previous section.

NIH Vaccine Research Center

Despite the fact that the original design and intent of the NIH was to conduct basic research, there are indications that, with careful planning and expansion, it may be able to adapt to meet targeted vaccine research and development needs. The establishment of the NIH Vaccine Research Center offers a promising template for future research endeavors of this nature. The concept and motivation for the NIH Vaccine Research Center grew out of the 1996 Levine Report to the NIH Office of AIDS Research that advocated a targeted approach to the development of the AIDS vaccine and to bridge the gap between basic and applied vaccine research initiatives. Based on this report, the Presidential Advisory Council on HIV/AIDS issued a recommendation to President Clinton that led to his announcement in 1997 that "the National Institutes of Health

[68] M. Hilleman, "Some Thoughts on Industrial Research in the Health Sciences," Industrial Research Institute (October 20, 1975). MA.
[69] J. Cohen, *Shots in the Dark* (New York: W.W. Norton and Company, 2001), 322.

will establish a new AIDS vaccine research center."[70] The idea behind the center was to consolidate and coordinate the efforts of approximately fifty scientists already working on problems related to the development of an HIV/AIDS.

Jon Cohen, while crediting Clinton with raising the profile of AIDS vaccine research, has argued that "Clinton created another illusion that a problem had been solved when, in reality, it had only been acknowledged."[71] The press and AIDS advocacy groups were equally cynical of Clinton's intentions, noting that it took two years after his announcement before appointed Dr. Gary Nabel, a gene therapy expert, to direct its activities.[72] Even then, a spokesman for the AIDS Vaccine Advocacy Coalition argued that "The president is patting himself on the back, but we say not enough is happening."[73]

Despite its slow start, in principle the VRC holds promise. Much like WRAIR or Merck (under Hilleman's reign), the Vaccine Research Center is designed to integrate all aspects of vaccine development, including interdisciplinary research in immunology, virology, molecular biology, vaccine design, clinical trials, and production. Similarly, the VRC is intended to enforce the sort of top-down coordination of these varied disciplines that was characteristic of one of OSRD's, AFEB's, or Hilleman's vaccine development projects. The aim is to drive fundamental research on the AIDS vaccine through late stage development and into clinical trials in the most efficient manner possible.

Furthermore, much like WRAIR, the VRC has the potential to breed the sort of "science integrator" that made valuable contributions to vaccine research efforts in the 1950's and '60's. The current lack of expertise in integrated vaccine development has complicated efforts to launch expanded targeted vaccine development initiatives. Dr. Anna Johnson-Winegar, Deputy Assistant to the Secretary of Defense on chemical and biological matters, has noted that the limited availability of biodefense vaccines is related to the fact that "the biotechnology and pharmaceutical industry as a whole is facing shortages of skilled personnel."[74] This problem is a direct result of industry contraction in the 1970's and 1980's. As early as 1978, a government advisory group warned the Department of Health Education and Welfare that the high number of

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[70] Commencement address, President at Morgan State University, The White House, Office of the Press Secretary, (May 18, 1997).
[71] J. Cohen, *Shots in the Dark* (New York: W.W. Norton and Company, 2001), 292.
[72] "Clinton Calls for AIDS Vaccine Push at NIH, But No New Funds," *Pharmaceutical Business News*, May 21, 1997; "President Unveils Government's First AIDS Research Center," *Drug and Biotechnology News*, June 14, 1999.
[73] "Clinton Breaks Ground on AIDS Research Center," *AIDS Weekly*, July 12, 1999.
[74] A. Johnson-Winegar, "The DOD and the Development and Procurement of Vaccines Against Dangerous Pathogens: A Role in the Military and Civilian Sector?" in the Institute of Medicine's, *Biological Threat*

companies exiting the vaccine business is lending to the "dissolution of an expert staff and a removal of commitment to further activity in the field."[75] The Vaccine Research Center, if well funded and staffed with top-notch scientists, has the potential to become a center of excellence for vaccine research as WRAIR had been, with the capacity to attract and train talented young scientists with the interdisciplinary skills required to conducted targeted vaccine research.

If the Vaccine Research Center concept were expanded to include the development of a wider range of vaccines within the NIH, there is some reason for hope that portions of the NIH could adapt to a new role as the lead agency for biodefense research and development. In particular, applying the VRC organizational structure to a biodefense vaccine initiative would go some distance toward resolving the governance problem for large scale biodefense R&D because it would permit top-down control and integration of the development process and it would create a central repository for expertise and funding. Despite these advantages, the VRC concept lacks two characteristics of historically successful targeted vaccine development programs. In its current form, the VRC does not have reliable access to institutions with strong manufacturing capabilities (currently, these capabilities are limited to large pharmaceutical companies with vaccine divisions) and the VRC lacks sufficient input from military research scientists working on HIV/AIDS. Both of these factors would have to be addressed before the VRC could be considered a viable prototype for the governance and performance of biodefense R&D.

Proposals: the "Top Report" and the "National Vaccine Authority"

The Top Report grew out of frustrations surrounding DOD's inability to encourage pharmaceutical companies with adequate manufacturing capabilities to respond to military vaccine development contracts. In 1998, Former Deputy Secretary of Defense, Mr. Rudy de Leon, requested the Acting Assistant Secretary of Defense for Health Affairs and the Director of Defense Research and Engineering to contract with Science Applications International Corporation (SAIC) – a private organization- to provide an independent expert assessment of DOD vaccine acquisition strategies. SAIC compiled an independent expert panel of individuals with expertise in the scientific, regulatory, and industrial aspects of vaccine development and supplied administrative support for the study.

Named for the chairman of the panel that conducted the independent investigation, Dr. Franklin Top, the report engages a number of questions about who will set policies and priorities for research, development and procurement of these vaccines, and how the DOD and HHS will

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and Terrorism: Assessing the Science and Response Capabilities: Workshop Summary (Washington, D.C.: National Academy Press, 2002), 91.

coordinate on these issues.[76] The panel concluded, "the scope and complexity of the DOD biological warfare defense vaccine requirements were too great for either the DOD or the pharmaceutical industry to accomplish alone."[77] In response to this problem, the Top Report proposed a government-owned, contractor-operated GOCO vaccine research, development, and manufacturing facility to develop, license, and manufacture vaccines against biological warfare agents and endemic disease threats of military significance.

History of the GOCO proposal The idea of building a GOCO facility has been suggested on a number of occasions since the industry began to lose interest in military contracts in the 1970's. The question was first raised in 1972 in the midst of military efforts to find an industrial partner to develop the meningitis vaccine. Colonel Robert Cutting of the AFEB recalled that "as a result of Squibb's withdrawal from the meningitis vaccine, and after a great deal of hand-wringing in anguish, an internal emergency committee was created at the DOD level, Dr. Wilbur's office, for the purpose of addressing this very specific question. They had several meetings . . . A great number of plans were laid as to what vaccines would be needed now and in the future."[78]

The Commission on Acute Respiratory Diseases sent a formal recommendation to members of the AFEB, advocating the establishment of GOCO vaccine manufacturing facilities, stating, "it is recommended that the AFEB in collaboration with the DOD and the US PHS, investigate the feasibility that the US government develop a facility whose major function would be research and development of vaccines. The possibility of the production of certain vaccines might also be considered for those preparations that are not commercially profitable."[79] Heads of the preventative medicine divisions of all three services wrote letters in support of the proposal and Dr. Denny, speaking for the AFEB commission on Acute Respiratory Diseases emphasized that, "there is indeed a huge problem [with vaccine innovation and supply]. This applies not only to adenovirus vaccines but other vaccines as well and I think this needs to be addressed very, very emphatically now."[80] The proposal stalled however because responsibility to push the proposal forward lay with the AFEB, which was, at that time, preoccupied with the government challenges to their budget and authority.

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[75] "A Risky Exodus from Vaccines," *Industrial Edition*, April 10, 1978.
[76] After serving 22 years at USAMRIID, Dr. Franklin Top, a biochemist from Yale, served five years as the Director of WRAIR. He is currently the Executive Vice President and Medical Director of Medimmune, a biotechnology company based in Maryland.
[77] Department of Defense, *Report on Biological Warfare Defense Vaccine Research and Development Programs*, (July 2001).
[78] Col. R. Cutting, comments, minutes, spring meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.
[79] Minutes, meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.

In a move that would become increasingly uncommon, industry stepped in and saved the day. Colonel Cutting recalled that "people were dancing around, trying to come to grips with this problem when all of a sudden Merck decided that they would make the meningitis vaccine."[81] Once Merck expressed an interest in developing the meningitis vaccine, all plans for a long-term solution to the problems of vaccine innovation and supply were dropped until 1976, when the idea of a GOCO was proposed at the National Immunization Work Group Conference.[82] Concerned by the steady attrition of vaccine producers from the industry, workshop attendees recommended building a "National Production Facility" to ensure a steady supply of vaccines. They envisioned a facility that would be responsible for developmental research to improve existing vaccines, pilot lot production of new vaccines, the manufacture of commercially unattractive vaccines, and the distribution of these vaccines. Participants were also hopeful that a national facility could offer a way around the growing problem of vaccine liability in the wake of the swine flu affair.

Workshop study groups eventually rejected the proposal for three reasons. First, there was concern that a lack of diversification would limit the variety of research approaches and thereby stifle innovation. Second, there were concerns that the distribution component of the proposal would disrupt the private medical system, since, at the time, over 50% of all immunizations were administered by private doctors. And third, a national facility would not eliminate the risk of product liability, but merely transfer the issue to the federal government.[83]

The DOD revisited the issue of building a GOCO facility again in 1993 when they faced biodefense vaccine supply constraints during the Gulf War. Just as the escalating AIDS epidemic forced the NIH to take a renewed look at their vaccine development strategies in the 1990's, the Gulf War rekindled the DOD's interest in the problems of vaccine innovation and supply. Facing potential exposure to biological and chemical weapons in the Gulf War, the FDA passed an interim rule waiving informed consent requirements for the use of investigational new drugs (INDs) and vaccines (pyridostigmine bromide and botulinum toxoid) to protect troops.[84] This decision was later widely criticized as DOD-developed, FDA-unapproved biodefense preventatives and therapeutics fell under suspicion for causing the Gulf War Syndrome. The

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[80] Dr. Denny, comments, minutes, spring meeting of the Armed Forces Epidemiology Board, (1972–1973). WR.

[81] Col. R. Cutting, comments, minutes of the annual spring meetings of the Armed Forces Epidemiology Board, (1972–1973). WR.

[82] *Reports and Recommendations of the National Immunization Work Groups*, submitted to the Office of the Assistant Secretary of Health (McLean, VA: JRB Associates, March 15, 1977).

[83] Ibid., 34.

[84] Under an IND, the FDA permits companies to begin testing a drug or vaccine on human populations with written consent from the subject.

subsequent medical and political fallout from the Gulf War Syndrome, coupled with the impracticality of adhering to informed consent regulations in a rapid mobilization scenario, prompted military officials to seek alternative vaccine acquisition strategies.

Following the Gulf War, the DOD decided to place responsibility for biodefense vaccine procurement in the Joint Program Office. According to Phillip Russell, former Commander of the U.S. Army R&D Command, this was a "disastrous policy decision" for it "effectively isolated the process from the medical departments and from anyone who understood either the medical departments and from anyone who understood either the science, the technologies, the economics, or the vaccine industry."[85] Russell's claims are well supported by the manner in which the JPO handled the acquisition of the adenovirus vaccine. Russell explained that, soon after the JPO assumed responsibility, the DOD investigated the option of building a GOCO vaccine manufacturing facility: "the study was well done and honest about the costs. In spite of the attractiveness of the idea to many, myself included, it was rejected as too costly."[86] In lieu of a GOCO, the DOD decided to hire a prime systems contractor to push DOD-developed IND vaccines through licensure. To this end, the DOD established the Joint Vaccine Acquisition Program (JVAP) in 1994 to administer the program and awarded $747 million to Dynport to contract private firms to develop and test these vaccines.

The number of DOD developed vaccines for biodefense under IND has grown since the 1960's. As evidenced by Table 2, military research laboratories have not lost their skill for the early stage development of biodefense vaccines. However, because the military does not possess the large scale manufacturing capabilities required to produce enough vaccine for clinical trials, these vaccines have languished under IND status. Further, the JVAP has been unable to contract for large pharmaceutical companies with the requisite manufacturing expertise to produce these vaccines in sufficient quantities because the market for these vaccines is small and limited to military settings. According to interviews conducted with a senior scientist and CDC official, the pharmaceutical industry "guffaws" at JVAP's paltry contracts, citing $1 billion as the average development cost for a new vaccine.[87] Without large-scale manufacturing assistance from industry, the military has been unable to produce enough vaccine to conduct large clinical trials. Without FDA approval, these vaccines are only produced in small amounts and are only indicated

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[85] P. Russell, "Vaccines for the Protection of the U.S. Forces: Research Success and Policy Failures," presentation to the Institute of Medicine: *Committee on a Strategy for Minimizing the Impact of Naturally Occurring Infectious Diseases of Military Importance: Vaccine Issues in the U.S. Military*, (Washington, D.C., 2000).

[86] Ibid.

[87] A. Smithson, "Ataxia: The Chemical and Biological Terrorism Threat and the U.S. Response" *Stimson Center Report*, Ch. 7, (2001).

for use in research settings with the informed consent of the recipient. This arrangement renders these vaccines useless to military and civilian populations in emergency situations.

Reactions to the Top Report and a reprise of a National Vaccine Authority

The 2001 Top Report examined the idea of building a GOCO facility for the fourth time since 1972. Why should the reception to this proposal be any different now? Announced just two months before the terrorist attacks of September, the Top Report was well- timed and is receiving political attention and support, if not within the vaccine industry, at least within the government.

The Top Report, though it focuses primarily on military biodefense needs, has been well received within the Department of Health and Human Services (HHS). One reason for this may be that the GOCO mechanism is not tailored to biodefense vaccines but appears to offer a solution for all commercially unattractive yet socially beneficial vaccines. In a move that illustrates this confluence of national security and public health objectives, the Institute of Medicine (IOM) posted an announcement after September 2001 in support of the GOCO proposal within the Top Report. They stated, "the establishment of a government-owned, contractor-operated facility for research, development, and production of vaccines is essential to meeting the country's public health needs, particularly those related to bioterrorism and the protection of our armed forces. This facility also should play a role in development and production of other vaccines required for the public health that are not currently available on the open market."[88]

In this announcement, the IOM also renewed their 1985 proposal to establish a National Vaccine Authority (NVA).[89] The IOM asserted that "the events following the tragedies of September 11, 2001 have reemphasized a serious defect in America's capacity to deal with biological agents used in terrorist attacks. The capacity to develop, produce, and store vaccines to deal with these agents is inadequate to meet the nation's needs."[90]

Like the GOCO proposal, the concept of a NVA is an old one that has suffered from poor political support in the past. The IOM originally proposed a National Vaccine Commission in the context of the 1985 report on the problems of vaccine supply and innovation. Commission responsibilities, according to this proposal, would include everything from coordinating and directing vaccine research and development projects to monitoring and directing the supply and distribution of vaccines. Congress responded to the IOM's recommendations in the 1986 when it

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[88] Statement on Vaccine Development, Council of the Institute of Medicine, November 5, 2001: www.iom.edu/IOM/IOMHome.nsf

[89] Institute of Medicine, *The Children's Vaccine Initiative: Achieving the Vision* (Washington, D.C.: National Academy Press, 1993).

established the National Vaccine Program (NVP) and charged it with setting vaccine R&D priorities and coordinating the R&D efforts of government research and labs and industry. However, the problem held little urgency for the government or the public and the program suffered from a chronic lack of political support and congressional funds.[91]

As the NVP foundered, the IOM proposed the concept of an NVA again in 1993 in the context of a report analyzing the proposals of Clinton's Vaccines for Children Initiative.[92] This second version of the proposal suggested broader powers for the NVA that would include shepherding under-supplied childhood vaccines through development and manufacturing and taking responsibility for their distribution. This proposal died along with this expanded vision for the Vaccines for Children Initiative, which sought to stockpile all pediatric vaccines and make them available to health care providers at lower prices. Industry lobbyists, independent studies, and a General Accounting Office study convinced policy planners that less government involvement was both good for the industry and good for the public. They argued that: 1) high prices were not the barrier to pediatric immunization rates and 2) a higher percentage of low-margin government vaccine purchases would lower industry R&D incentives.[93]

The argument for a NVA became stronger in 2001 when biodefense vaccines became the subjects of government support. A NVA, under the IOM's revised proposal, would constitute a joint HHS/DOD endeavor to oversee the operations of the proposed GOCO and all related vaccine acquisition activities. This includes the formation of an inter-agency management group to coordinate research objectives with military and civilian biodefense policies and procurement needs. They propose that the NVA (1) conduct in-house vaccine-related R&D, (2) assist industry with pilot-lot production, (3) arrange procurement contracts from industry, and (4) produce vaccines when it is impossible to interest industry in the large-scale production of a particular vaccine.

Following the IOM statement, in January of 2001, Dr. David Satcher, the Surgeon General of the PHS, wrote to Secretary of Defense Donald Rumsfeld asking him to approve the DOD plan, advocating it as a useful model for the initial production of vaccines to protect civilian populations against biological attacks. He writes, "a GOCO production facility, under the proper conditions, could assure the availability of these vaccines for military as well as civilian use. . .we

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[90] Statement on Vaccine Development, Council of the Institute of Medicine, November 5, 2001: www.iom.edu/IOM/IOMHome.nsf

[91] R. Nowak, "U.S. National Program Is Going Nowhere Fast," *Science*, 256 (1994), 1375.

[92] Institute of Medicine, *The Children's Vaccine Initiative: Achieving the Vision* (Washington, D.C.: National Academy Press, 1993).

want to encourage DOD to proceed with plans to develop a GOCO vaccine production capability and offer our technical assistance within the resources available to HHS."[94] In this context, Dr. Satcher perceived military and civilian defense protection needs to be quite similar and he indicated his desire that close collaboration between the DOD and HHS at this juncture could avoid the future need for separate GOCO production facilities.

Industry, predictably, has not welcomed the most recent reincarnation of the NVA and GOCO proposals. Wayne Pisano, Executive Vice President of Aventis-Pasteur, has argued that "if the government enters the vaccine manufacturing business, industry may ultimately be unable to compete with a subsidized operation. The result is, potentially, the withdrawal of private manufactures from the U.S. market and the loss of innovation and timely introduction of new products into the U.S."[95] His comments assume, however, that the market was already functioning well enough to provide vaccines of concern to HHS and DOD. Pisano saves most of his arguments for the IOM NVA proposal, which entertains the idea of assuming responsibility for a number of childhood vaccines in low supply. Pisano's arguments may hold for this vaccine category given that industry has already invested in the development of these vaccines and would likely be willing to increase production if threatened with government encroachment. Under these circumstances, however, it is unlikely that the government would get involved in pediatric vaccine production given that the IOM NVA proposal explicitly forbids it unless all attempts to contract industry had failed.[96]

The government is far more likely to get involved in the development of biodefense vaccines, however, given that (as Table 2 demonstrates) the market has not functioned well for these vaccines. Although Pisano asserts that "industry is ready, willing, and able to take on limited-market products, such as anthrax, and smallpox," his assertions fly in the face industry actions over the past thirty years.[97] A primary motivation for the DOD's GOCO proposal was based on the observation that "large, well-established pharmaceutical industry (i.e. vaccine) manufacturers are unlikely to reverse their decades-long trend of relatively inconsequential support for DOD

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[93] U.S. General Accounting Office, *Vaccines for Children: Reexamination of Program Goals and Implementation Needed to Ensure Vaccination*, GAO/PEMD-95-22 (Washington DC: June, 1995); H. Grabowski and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: the AEI Press, 1997).
[94] Dr. David Satcher, letter to Donald Rumsfeld, Jan 31 2001 in the Department of Defense's *Report on Biological Warfare Defense Vaccine Research and Development Programs* (July 2001).
[95] W. Pisano, "Strengthening the Supply of Routinely Recommended Vaccines in the U.S.: Industry Perspective," presented at the National Vaccine Advisory Committee Meeting, (February 11–12, 2002).
[96] Statement on Vaccine Development, Council of the Institute of Medicine, November 5, 2001: www.iom.edu/IOM/IOMHome.nsf
[97] Ibid.

vaccine production requirements."[98] While industry did respond to recent government requests to develop a smallpox vaccine, there is no guarantee that they will do so again for other biodefense vaccines. A government-owned vaccine research, development, and manufacturing facility is only intended to provide the government with manufacturing capabilities so that it can step-in in for industry in those instances where the market fails.[99]

Another industry opponent of the Top Report, William Haseltine, CEO of Human Genome Sciences, was recently quoted as saying: "you don't ask the DOD to build fighter planes; why should it make vaccines?"[100] According to the article, Haseltine "believes that the government should invest not in production facilities but in the basic science of infectious disease and coax academics into long-term partnerships with industry."[101]

Such objections reveal a poor understanding of the factors that have inhibited vaccine innovation over the years. Haseltine is correct in his assertion that it matters not where vaccines are manufactured, be it under the auspices of government or industry. He cannot assume, however, as the case of NIH's early vaccine development attempts have demonstrated, that throwing more money into basic science will solve the problems of vaccine innovation and supply. The "blueprints" for vaccine manufacturing are not as straightforward as they might be for fighter planes and the managerial and organizational challenges are greater at the later stages of vaccine development when pilot vaccines must be scaled-up for large scale manufacturing and clinical testing. Furthermore, the tightly knit military-industrial culture that once navigated these difficult technology transfers from military to industrial labs is no longer as strong as it once was. Co-locating research, development and manufacturing capabilities, as these proposals recommend, offers but one way to overcome this problem. It matters not who manufactures vaccines or where they are manufactured, provided that mechanisms are in place to ensure that they are manufactured, that strong communication exists between the developers and the

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[98] Department of Defense, *Report on Biological Warfare Defense Vaccine Research and Development Programs*, (July 2001), 3.

[99] Further steps must be taken to define the terms for government intervention and to assure industry that the government will not encroach on viable markets. Furthermore, options for government vaccine projects to be transferred to private industry should market opportunities arise should also be defined. For example, if a manufacturer deemed capable of producing sufficient quantities of quality vaccine expresses interest in a government vaccine, it should be able to sign multi-year government contracts to produce the vaccine. The contract would require them to give a year's notice if they should decide to cease production for commercial reasons. Aventis-Pasteur has indicated that industry would be willing comply with a notification clause of this nature. (W. Pisano, "Strengthening the Supply of Routinely Recommended Vaccines in the U.S.: Industry Perspective," presented at the National Vaccine Advisory Committee Meeting, (February 11–12, 2002).)

[100] J. Cohen and E. Marshall, "Should the Government Make Vaccines?" *Technology Review* (May 2002), 43.

[101] Ibid.

manufacturers, and that the entire process is coordinated under one governing body at all stages: from interagency coordination and policy-setting, to research, development, production, and licensure. Taken together, the DOD and HHS proposals would encourage this version of an integrated development process.

Elements of historically successful vaccine development programs

These proposals have received strong backing outside of industry, in part because, just as it was politically expedient for Clinton to support NIH's VRC proposal, so too is it politically attractive for the government to offer a concrete response to public fears regarding vaccine availability in the wake of the recent anthrax attacks. What supporters may not recognize, however, is that the DOD and IOM proposals contain many elements of historically successful targeted vaccine development programs. Identifying what these elements are will provide guideposts for policy planners as both the concept and the details of a vaccine development program are negotiated.

First, as OSRD did in World War II, the proposed arrangement would capitalize on the recent willingness of members of industry, government and academia to lend their time and efforts to vaccine development endeavors. This governance structure would not merely harness talent however; it would provide a mechanism by which to coordinate a wide range of inter-institutional efforts. An examination of CMR in World War II demonstrated that close coordination between defense planners and research teams through advisory committees played a key role in the success of vaccine development programs, for it ensured that operational needs were well articulated and accounted for in all R&D planning sessions. Just as members of OSRD's CMR held joint memberships in the Division of Preventative Medicine, the Chemical Warfare Service, the Office of the Quartermaster General, etc., so too would NVA members hold joint positions within the CDC, NIH, DOD, OHS, CIA, and FEMA, to name a few. In a departure from World War II models, biodefense planning efforts that involve civilian populations may also call for the participation of physicians, governors, and public health officials on these advisory committees.

Second, then as now, targeted vaccine development is an inherently interdisciplinary endeavor, requiring input from immunologists, virologists, bacteriologists, epidemiologists, manufacturing and licensing experts--and increasingly biochemists, molecular biologists, and genetic engineers. The organizational structure of a NVA-governed research, development and manufacturing facility would gather many of these experts under one roof on project by project basis, and thereby facilitate the sort of "bench to batch" processes that characterized historically successful vaccine development at WRAIR and in industry during the postwar period.

The Top Report stressed the importance of maintaining all activities under one roof, noting that both industry and the military have failed in their attempts to outsource manufacturing activities. The report explains that, unlike chemicals, vaccines are produced through the biological processes of microbial or mammalian cells themselves, which requires strict and consistent oversight in a single facility and which makes it more difficult to pre-specify and outsource this responsibility to another facility.

While the Top Report recognizes a valid problem, it does not grasp the historical source of these outsourcing difficulties. As the development of the meningitis vaccine demonstrates, this sort of outsourcing was possible in the postwar period when military-industrial relations were strong. As relations became strained in the late 1970's, however, it became increasingly difficult to transfer the tacit forms of knowledge required to successfully outsource these manufacturing responsibilities. Thus, the decision to co-locate development and manufacturing activities is a good one, not because it is inherently impossible to outsource vaccine manufacturing responsibilities, but because this arrangement will compensate for communication weaknesses in the development chain created by the decline of the military-industrial culture of collaboration.

Maintaining all of these activities under one roof does not merely overcome outsourcing difficulties as the Top Report contends. History has demonstrated that an integrated development process of this nature increases learning opportunities, permits vaccine research scientists and bioengineers to bridge the "basic-applied gap," and thereby facilitates innovation. The proposed governance structure is also likely to accelerate the interdisciplinary and inter-institutional transfer of knowledge. Each new project would, by design, demand the transfer of people, technology, and ideas to the projects that needed them most. In this manner, these proposals address arguments raised by Hilleman and others that the problems besetting vaccine development programs such as the HIV/AIDS vaccine effort are largely organizational and managerial in nature. As was the case in World War II, this arrangement would integrate the talents of industry, government, and academia, permitting the rapid integration and application of all existing knowledge concerning the development of an individual vaccine.

These proposals are also responsive to many of the factors that have hindered military-industrial collaboration in recent years and they create incentives that are likely to encourage industry participation over the long-term. The DOD's failure to secure industry participation in the JVAP program was instructive. Industry executives argued that the industrial base is already at full capacity and that accepting a DOD contract would require them to build new dedicated facilities. Further, they explained that industry would need assurance of a continuous demand and high utilization rate to justify building these facilities, whereas these facilities would often

stand idle given the episodic nature of military biodefense needs. Industry is also uneasy about the future political and financial stability and legal liability of a DOD-funded biodefense program. The Top Report addresses each of these concerns. If the government built and maintained the manufacturing facility, utilization rates would cease to be an industry concern, since industry would not need to make a return on a facility investment. Further, the proposal recommends granting multi-year contracts that would be immune to budgetary fluctuations and that would extend indemnity to all manufacturers of biodefense vaccines. Additionally, decision-making responsibilities would lie with the product development team itself, permitting the program to be product rather than budget focused. This arrangement would remove some of the bureaucratic rigidity that thwarted military-industrial collaboration in the 1970's.

Finally, unlike the NIH VRC model, the DOD and IOM proposals suggest an integral role for both military and industrial developers, permitting close collaboration between vaccine developers and their lead-users. The military remains a valuable development partner for industry, in part because they remain the most likely "users" of these vaccines as the U.S. contemplates military operations in countries with BW capabilities. In addition to its lead-user status, the military also continues to be a valuable development partner by virtue of its experience and expertise in the development, acquisition, and administration of biodefense vaccines. The military's network of international laboratories for clinical testing will also be invaluable to future efforts to develop commercially unattractive vaccines against diseases endemic to other countries that could be used as weapons in countries unfamiliar with these diseases. According to the Top Report proposal, contractors would have direct access to military labs, research scientists, and administrative officials, and they would be in a position to receive valuable advice and insight from the military on the performance needs of current and future vaccines. Though none of these proposals explicitly recognize the advantages of this arrangement, the history of vaccine development indicates that this form of collaboration has generated high rates of vaccine innovation in the past.

V. Conclusions

A review of successful vaccine development initiatives suggests that renewed national security interest in biodefense bodes well for the future of vaccine innovation and supply. As witnessed in World War II, an atmosphere of urgency encourages institutions and individuals to overcome professional, bureaucratic, and economic disincentives to collaboration for the sake of

the nation. Industry's responsiveness to the government's recent request for proposals to fill a smallpox vaccine contract indicates that history may repeat itself on this dimension.

Unlike World War II however, the potential inherent in this new sense of urgency has not been effectively harnessed into a coordinated biodefense R&D effort. History has also indicated that, as urgency subsides, so does this culture of collaboration. The present "war on terrorism" is by its very nature likely to be long and sustained; therefore, the biodefense apparatus that supports it must be durable as well.

The DOD and the IOM have offered a number of promising proposals that would effectively target and coordinate vaccine development efforts. As the details of these proposals are negotiated, it is important to be able to identify the elements that are essential to targeted vaccine development endeavors. While these proposals have been received with enthusiasm within the government, there does not appear to be a clear understanding about which recommendations are likely to generate high rates of vaccine innovation and why some recommendations might be more effective than others. For example, the administration's recent budget request designating the NIH as the lead-agency to coordinate biodefense R&D, is at odds with historical experience, which suggests that the NIH is currently not suited to carry-out targeted vaccine R&D.

Proposals contained within the Top Report and the IOM announcement, taken together, could provide the foundation for an effective governance structure as well as a new center of excellence for targeted vaccine research, development, and manufacturing activities. A governance structure of this sort could provide a mechanism to reunite lead-users with product developers and could also furnish a forum in which to teach vaccine research scientists the interdisciplinary skills required to bring vaccines through development. Adopting a governance structure of this sort would not merely harness the potential inherent in an atmosphere of urgency; it would provide a structure for inter-institutional and interdisciplinary cooperation, paving the way for the emergence of new and productive culture of collaboration.

Conclusions

Since the rise of the industrial research and development lab, academic approaches to the history of technological innovation have become intertwined with industrial history and have focused on the interplay of technological forces and capitalistic systems.[1] Within this framework, the thoughts and actions of the individual scientist within a particular cultural context appear less relevant and, increasingly, these studies have interpreted technological innovation as a rational function of economic incentives, individual firm capabilities, and available stock of "scientific knowledge" or "technological opportunities."[2]

Recent historical investigations of vaccine innovation are no exception to this tradition as they have analyzed innovation patterns with reference to the profit-maximizing behavior of commercial vaccine developers.[3] However, these studies were based on an inaccurate picture of innovation patterns (i.e. incomplete vaccine license data) and, consequently, may have over-emphasized the historical role of firm-based incentives. As Chapter One demonstrates, industrial innovation rates were at their highest in the 1940's, an era in which economic incentives were poor, before firms had built significant in-house R&D capabilities, and when technological opportunities for new vaccine development were modest. Conversely, Chapter Four demonstrates that innovation rates declined since the late 1970's, after all three factors improved; economic incentives improved (due to consolidation, product-line monopolies, and the passage of the Vaccine Compensation Act of 1986), investments in R&D capabilities increased, and technological opportunities abounded (due to advances in molecular biology and genetic engineering).

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[1] P. Uselding, "Business History and the History of Technology," *Business History Review* 54 (1980): 443-452.

[2] A. Chandler, *Scale and Scope; The Dynamics of Industrial Capitalism* (Cambridge: Harvard University Press, 1990); L. Reich, *The Making of American Industrial Research; Science and Business at GE and Bell, 1876-1926* (Cambridge: Cambridge University Press, 1985); D. Houndshell and J. Smith, *Science and Corporate Strategy: Du Pont R & D, 1902-1980* (New York: Cambridge University Press, 1988); E. Pugh, *Building IBM, Shaping an Industry and Its Technology* (Cambridge: MIT Press, 1984); G. Dosi, "Technological Paradigms and Technological Trajectories; A Suggested Interpretation of the Determinants and Directions of Technological Change," *Research Policy* 11 (1982): 147-162; R. Foster, "Timing Technological Transitions," ed. M. Horwitch, *Technology and the Modern Corporation: A Strategic Perspective* (New York: Pergamon Press, 1986).

[3] L. Galambos J. and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995); Office of Technology, *A Review of Selected Federal Vaccine and Immunization Policies: Based on Case Studies of Pneumococcal Vaccine* (Washington, D.C., 1979); Institute of Medicine, *Vaccine Supply and Innovation* (Washington, D.C.: National Academy Press, 1985); H. Grabowski, and J. Vernon, *The Search for New Vaccines* (Washington, D.C.: The AEI Press, 1997).

Given the inability of these factors to explain broad patterns of innovation in the vaccine industry, it becomes necessary to evaluate non-market factors existing outside of the firm that relate to the wider cultural context in which development decisions are made. These include 1.) the salience of disease-based national security and public health threats and the sense of urgency surrounding them, 2.) the presence of effective inter-institutional governance structures to coordinate vaccine R&D, and 3.) the strength of a military-industrial culture of collaboration.

All three factors were present during the 1940's. The perceived threat of disease to national security was well accepted. World War II vaccine development programs effectively harnessed this sense of urgency and coordinated the efforts of industry, academia, and the military to develop new vaccines. Finally, in what was a positive, yet unintended consequence, these programs engendered a productive culture of military-industrial collaboration for vaccine development.

The experience of participating in World War II vaccine development programs forged individual relationships and military-industrial networks that shaped postwar ideologies and practices within the vaccine industry and continued to stimulate innovation well after the war ended and the governance structure for vaccine R&D dissolved. Cold War anxieties during the 1950's and 1960's further reinforced this culture by driving DOD investments in vaccine R&D and by encouraging OSRD and WRAIR alumni in the industrial sector to accept military contracts despite economic disincentives.

The postwar expansion of Merck's vaccine division, along with the development of the meningitis and influenza vaccines, highlight the significant role that individuals and their cultural contexts continued to play in institutionally-based histories of technological development. These cases demonstrate the degree to which the beliefs, practices, and shared experiences of individuals such as Vannevar Bush, George Merck, Maurice Hilleman, James Sorrentino, and Donald Metzgar influenced historical patterns of vaccine development. Specifically, these cases highlight the enduring role that non-economic factors such as personal friendships, beliefs, and R&D practices played in shaping historical patterns of innovation in the postwar period.

By the late 1970's, the personal networks, ideologies, and R&D practices that supported a military-industrial culture of collaboration began to unravel. The salience of disease-related national security and public health threats diminished as the Cold War waned and as the incidence of infectious disease fell in the U.S.. In this environment, economic concerns predominated, and both industry and the military began to reduce investments in vaccine research. Furthermore, the end of the draft stemmed the flow of talented research scientists from universities to WRAIR and, in turn, from WRAIR to industry. As WRAIR began to lose its

reputation as a center of excellence for vaccine research, industry began to turn to the NIH for collaborative research partners and new hires. However, as the HIV/AIDS vaccine development program demonstrates, NIH-sponsored academic scientists were highly specialized and loosely organized and they proved less adept at targeted vaccine research initiatives than their military counterparts had been.

As these transformations to the post-Vietnam War landscape for vaccine R&D undermined the military-industrial culture of collaboration, two historically significant sources of vaccine innovation were effectively lost: the military's lead-user perspective and their interdisciplinary approach to vaccine R&D. Thus, by the 1980's, none of the factors I identify as having contributed to the high rates of innovation witnessed in the 1940's remained. In lieu of a sense of urgency surrounding disease threats, an effective governance structure, or a strong military-industrial culture of collaboration, it appears that the auspicious market characteristics of the 1980's and 1990's (i.e. improved economic incentives, technological opportunities, and firm capabilities) were not sufficient to raise innovation rates.

This perspective on the sources of innovation in the vaccine industry sheds light on contemporary issues raised by the airliner and anthrax attacks of 2001. As federal planners scramble to find ways to protect the nation from a growing list of feared biological threats, many are wondering about the best way to facilitate the vaccine development process. Indeed, some proposals would have the government coordinate and control aspects of this vaccine development process. Is there any wisdom in this approach?

The answer to this question depends on one's historical perspective on the sources of innovation in the vaccine industry. Galambos and Sewell, for example, conclude their historical analysis of vaccine innovation in favor of the status quo; they favor a mixed system of industry, government, and academic players, each of whom responds independently to a different set of economic, political, and scientific incentives. In what amounts to a laissez-faire approach to vaccine innovation, they argue that this tripartite system, when left to its own devices, best serves the public's long-term interest in disease control.[4] Any study based on publicly available vaccine license data would support this conclusion because this data systematically over-represents innovation rates in recent years, giving the impression that the vaccine industry has, indeed, effectively responded to economic and technological opportunities for vaccine development as they arose. However, as my research shows, these innovation patterns are not always consistent with such interpretations and require further explanation.

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[4] L. Galambos J. and Sewell, *Networks of Innovation: Vaccine Development at Merck, Sharp & Dohme, and Mulford, 1895-1995* (Cambridge: Cambridge University Press, 1995). p. 250.

The laissez-faire system that Galambos and Sewell advocate met with high rates of innovation in the postwar period but, as Chapter Three reveals, the success of this system cannot be attributed to the inherent rationality of free-markets. Rather, this system was able to function ungoverned only insofar as the informal culture that supported military-industrial collaboration remained intact. Within this culture, the concept of the vaccine as something above market transactions prevailed, and incentives ranging from patriotism and social obligation to opportunism offset the inherent lack of economic incentives for industrial participation in vaccine development. Dependence on a laissez-faire system therefore amounts to a dependence on a unique culture of collaboration that began to unravel during the 1970's.

There is early evidence that, in the wake of the terrorist attacks of 2001, many of the conditions that once supported military-industrial collaboration during and after World War II may return. Anthrax attacks raised the visibility of biological threats and reinstated the view of vaccines from that of an economic commodity to that of an instrument essential to national security and public health. In this atmosphere of urgency and patriotism, industry has demonstrated a willingness to assist the government in low-margin vaccine production, and the Bush Administration has requested unprecedented sums for vaccine research at NIH.

Unlike World War II, however, there is no governing structure in place to harness the R&D efforts of industrial, academic, and government labs. Nevertheless, vaccine innovation proceeded apace in the absence of governance structure in the postwar era; could it not do so now?

The answer is two-fold. First, transformations to the landscape for vaccine R&D illustrated in Chapter Four have diminished the capacity of the vaccine development community to self-organize an effective response to targeted vaccine development needs. For example, the personal networks of OSRD and WRAIR alumni that facilitated military-industrial collaboration in the postwar period no longer operate. Industrial vaccine research scientists today are more likely to hail from academia or the NIH than the military and are less likely to demonstrate those interdisciplinary skills required for targeted vaccine development that WRAIR's "science integrators" once possessed. Further, the task of a would-be "science integrator" is more complicated today than it was before vaccine development expertise became distributed among a wider variety of institutions that now include biotechnology companies and the NIH in addition to the military and the pharmaceutical industry. Finally, the 2003 budget request indicates that the Bush Administration intends to concentrate vaccine development initiatives within the NIH. In the absence of a plan to reorganize research practices within the NIH, this move is likely to

further undermine the type of targeted R&D required to develop biodefense vaccines within a reasonable time frame.

Second, given the level of distrust and separation that developed between the military, the pharmaceutical industry and Congress since the 1970's, productive collaboration is unlikely to ensue in the absence of an effective governance structure. Although a sense of urgency will inspire collaborative efforts in the short term, history demonstrates that, as urgency subsides, so too will this spirit of cooperation. Given the protracted time frame over which the nation is likely to face bioterrorist threats, the government will have to call on industry to develop and supply biodefense vaccines for aging stockpiles long after today's sense of exigency has dissipated. This situation demands more durable solutions in the form of a governance structure for targeted vaccine development.

Since learning that terrorists had hijacked the microbe, disparate groups within the military, industry, and academia have demonstrated a willingness to dedicate the resources of time and money and to put aside bureaucratic differences in order to devise novel and creative solutions to the persistent problems of vaccine innovation and supply. A number of promising proposals are already on the table. The Institute of Medicine, for example, has recommended an inter-agency governance structure that would coordinate vaccine R&D policies with civilian and military operational objectives for biodefense. This proposed governing body would also set an agenda for a targeted research, development and manufacturing center with civilian and military operational objectives for biodefense. Similarly, the DOD-sponsored Top Report has recommended building a government-owned contractor-operated facility that would serve as a center for research, development, and manufacturing activities for biodefense vaccines. These facilities would rely on a combination of public and private sector development expertise, industry's manufacturing skills and a reliable flow of public funds to supplement production when the social returns from developing a particular vaccine exceed the financial returns from doing so.

Many of the details of these proposals still need to be determined and clear boundaries need to be set so that government sponsored vaccine development programs do not encroach on viable vaccine markets. In principle, however, these proposals offer a solution to the governance problems that have beset vaccine development since the informal culture of military-industrial collaboration lost force in the late 1970's. If history is any guide, efforts to coordinate military and industrial scientists in this manner will provide a framework within which productive collaborative relationships can flourish, yielding dramatic improvements in vaccine innovation and supply.

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Appendix 1: Vaccine License Data

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1903	Bayer Corporation	Diphtheria Antitoxin	08/21/1903	11/30/1970	I	All Bayer listings were originally licensed to Cutter Labs in Berkeley, CA. Bayer did not acquire Cutter until 1974.
1903	Bayer Corporation	Smallpox Vaccine	08/21/1903	06/11/1973	I	
1903	Pocono Laboratories	Smallpox Vaccine	08/21/1903	07/01/1908	P	Glycerinated vaccinia virus; scarification with bifurcated needle (J. Widmer, *The Spirit of Swiftwater*, Connaught Labs, 1997.)
1907	Parke-Davis	Diphtheria Antitoxin	11/15/1907	11/24/1969	I	
1907	Parke-Davis	Tetanus Antitoxin	11/15/1907	03/21/1973	I	
1908	Lederle Laboratories	Diphtheria Antitoxin	00/00/1908	01/19/1914	I	PHS, *Biological Products*, Publication 50, 1908
1908	Lederle Laboratories	Tetanus Antitoxin	00/00/1908		I	PHS, *Biological Products*, Publication 50, 1908
1908	Lederle Laboratories	Typhoid Vaccine	00/00/1908		C	PHS, *Biological Products*, Publication 50, 1908
1911	Cutter Biological	Plague Vaccine	00/00/1911	05/14/1942	C	
1912	Slee Laboratories	Diphtheria Antitoxin	00/00/1912	12/12/1927	I	*Licensed Biologicals*, Slee Laboratories, 1912: AP Archives
1912	Slee Laboratories	Smallpox Vaccine	07/12/1912		LT	Transferred from Pocono Labs (*Licensed Biologicals*, Slee Laboratories, 1912: AP Archives)
1912	Slee Laboratories	Tetanus Antitoxin	00/00/1912		I	*(Licensed Biologicals*, Slee Laboratories, 1912: AP Archives) also produced gas gangrene antitoxin for armed forces in 1913-1914 although there is no record of a license
1914	Bayer Corporation	Pertussis Vaccine	08/03/1914	10/30/1970	C	
1914	Bayer Corporation	Tetanus Antitoxin	08/03/1914	10/30/1970	I	
1914	Lederle Laboratories	Diphtheria Antitoxin	01/19/1914	06/13/1977	LT	
1914	Lederle Laboratories	Pertussis Vaccine	01/19/1914	05/29/1980	C	
1914	Lederle Laboratories	Tetanus Antitoxin	01/19/1914	05/05/1976	I	
1914	Parke-Davis	Pertussis Vaccine	00/00/1914	04/16/1952	C	
1914	Wyeth	Cholera Vaccine	00/00/1914		I	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
	Laboratories					
1914	Wyeth Laboratories	Typhoid Vaccine	00/00/1914		I	for military use only; acetone-killed and dried
1914	Wyeth Laboratories	Typhoid Vaccine	00/00/1914		I	
1915	Eli Lilly Laboratory	Pertussis Vaccine	03/31/1915	03/07/1978	I	
1915	Eli Lilly Laboratory	Rabies Vaccine	06/07/1915	08/11/1982	I	
1916	Bayer Corporation	Typhoid Vaccine	03/06/1916	10/30/1970	I	
1916	Parke-Davis	Typhoid Vaccine	03/24/1916	02/24/1969	I	
1917	Eli Lilly Laboratory	Cholera Vaccine	10/31/1917	06/07/1979	C	inactivated- first license reported by CBER- although there is some evidence that Wyeth was licensed to produce this vaccine in 1914 (PHS, *Biological Products*, Publication 50, 1914)
1917	MPHBL	Diphtheria Antitoxin	03/20/1917	10/26/1988	I	Massachusetts Public Health Biological Laboratories
1917	MPHBL	Smallpox Vaccine	03/20/1917	12/22/1976	I	
1917	MPHBL	Typhoid Vaccine	03/20/1917	10/26/1988	I	
1918	Parke-Davis	Perfringens Antitoxin	09/23/1918	03/21/1973	C	
1926	Merrell-National Laboratories	Pertussis Vaccine	10/16/1926	01/03/1978	I	National Drug bought Slee Labs in 1926. National did not merge with Merrell-Richardson until 1961, but CBER begins listing National in its merged form at this time.
1926	MBPI	Diphtheria Antitoxin	05/17/1926	05/11/1987	I	Michigan Biologic Products Institute
1926	MBPI	Typhoid Vaccine	07/26/1926	06/25/1985	I	
1927	Merrell-National Laboratories	Diphtheria Antitoxin	12/12/1927	01/03/1978	LT	
1927	Merrell-National Laboratories	Tetanus Antitoxin	12/14/1927	01/03/1978	LT	
1927	Merrell-National Laboratories	Typhoid Vaccine	01/14/1927		I	*Biologics by National*, The National Drug Company (1956): AP Archives
1927	Parke-Davis	Diphtheria Toxoid	08/17/1927	10/14/1981	P	active immunization
1928	Bayer Corporation	Diphtheria Toxoid	02/01/1928	10/30/1970	I	
1929	Bayer Corporation	Perfringens Antitoxin	06/14/1929	06/14/1965	I	
1929	Merrell-National Laboratories	Diphtheria Toxoid	09/28/1929	01/03/1978	I	
1932	Dow Chemical	Pertussis Vaccine	10/01/1932	06/07/1977	I	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
	Company					
1932	MPHBL	Diphtheria Toxoid	07/07/1932	05/19/1980	I	
1933	Lederle Laboratories	Staphylococcus Toxoid	04/03/1933	05/21/1980	C	
1933	Merck and Company	Tetanus Toxoid	12/11/1933	01/31/1986	P	active immunization
1933	Parke-Davis	Tetanus Toxoid	00/00/1933	09/25/1940	P	A. Beneson, "Immunization and Military Medicine," *Review of Infectious Diseases* 6, 1 (1984).
1934	Dow Chemical Company	Diphtheria Toxoid	09/18/1934	06/07/1977	I	
1934	Merrell-National Laboratories	Tetanus Toxoid	05/25/1934	01/03/1978	I	
1934	Merrell-National Laboratories	Tetanus Toxoid Adsorbed	05/25/1934	01/03/1978	P	first use of alum adjuvant- improved immune response; A. Beneson, "Immunization and Military Medicine," *Review of Infectious Diseases* 6, 1 (1984); *Biologics by National*, The National Drug Company (1956): AP Archives.
1935	Eli Lilly Laboratory	Tetanus Toxoid	12/10/1935	06/07/1979	I	
1935	Lederle Laboratories	Tetanus Toxoid	06/15/1935	03/04/1994	I	
1935	MBPI	Pertussis Vaccine	11/22/1935	02/03/1977	I	
1936	Dow Chemical Company	Tetanus Toxoid	08/01/1936	06/07/1977	I	
1936	Parke-Davis	Staphylococcus Toxoid	06/06/1936	03/21/1973	I	
1936	Texas Department of Health Resources	Diphtheria Toxoid	01/06/1936	02/06/1979	I	
1937	Lederle Laboratories	Smallpox Vaccine	03/01/1937	05/24/1978	I	
1937	Merrell-National Laboratories	Smallpox Vaccine	03/05/1937	01/03/1978	I	
1937	MBPI	Smallpox Vaccine	03/03/1937	06/25/1985	I	
1937	Parke-Davis	Staphylococcus Antitoxin	11/27/1937	08/08/1944	I	
1940	Bayer Corporation	Tetanus Toxoid	09/25/1940	11/01/1979	I	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1940	Parke-Davis	Tetanus Toxoid	05/04/1940	10/14/1981	I	
1941	Lederle Laboratories	Botulism Antitoxin	10/19/1941	03/12/1981	C	
1941	Lederle Laboratories	Cholera Vaccine	12/26/1941	10/23/1996	I	
1942	Bayer Corporation	Plague Vaccine	05/14/1942	05/24/1995	P	whole cell, formalin inactivated. Earlier vaccine of unproven efficacy
1942	Eli Lilly Laboratory	Typhus Vaccine	00/00/1942	06/07/1979	P	WJ Draper (acting Surgeon General) to Senator David Walsh, Feb 4, 1942 (NA: RG 443, E. 1 , dec. file #0470-132)
1942	Lederle Laboratories	Typhus Vaccine	00/00/1942	00/00/1967	P	WJ Draper (acting Surgeon General) to Senator David Walsh, Feb 4, 1942 (NA: RG 443, E. 1 , dec. file #0470-132)
1942	Sharp and Dohme	Typhus Vaccine	00/00/1942		P	WJ Draper (acting Surgeon General) to Senator David Walsh, Feb 4, 1942 (NA: RG 443, E. 1 , dec. file #0470-132)
1942	Lederle Laboratories	Rocky Mountain Spotted Fever Vaccine	04/13/1942	06/11/1979	C	
1942	Merrell-National Laboratories	Cholera Vaccine	02/27/1942	03/25/1976	I	
1942	Parke-Davis	Rabies Vaccine	08/05/1942	03/21/1973	P	non-nervous tissue origin
1942	Parke-Davis	Typhus Vaccine	03/25/1942	08/05/1947	P	Col. A. Long, "The Army Immunization Program", in *Preventative Medicine During WWII, Vol. III*, (OSG, Dept. of the Army: WDC, 1955).
1944	Wyeth Laboratories	Diphtheria Toxoid	05/19/1944	09/11/1970	I	
1944	Wyeth Laboratories	Smallpox Vaccine	05/19/1944		P	Lyophilized calf lymph vaccine- Wyeth ceased commercial manufacture in 1982 but maintains license
1944	Wyeth Laboratories	Tetanus Toxoid	05/19/1944		I	
1945	Eli Lilly Laboratory	Influenza Virus Vaccine	11/09/1945	04/11/1977	C	
1945	Lederle Laboratories	Influenza Virus Vaccine	12/07/1945		C	Flu-immune; split viron
1945	Merck and Company	Influenza Virus Vaccine	11/30/1945	03/15/1995	C	
1945	Parke-Davis	Influenza Virus Vaccine	11/26/1945	04/20/1998	C	Fluogen; split viron
1947	Merrell-National Laboratories	Influenza Virus Vaccine	09/16/1947	01/03/1978	I	Sharples purified, grown in chick embryo. National also manufactured Japanese Encephalitis vaccine on a government

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
						contract, not licensed
1948	Bayer Corporation	Pertussis Vaccine Adsorbed	09/03/1948	10/30/1970	P	More immunogenic
1948	Sharp and Dohme	Rocky Mountain Spotted Fever	00/00/1948		I	Leonard Scheele (SG) to Dr. Underwood (Sec. State Board of Health, Mississippi) Sept. 27, 1948 (NA: RG 443, E1., decimal file # 0470)
1948	Squibb and Sons	Pneumococcal Vaccine, Polyvalent	00/00/1948	00/00/1954	R	first active immunization against pneumococcal pneumonia (C) and first polysaccharide vaccine (P) M. Heidelberger, "A 'Pure' Organic Chemist's Downward Path" *Annual Review of Biochemistry*, 48 (1979):1-21.
1949	Bayer Corporation	Diphtheria and Tetanus Toxoids Adsorbed	05/04/1949	10/30/1970	A	
1949	Bayer Corporation	Diphtheria and Tetanus Toxoids and Pertussis Vaccine	05/04/1949	10/30/1970	A	
1949	Bayer Corporation	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	05/04/1949	10/30/1970	P	This license was issued to Cutter Labs although CBER lists it under Bayer
1949	Bayer Corporation	Diphtheria Toxoid Adsorbed	05/04/1949	10/30/1970	P	improved immune response- first recorded use of alum according to CBER
1949	Bayer Corporation	Diphtheria Toxoid and Pertussis Vaccine Adsorbed	05/04/1949	10/30/1970	A	
1949	Bayer Corporation	Gas Gangrene Polyvalent Antitoxin	05/04/1949	06/14/1965	A	A. Beneson, "Immunization and Military Medicine," *Review of Infectious Diseases*, 6, 1 (1984).
1949	Bayer Corporation	Tetanus and Gas Gangrene Polyvalent Antitoxin	05/04/1949	06/14/1965	A	
1949	Bayer Corporation	Tetanus Toxoid Adsorbed	05/04/1949	10/30/1970	I	
1949	Lederle Laboratories	Diphtheria and Tetanus Toxoids Adsorbed	07/26/1949	07/29/1970	A	OTA, *A Review of Selected Federal Vaccine and Immunization Policies,* (1979). Appendix 2: "Profile of vaccine establishments and products currently licensed in the U.S. (1979)."
1949	Lederle Laboratories	Gas Gangrene Polyvalent Antitoxin	05/04/1949	03/12/1981	A	OTA, *A Review of Selected Federal Vaccine and Immunization Policies,* (1979). Appendix 2: "Profile of vaccine establishments and products currently licensed in the U.S. (1979)."

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1949	Lederle Laboratories	Tetanus and Gas Gangrene Polyvalent Antitoxin	05/04/1949	05/05/1976	A	
1949	MPHBL	Tetanus Toxoid	05/16/1949	10/11/1989	I	
1949	Merrell-National Laboratories	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	05/16/1949	01/03/1978	P	Developed by Bolyn in 1944 at National Drug - used a smaller fraction of alum as precipitant for toxoid- other preparations used larger amounts (1/2%) which produced side effects (J. Widmer, *The Spirit of Swiftwater*, Connaught Labs, 1997).
1949	Parke-Davis	Tetanus and Gas Gangrene Polyvalent Antitoxin	04/08/1949	03/21/1973	A	
1950	Eli Lilly Laboratory	Mumps Vaccine	01/27/1950	04/11/1977	C	inactivated
1950	Lederle Laboratories	Mumps Vaccine	06/22/1950	05/24/1978	C	inactivated
1950	MPHBL	Tetanus Antitoxin	05/11/1950	01/10/1994	I	
1950	MBPI	Diphtheria and Tetanus Toxoids Adsorbed	05/23/1950	08/27/1970	I	PHS, *Biological Products*, revised 1952.
1950	Texas Department of Health Resources	Typhoid Vaccine	07/11/1950	02/06/1979	I	
1950	University of Illinois	BCG Vaccine	07/07/1950	05/29/1987	C	derived from original BCG strain
1951	Bayer Corporation	Diphtheria and Tetanus Toxoids	06/01/1951	10/30/1970	I	
1951	Texas Department of Health Resources	Diphtheria and Tetanus Toxoids Adsorbed	05/11/1951	07/27/1970	I	PHS, *Biological Products*, revised 1952.
1952	Eli Lilly Laboratory	Streptococcus Vaccine	04/17/1952	10/27/1978	C	
1952	Merck and Company	Cholera Vaccine	09/04/1952	01/31/1986	P	
1952	Parke-Davis	Diphtheria and Tetanus Toxoids	07/29/1952	10/14/1981	I	
1952	Parke-Davis	Diphtheria and	07/29/1952	10/14/1981	I	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		Tetanus Toxoids and Pertussis Vaccine Adsorbed				
1952	Parke-Davis	Diphtheria Toxoid Adsorbed	02/20/1952	10/14/1981	I	
1952	Parke-Davis	Pertussis Vaccine	04/16/1952	10/14/1981	I	
1952	Parke-Davis	Pertussis Vaccine Adsorbed	02/20/1952	10/14/1981	I	
1952	Parke-Davis	Tetanus Toxoid Adsorbed	07/08/1952	10/14/1981	I	
1952	Wyeth Laboratories	Cholera Vaccine	08/16/1952		P	agar grown, phenol-inactivated
1952	Wyeth Laboratories	Pertussis Vaccine	07/16/1952	05/19/1987	I	
1952	Wyeth Laboratories	Typhoid Vaccine	07/16/1952		I	
1953	Merrell-National Laboratories	Yellow Fever Vaccine	05/22/1953	01/03/1978	LT	(live, 17D virus) assumed work from the PHS Internal Memo, National Drug Company, (1955): AP Archives
1954	Eli Lilly Laboratory	Typhoid Vaccine	02/04/1952	11/13/1978	I	
1954	Texas Department of Health Resources	Pertussis Vaccine	12/27/1954	02/06/1979	I	
1954	Wyeth Laboratories	Diphtheria and Tetanus Toxoids Adsorbed	12/17/1954	09/11/1970	I	Plotkin Appendix
1955	Bayer Corporation (Cutter)	Poliovirus Vaccine Inactivated (Monkey Kidney Cell)	04/12/1955	12/28/1978	C	
1955	Merck and Company	Poliovirus Vaccine Inactivated (Monkey Kidney Cell)	04/12/1955	08/29/1980	C	
1955	Merrell-National Laboratories	Diphtheria and Tetanus Toxoids Adsorbed for Adult Use	03/07/1955	01/03/1978	I	
1955	Pittman Moore	Poliovirus Vaccine	04/12/1955		C	J. Smith, *Patenting the Sun*, (William Morrow Co., NYC, 1990)

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		Inactivated				
1955	Wyeth	Poliovirus Vaccine Inactivated	04/12/1955		C	J. Smith, *Patenting the Sun*, (William Morrow Co., NYC, 1990)
1955	Eli Lilly Laboratory	Poliovirus Vaccine Inactivated	04/12/1955		C	J. Smith, *Patenting the Sun*, (William Morrow Co., NYC, 1990)
1955	Parke-Davis	Poliovirus Vaccine Inactivated (Monkey Kidney Cell)	04/12/1955	07/29/1980	C	
1956	Bayer Corporation	Diphtheria and Tetanus Toxoids Adsorbed for Adult Use	11/16/1956	11/30/1970	I	
1956	MBPI	Diphtheria Toxoid Adsorbed	08/18/1956	08/27/1970	I	Plotkin Appendix
1957	Parke-Davis	Adenovirus Vaccine	09/23/1957	07/29/1963	C	inactivated
1959	Parke-Davis	Adenovirus and Influenza Virus Vaccines Combined Aluminum Phosphate Adsorbed	09/22/1959	07/29/1963	A	inactivated
1959	Parke-Davis	Diphtheria, Tetanus Toxoids, Pertussis, Poliomyelitis Vaccines Adsorbed	03/25/1959	10/14/1981	A	
1959	Texas Department of Health Resources	Tetanus Toxoid	09/22/1959	02/06/1979	I	
1960	Merck and Company	Poliovirus Vaccine Inactivated	07/05/1960		I	Purivax; higher purity and potency than other available IPV's (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1960	Parke-Davis	Poliomyelitis Vaccine Adsorbed	10/04/1960	07/29/1980	P	
1961	Merrell-National Laboratories	Smallpox Vaccine	10/15/1961	01/03/1978	I	freeze-dried, for government and domestic use AP Archives
1961	Pfizer	Poliovirus Live Oral Type 2	10/06/1961	06/12/1979	P	
1961	Pfizer	Poliovirus Live Oral	03/27/1962	06/12/1979	P	OTA, *A Review of Selected Federal Vaccine and Immunization*

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes	
		Type 3				*Policies,* (1979). Appendix 2 "Profile of vaccine establishments and products currently licensed in the U.S. (1979)."	
1961	Pfizer	Poliovirus Live Oral Type 1	08/17/1961	06/12/1979	P	Sabin	
1961	Wyeth Laboratories	Influenza Virus Vaccine	12/13/1961		I	Flushield; split viron	
1962	Lederle Laboratories	Poliovirus Live Oral Type 1	03/27/1962		I		
1962	Lederle Laboratories	Poliovirus Live Oral Type 2	03/27/1962		I		
1962	Lederle Laboratories	Poliovirus Live Oral Type 3	03/27/1962		I	OTA, *A Review of Selected Federal Vaccine and Immunization Policies,* (1979). Appendix 2 "Profile of vaccine establishments and products currently licensed in the U.S. (1979)."	
1963	Lederle Laboratories	Poliovirus Live Oral Trivalent	06/25/1963	10/02/1985	A	Orimune; Sabin Strains types 1,2,3	
1963	Merck and Company	Measles Virus Vaccine Live	03/21/1963		C	Rubeovax; Live Attenuated- derived from Ender's Edmonston strain- propagated in chick embryo cell cultures	
1963	Merck and Company	Typhoid Vaccine	04/25/1963	01/31/1986	I		
1963	Parke-Davis	Diphtheria, Tetanus Toxoids, Pertussis, Poliomyelitis Vaccines Adsorbed	12/20/1963	10/14/1981	I		
1965	Dow Chemical Company	Measles Virus Vaccine Live	02/05/1965	06/21/1978	I	cultured in dog kidney cells, withdrawn because too reactogenic	
1965	Merck and Company	Smallpox Vaccine	09/21/1965	07/29/1980	I		
1966	Lederle Laboratories	Measles Virus Vaccine Live	05/03/1966	05/21/1980	I		
1966	Pfizer	Poliovirus Live Oral Trivalent	10/28/1966	06/12/1979	I		
1967	Connaught Laboratories Inc	BCG Vaccine	03/31/1967	05/21/1990	I	same as 1950 vaccine	
1967	Connaught Laboratories Ltd	Smallpox Vaccine	10/23/1967	04/01/1980	I		
1967	Lederle Laboratories	Typhus Vaccine	05/24/1967	11/20/1980	P		citation
1967	Massachusetts	Diphtheria and	10/18/1967	07/27/1970	I		citation

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
	Public Health Biological Laboratories	Tetanus Toxoids Adsorbed				
1967	Merck and Company	Measles Live and Smallpox Vaccine	12/17/1967	03/12/1987	A	combined with Dryvax from Wyeth
1967	Merck and Company	Mumps Virus Vaccine Live	12/28/1967	01/06/1986	P	Mumpsvax; first live attenuated mumps vaccines
1967	MBPI	Pertussis Vaccine Adsorbed	10/12/1967	11/12/1998	I	
1968	Bayer Corporation	Cholera Vaccine	10/03/1968	10/30/1970	I	
1968	Connaught Laboratories	Botulism Antitoxin	08/16/1968	02/24/2000	I	
1968	Merck and Company	Measles Virus Vaccine Live	11/26/1968	01/06/1986	I	Attenuvax; more attenuated version: 14 additional passages of Rubeovax produced the Moraten strain(*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1969	Merck and Company	Rubella Virus Vaccine Live	06/09/1969	09/18/1978	C	Mervax II; live attenuated virus
1969	Phillips Roxanne Laboratories	Rubella Virus Vaccine Live	12/09/1969	01/06/1986	C	Plotkin Appendix
1970	Dow Chemical Company	Diphtheria and Tetanus Toxoids Adsorbed	09/11/1970	06/07/1977	LT	name change
1970	Dow Chemical Company	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	09/11/1970	06/07/1977	LT	name change
1970	Dow Chemical Company	Diphtheria Toxoid and Pertussis Vaccine Adsorbed	09/11/1970	06/07/1977	LT	name change
1970	Dow Chemical Company	Tetanus Toxoid Adsorbed	09/01/1970	06/07/1977	LT	name change
1970	Eli Lilly Laboratory	Diphtheria and Tetanus Toxoids	09/09/1970	06/07/1979	LT	name change
1970	Eli Lilly Laboratory	Diphtheria and Tetanus Toxoids Adsorbed	09/09/1970	06/07/1979	LT	name change: R. Rader, *Biopharma* (Rockville: Biotechnology Information Institute, 2001).

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1970	Eli Lilly Laboratory	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	09/09/1970	12/02/1985	LT	name change
1970	Eli Lilly Laboratory	Tetanus Toxoid Adsorbed	09/09/1970	06/07/1979	LT	name change
1970	Lederle Laboratories	Diphtheria and Tetanus Toxoids Adsorbed	07/29/1970		LT	name change
1970	Lederle Laboratories	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	07/24/1970	08/14/1998	LT	Tri-immunol; name change
1970	Lederle Laboratories	Tetanus Toxoid Adsorbed	08/29/1970		LT	name change
1970	MPHBL	Diphtheria and Tetanus Toxoids Adsorbed	07/27/1970	08/03/2000	LT	name change
1970	MPHBL	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	07/27/1970	12/22/1998	LT	name change
1970	MPHBL	Tetanus Toxoid Adsorbed	07/29/1970		LT	name change
1970	Merck and Company	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	08/31/1970	01/31/1986	LT	name change
1970	Merck and Company	Rubella and Mumps Virus Vaccine Live	08/30/1970	01/06/1986	A	Biavax II
1970	Merck and Company	Diphtheria and Tetanus Toxoids Adsorbed for Adult Use	08/31/1970	01/31/1986	LT	name change
1970	Merck and Company	Tetanus Toxoid Adsorbed	08/31/1970	01/31/1986	LT	name change
1970	Merrell-National Laboratories	Diphtheria and Tetanus Toxoids and	10/15/1970	01/03/1978	LT	name change

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1970	Merrell-National Laboratories	Pertussis Vaccine Influenza Virus Vaccine bivalent	04/10/1970	06/07/1979	P	Fluzone; More purified due to ultracentrifuge. First use of automated egg harvesting J. Widmer, *The Spirit of Swiftwater* (Swiftwater: Connaught Laboratories, 1997).
1970	Merrell-National Laboratories	Tetanus Toxoid Adsorbed	10/15/1970	01/03/1978	LT	name change
1970	MBPI	Anthrax Vaccine Adsorbed	11/04/1970	11/12/1998	I	
1970	MBPI	Diphtheria and Tetanus Toxoids Adsorbed	08/27/1970	11/12/1998	LT	name change
1970	MBPI	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	08/27/1970	11/12/1998	LT	name change
1970	MBPI	Diphtheria Toxoid Adsorbed	08/27/1970	11/12/1998	LT	name change
1970	MBPI	Tetanus Toxoid Adsorbed	08/27/1970	11/12/1998	LT	name change
1970	Smith Kline Beecham	Rubella Virus Vaccine Live	03/12/1970	10/05/1982	I	
1970	Texas Department of Health Resources	Diphtheria and Tetanus Toxoids Adsorbed	07/27/1970	02/06/1979	LT	name change
1970	Texas Department of Health Resources	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	07/27/1970	02/06/1979	LT	name change
1970	Wyeth Laboratories	Diphtheria and Tetanus Toxoids Adsorbed	09/11/1970		LT	name change
1970	Wyeth Laboratories	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	09/11/1970		LT	name change
1970	Wyeth	Diphtheria Toxoid	09/11/1970	05/19/1987	LT	name change

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
	Laboratories	Adsorbed				
1970	Wyeth Laboratories	Tetanus Toxoid Adsorbed	09/11/1970		LT	name change
1971	Merck and Company	Measles and Rubella Vaccine Live	04/22/1971	09/18/1978	A	MR Vax II
1971	Merck and Company	Measles, Mumps and Rubella Virus Vaccine Live	04/22/1971	09/18/1978	A	MMR Vax II
1973	Merck and Company	Measles and Mumps Vaccine Live	07/18/1973	01/06/1986	A	MM Vax
1974	Dow Chemical Company	Measles and Rubella Vaccine Live	04/17/1974	06/21/1978	I	
1974	Dow Chemical Company	Measles, Mumps and Rubella Virus Vaccine Live	04/17/1974	06/21/1978	I	
1974	Dow Chemical Company	Mumps Virus Vaccine Live	04/17/1974	06/21/1978	I	
1974	Dow Chemical Company	Rubella Vaccine Live	03/01/1974	06/21/1978	I	
1974	Merck and Company	Meningococcal Polysaccharide Vaccine, Group C	04/02/1974	03/15/1995	C	
1975	Merck and Company	Meningococcal Polysaccharide Vaccine, Group A	07/11/1975	03/15/1995	C	
1975	Merck and Company	Meningococcal Polysaccharide Vaccine, Groups A and C Combined	10/06/1975	03/15/1995	A	
1975	Merrell-National Laboratories	Meningococcal Polysaccharide Vaccine, Group A	09/19/1975	01/03/1978	C	
1975	Merrell-National Laboratories	Meningococcal Polysaccharide Vaccine, Group C	07/11/1975	01/03/1978	C	
1976	Merrell-National Laboratories	Meningococcal Polysaccharide Vaccine, Groups A	12/13/1976	01/03/1978	A	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		and C Combined				
1977	Merck and Company	Pneumococcal Vaccine, Polyvalent	11/21/1977	01/06/1986	A	Pneumovax; new strains- 14-valent
1978	Connaught Laboratories	Diphtheria Antitoxin	01/03/1978	12/09/1999	LT	
1978	Connaught Laboratories	Influenza Virus Vaccine	01/03/1978	12/09/1999	LT	Fluzone
1978	Connaught Laboratories	Tetanus Antitoxin	01/03/1978	09/22/1980	LT	from Merrell-National
1978	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids and Pertussis Vaccine	01/03/1978	10/29/1982	LT	from Merrell-National J. Widmer, *The Spirit of Swiftwater* (Swiftwater: Connaught Laboratories, 1997).
1978	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	01/03/1978	12/09/1999	LT	from Merrell-National
1978	Connaught Laboratories Inc	Diphtheria Toxoid	01/03/1978	06/21/1994	LT	
1978	Connaught Laboratories Inc	Meningococcal Polysaccharide Vaccine, Group A	01/03/1978	12/09/1999	LT	Menomune A; from Merrell-National
1978	Connaught Laboratories Inc	Meningococcal Polysaccharide Vaccine, Group C	01/03/1978	12/09/1999	LT	Menomune C; from Merrell-National
1978	Connaught Laboratories Inc	Meningococcal Polysaccharide Vaccine, Groups A and C Combined	01/03/1978	12/09/1999	LT	Menomune A/C; from Merrell-National
1978	Connaught Laboratories Inc	Pertussis Vaccine	01/03/1978	12/19/1997	LT	from Merrell-National
1978	Connaught Laboratories Inc	Smallpox Vaccine	01/03/1978	12/19/1997	LT	
1978	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids Adsorbed for Adult Use	01/03/1978	12/09/1999	LT	from Merrell-National
1978	Connaught Laboratories Inc	Tetanus Toxoid	01/03/1978	12/09/1999	LT	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1978	Connaught Laboratories Inc	Tetanus Toxoid Adsorbed	01/03/1978	12/09/1999	LT	from Merrell-National
1978	Connaught Laboratories Inc	Yellow Fever Vaccine	01/03/1978	12/09/1999	LT	YF-Vax
1978	Merck and Company	Measles and Rubella Vaccine Live	09/18/1978	01/06/1986	I	reformulated to include RA 27/3 strain from the Wistar Institute(*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1978	Merck and Company	Measles, Mumps and Rubella Virus Vaccine Live	09/18/1978	01/06/1986	I	MMR Vax II; reformulated to include RA 27/3 strain from the Wistar Institute(*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1978	Merck and Company	Rubella Virus Vaccine Live	09/18/1978		I	replace with RA 27/3 strain developed at Wistar Institute(*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1979	Lederle Laboratories	Pneumococcal Vaccine, Polyvalent	08/15/1979	01/06/1986	A	Pnu-imune 23
1980	Wyeth Laboratories	Adenovirus Vaccine Live Oral Type 4	07/01/1980		P	ceased manufacture in '96
1980	Wyeth Laboratories	Adenovirus Vaccine Live Oral Type 7	07/01/1980		P	ceased manufacture in '96
1981	Connaught Laboratories Inc	Meningococcal Polysaccharide Vaccine, Groups A,C,Y, W135 Combined	11/23/1981	12/09/1999	A	Menomune A/C/Y/W-135
1981	Merck and Company	Hepatitis B Vaccine	11/16/1981	03/15/1995	C	
1982	Merck and Company	Meningococcal Polysaccharide Vaccine, Groups A,C,Y, W135 Combined	12/14/1982	03/15/1995	A	
1982	Wyeth Laboratories	Rabies Vaccine	08/11/1982	08/07/1986	I	
1983	Merck and Company	Pneumococcal Vaccine, Polyvalent	07/07/1983	01/06/1986	A	incorporate more strains- 23 valent
1984	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids Adsorbed	09/18/1984	12/09/1999	LT	

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1985	Connaught Laboratories Inc	Haemophilus b Polysaccharide Vaccine	12/20/1985	12/09/1999	C	HibVax
1985	Lederle Laboratories	Haemophilus b Polysaccharide Vaccine	12/20/1985	10/23/1996	C	Hib-immune
1985	Lederle Laboratories	Poliovirus Live Oral Trivalent	10/02/1985		LT	name change: R. Rader, *Biopharma* (Rockville: Biotechnology Information Institute, 2001).
1985	Praxis Biologics	Haemophilus b Polysaccharide Vaccine	04/12/1985	07/08/1994	C	b-CAPSA-1
1986	Lederle Laboratories	Pneumococcal Vaccine, Polyvalent	01/06/1986		LT	name change
1986	Merck and Company	Hepatitis B Vaccine (Recombinant)	07/23/1986		P	Recombivax HB; recombinant- no risk of infection associated with plasma derived vaccine
1986	Merck and Company	Measles and Mumps Vaccine Live	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1986	Merck and Company	Measles and Rubella Vaccine Live	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1986	Merck and Company	Measles, Mumps and Rubella Virus Vaccine Live	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1986	Merck and Company	Mumps Virus Vaccine Live	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1986	Merck and Company	Pneumococcal Vaccine, Polyvalent	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1986	Merck and Company	Rubella and Mumps Virus Vaccine Live	01/06/1986		LT	name change (*Licensure dates for products developed by Virus and Cell Biology Research* (1996): Merck Archives)
1987	Bionetics Research	BCG Vaccine	05/29/1987	06/21/1989	LT	from Univ. of Illinois
1987	Connaught Laboratories Inc	Haemophilus b Conjugate Vaccine (Diphtheria Toxoid Conjugate)	12/22/1987	12/09/1999	P	Prohibit; conjugation improves immunity; safe for children under 18 mos.
1987	Connaught Laboratories Inc	Poliovirus Vaccine Inactivated (Human Diploid Cell)	11/20/1987	02/24/2000	I	Poliovax
1988	MBPI	Rabies Vaccine	03/18/1988	11/12/1998	I	fetal rhesus lung culture- alum adsorbed

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		Adsorbed				
1988	Praxis Biologics	Haemophilus b Conjugate Vaccine (Diphthera CRM197 Protein Conjugate)	12/21/1988	12/06/1994	I	immunization of children 18 months to 5 years
1989	Merck and Company	Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)	12/20/1989	00/00/1990	I	Pedvax Hib; PLA for the immunization of children 18 months to 5 yrs.
1989	Organon Teknika Corporation	BCG Vaccine	06/21/1989	00/00/1994	LT	from Bionetics Research
1989	Smith Kline Beecham Biologicals	Hepatitis B Vaccine (Recombinant)	08/28/1989		I	Energix B
1990	Connaught Laboratories Inc	BCG Live	05/21/1990		I	Thera-Cys; new indication: treatment of carcinoma-in-situ-bladder, manuf in Toronto (fda.gov/cber/efoi/approve)
1990	Merck and Company	Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)	00/00/1990		Is	Pedvax Hib; indication: extend use to infants 2 months and up (fda.gov/cber/efoi/approve)
1990	Praxis Biologics	Haemophilus b Conjugate Vaccine (Diphthera CRM197 Protein Conjugate)	10/04/1990		Is	Indication: use in younger infants (fda.gov/cber/efoi/approve)
1991	Connaught Laboratories Inc	Rabies Vaccine	12/27/1991	02/24/2000	I	Rabie-vax
1991	Lederle Laboratories	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	12/17/1991		A	Acel-immune; combined new aP component developed by Takeda Chemical Industry in Japan: PLA for 4th and 5th dose of immunization schedule
1992	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	08/20/1992	12/09/1999	I	Tripedia; aP component developed by Biken in Japan: PLA for 4th and 5th dose of immunization schedule
1993	Lederle Laboratories	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed and	03/30/1993		A	TetraImmune

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate)				
1994	Greer Laboratories	Plague Vaccine	10/05/1994		LT	from Bayer, DOD sole purchaser, ceased manufacture in 1998 when failed GMP inspections
1994	Lederle Laboratories	Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate)	12/06/1994		LT	HibTiter; from Praxis
1994	Organon Teknika Corporation	BCG Vaccine	00/00/1994	01/10/1995	I	Connaught already licensed for new indication (CIS treatment) in '90 (fda.gov/cber/efoi/approve)
1995	Merck and Company	Varicella Virus Vaccine Live	03/17/1995		C	Varivax; 12 months and older-isolated Japanese child Research Institute Osaka
1995	Organon Teknika Corporation	BCG Vaccine	01/10/1995		LT	Tice BCG; supplement- changed production from Chicago, IL to Durham, NC
1995	Smith Kline Beecham Biologicals	Hepatitis A Vaccine Inactivated	02/22/1995		C	Havrix
1996	Connaught Laboratories Inc	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	07/31/1996		Is	Tripedia; new indication: primary series in infant and child (fda.gov/cber/efoi/approve)
1996	Connaught Labs Inc	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)	09/27/1996		Is	manuf: suitable for reconstitution with DTaP (fda.gov/cber/efoi/approve)
1996	Lederle Laboratories	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	12/30/1996		Is	Acel-immune; new indication: three dose primary series in children at least 6 wks of age for 4th and 5th dose of DTaP (fda.gov/cber/efoi/approve)
1996	Merck and Company	Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) and Hep B (Recombinant) Vaccine	10/02/1996		A	Comvax; 6wks to 15 months; born to Hep B surface antigen negative mothers

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1996	Merck and Company	Hepatitis A Vaccine Inactivated	03/29/1996		P	Vaqta; nuclease enzyme purification process
1997	Connaught Laboratories	Diphtheria and Tetanus Toxoids Adsorbed	04/11/1997	02/24/2000	Is	Infants and children 6wks to 7yrs.
1997	Smith Kline Beecham Biologicals	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	01/29/1997		Is	Infanrix; new indication: primary booster of infant and child except as 5th dose of child with 4 of DTaP
1998	BioPort Corporation	Anthrax Vaccine Adsorbed	11/12/1998		LT	
1998	BioPort Corporation	Diphtheria and Tetanus Toxoids Adsorbed	11/12/1998		LT	
1998	BioPort Corporation	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	11/12/1998		LT	from MBPI
1998	BioPort Corporation	Diphtheria Toxoid Adsorbed	11/12/1998		LT	from MBPI
1998	BioPort Corporation	Pertussis Vaccine Adsorbed	11/12/1998		LT	from MBPI
1998	BioPort Corporation	Rabies Vaccine Adsorbed	11/12/1998		LT	from MBPI
1998	BioPort Corporation	Tetanus Toxoid Adsorbed	11/12/1998		LT	from MBPI
1998	Connaught Laboratories Inc	BCG Vaccine	10/09/1998	02/04/2000	LT	R. Rader, *Biopharma* (Rockville: Biotechnology Information Institute, 2001).
1998	North American Vaccine	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	07/29/1998		I	Certiva; obtained exclusive aP patent from govt: single purified pertussis toxoid protein detoxified with hydrogen peroxide
1998	Parkdale Pharmaceuticals, Inc.	Influenza Virus Vaccine	04/20/1998		LT	Fluogen; from Parke-Davis, cease manuf. in 2000
1998	Smith Kline Beecham Biologicals	Hepatitis B Vaccine (Recombinant)	07/07/1998		Is	Energix B; Indication: (fda.gov/cber/efoi/approve)

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1998	Wyeth Laboratories	Rotavirus Vaccine, Live Oral Tetravalent	03/31/1998		C	Rotashield; primary immunization of infants—(withdrawn from market 10/15/99 for causing intussusception of the bowel in infants)
1999	Aventis Pasteur	Meningococcal Polysaccharide Vaccine, Group A	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur	Meningococcal Polysaccharide Vaccine, Group C	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur	Meningococcal Polysaccharide Vaccine, Groups A and C Combined	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur Inc	Haemophilus b Polysaccharide Vaccine	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur Inc	Yellow Fever Vaccine	12/09/1999		LT	
1999	Aventis Pasteur Limited	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	12/09/1999		LT	Tripedia
1999	Aventis Pasteur Limited	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed	12/09/1999		LT	
1999	Aventis Pasteur Limited	Diphtheria Antitoxin	12/09/1999		LT	
1999	Aventis Pasteur Limited	Haemophilus b Conjugate Vaccine (Diphtheria Toxoid Conjugate)	12/09/1999		LT	ActHib; from Connaught
1999	Aventis Pasteur Limited	Influenza Virus Vaccine	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur Limited	Meningococcal Polysaccharide Vaccine, Groups A, C, Y, W135 Combined	12/09/1999		LT	from Connaught Labs, Inc

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
1999	Aventis Pasteur Limited	Diphtheria and Tetanus Toxoids Adsorbed for Adult Use	12/09/1999		LT	from Connaught
1999	Aventis Pasteur Limited	Tetanus Toxoid	12/09/1999		LT	from Connaught Labs, Inc
1999	Aventis Pasteur Limited	Tetanus Toxoid Adsorbed	12/09/1999		LT	from Connaught
1999	Aventis-Pasteur	Pertussis Vaccine	07/29/1999		LT	from Connaught Labs, Inc
1999	Merck and Company	Hepatitis B Vaccine (Recombinant)	08/27/1999		Is	Recombivax HB; Manufacturing change: remove thimerosal preservative (fda.gov/cber/efoi/approve)
1999	Merck and Company	Hepatitis B Vaccine (Recombinant)	09/23/1999		Is	Recombivax HB; Indication: 2 additional doses of 10mcg formulation (1.0 ml) for 0,4,6 mo as alternative regimen for routine vaccination of adolescents 11-15 yrs. (fda.gov/cber/efoi/approve)
1999	SmithKline Beecham Biologicals	Hepatitis B Vaccine (Recombinant)	12/14/1999		Is	Energix B; Indication: (fda.gov/cber/efoi/approve)
2000	Aventis Pasteur Limited	BCG Vaccine	02/24/2000		LT	from Connaught
2000	Aventis Pasteur Limited	Botulism Antitoxin	02/24/2000		LT	from Connaught
2000	Aventis Pasteur Limited	Diphtheria and Tetanus Toxoids Adsorbed	02/24/2000		LT	
2000	Aventis Pasteur Limited	Diphtheria and Tetanus Toxoids Adsorbed, Acellular Pertussis Vaccine	08/24/2000		Is	Tripedia; new indication: approved for 5th consecutive dose for children 4-6 years of age (fda.gov/cber/efoi/approve)
2000	Aventis Pasteur Limited	Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)	02/04/2000		LT	from Pasteur Merieux
2000	Aventis Pasteur Limited	Poliovirus Vaccine Inactivated (Human Diploid Cell)	02/24/2000		LT	from Connaught Labs, Inc
2000	Aventis Pasteur Limited	Poliovirus Vaccine Inactivated (Monkey	02/04/2000		LT	from Connaught Labs, Inc

Year	Manufacturer	Product Name	Approved	Revoked	Innov type	Notes
		Kidney Cell)				
2000	Aventis Pasteur Limited	Rabies Vaccine	02/24/2000		LT	2/4/2000 from Aventis Pasteur SA
2000	Aventis Pasteur Limited	Typhoid Vi Polysaccharide Vaccine	02/04/2000		LT	from Aventis Pasteur SA
2000	BioChem Pharma Inc	BCG Live	03/09/2000		I	new indication: treatment of bladder cancer (fda.gov/cber/efoi/approve)
2000	Lederle Laboratories	Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein)	02/17/2000		P	Prevnar; conjugated- induces long-term immunity and can be used in children under 2 against invasive disease by streptococcus Pneumoniae
2000	Merck and Company	Hepatitis A Vaccine Inactivated	11/17/2000		Is	Vaqta; Indication: increase age range from 2-17 to 2-18; also change timing of adult booster doses(fda.gov/cber/efoi/approve)
2000	Smith Kline Beecham Biologicals	Hepatitis B Vaccine (Recombinant)	11/17/2000		Is	Energix B; Manufacturing .change: remove thimerosal preservative (fda.gov/cber/efoi/approve)

Data Sources:

Unless otherwise indicated, vaccine license data was obtained through the Freedom of Information Act from the Center for Biologics Evaluation and Research of the Food and Drug Administration.