Parallel Path: Poliovirus Research in the Vaccine Era

Michele S. Garfinkel and Daniel Sarewitz
Center for Science, Policy, & Outcomes, Washington, D.C.*

Keywords: scientific responsibility, societal outcomes, research policy

ABSTRACT: *One goal of the scientific research enterprise is to improve the lives of individuals and the overall health of societies. This goal is achieved through a combination of factors, including the composition of research portfolios. In turn, this composition is determined by a variety of scientific and societal needs. The recent history of polio research highlights the complex relations between research policy, scientific progress and societal benefits. Here, we briefly review the circumstances leading to the possibility of eradication of poliovirus, evaluate the research environment that emerged following the introduction of a vaccine, and compare and contrast the current research framework with that for other infectious diseases. From this analysis, policy lessons with general applicability to scientific research are identified.*

The recent history of polio research highlights the complex relations between research policy, scientific progress and societal benefits. The polio story is a source of insight about how choices of research directions are made, how such choices connect to societal goals, how research directions change over time, and how intellectual and financial resources for research are allocated.

In the United States, early poliovirus research was funded almost exclusively from what is now known as the March of Dimes. In 1926, Franklin Roosevelt, having bought Warm Springs, a spa in Georgia, subsequently appointed Basil O'Connor (his former law partner) to direct a non-profit concern (The Warm Springs Foundation) initially located there. By 1938 the Foundation had been reorganized as the National

Address for correspondence: Michele S. Garfinkel, The Center for the Advancement of Genomics, 1901 Research Boulevard, Suite 600, Rockville MD 20850, USA; email mgarfinkel@tcag.org.
* The Center for Science, Policy, & Outcomes is a project of Columbia University in the City of New York, 1 Thomas Circle NW, Suite 1075, Washington, DC 20005, USA.
Paper received, 31 January 2002: revised, 1 October 2002: accepted, 10 June 2003.

Foundation for Infantile Paralysis; O'Conner was in charge of the fundraising efforts, and subsequently distributed funds more or less as he saw fit, with advice from various scientists and medical doctors as to the soundness of specific ideas.[1]

Notably, government-funded research on poliovirus did not really begin until nearly ten years after a robust vaccine was available, and fundamental understanding of the polio virus did not emerge until later still. This aspect of the history of poliovirus research, beginning with advances leading to vaccines and continuing with funding in the post-vaccine era, might provide a good model for understanding some of the myriad ways in which science and society advance as a result of both technological and policy innovations. Such insights can help inform and improve overall U.S. health research policy, including research on eradicable diseases.

Background: Research and Vaccines

Research policy with regard to poliovirus is entangled with the biology of the virus. The natural history of poliovirus in human populations is complex, and has recently become well understood.[2] Before the 18th century there was a high level of natural immunity and boosting; in the "immediate pre-vaccine era" increased sanitation and decreased early exposure led to more susceptible populations. The highest infection rates in the United States resulted in about 20,000 paralytic cases in an epidemic year. In general, death occurs in 2-5% of all detectable cases of poliovirus-caused disease; the number of permanently paralyzed varies by serotype. The major concern now is post-polio syndrome (pain and progressive muscle weakness) in 25-40% of all cases (whether paralytic or not), 30-40 years after the initial bout. Of the approximately 10-20 million polio survivors worldwide who are alive today, 4-8 million may be at risk for post-polio syndrome.[3]

Following introduction of the polio vaccine in 1955, the rate of new poliovirus infections in the United States decreased rapidly through the late 1960s and reached essentially zero by the mid-1970s. As with smallpox, poliovirus is a good target for eradication because it meets a small but critical number of requirements for such an effort to succeed. It has no animal reservoir or long-term human carriers, and the virus does not persist long-term in the environment. An inexpensive, easily administered vaccine (the oral polio vaccine, or OPV) is available, and it confers life-long immunity. Based on these criteria, only a few other microbes are even theoretically eradicable; one of them, measles, is the next slated for elimination.[4]

Two advances in the mid- to late 1940s put vaccinologists on a clear path to a robust vaccine. In 1943 Jonas Salk and Thomas Francis, Jr., developed a successful killed vaccine against the influenza virus, giving researchers confidence that useful killed vaccines were feasible. More importantly, in 1949, John Franklin Enders and his colleagues, Thomas Huckle Weller and Frederick Chapman Robbins, in a spectacular research advance, developed a way to culture poliovirus *in vitro* in non-neural cells. This allowed researchers to collect and concentrate vast quantities of the virus starting from a source of only one monkey kidney, where previously 200 kidneys were required to gather enough virus to conduct useful experiments.[1] This novel contribution was so

significant that Enders, Weller, and Robbins were awarded a Nobel prize—a consideration extended neither to Salk nor to Albert Sabin, the developer of the live attenuated vaccine. The prize was awarded in 1954, before Salk's vaccine had been widely distributed. The presentation speech noted explicitly that the discovery removed a practical burden that virologists had long struggled with and gave them level footing with bacteriologists in the quest to prevent and cure human disease. The ability to culture viruses *in vitro* led directly to Salk's development of the inactivated (killed) polio vaccine (IPV) and field trials in 1952-1954; by 1955 virtually every American school-age child and many adults had been vaccinated.[5]

Contemporaneously, Sabin was developing a live vaccine (that would eventually become the oral polio vaccine).[1,4,5] In the late 1950s, the key issue for polio vaccine research was the robustness of immunity provoked by the vaccine. For a number of reasons, the live attenuated viruses conferred greater immunity, and in 1961 the American Medical Association for all practical purposes ended the debate over live vs. killed vaccines by endorsing Sabin's approach,[5] and the United States used this formulation exclusively for several decades. Debate continued for several decades more, however, over continued use of the OPV in areas where the virus had been eradicated. Use of the killed vaccine is now preferred in polio-free regions (including the United States, where the depletion of OPV stocks signals the end of live virus vaccinations there) and is strongly preferred for the first two vaccinations of naïve recipients (to prevent vaccine-associated paralytic polio). The situation in other countries varies; in the Netherlands, for example, the killed vaccine was the only one ever used.[6]

Still, the Sabin oral live vaccine remains the best choice for interrupting viral transmission during localized outbreaks. The vaccine strain is passed, via excretion from immunized individuals to those who themselves are missed during "mop-up" vaccination (dependent, interestingly, on poor sanitation at the community level).[7] At the same time, the presence of live virus, even if vaccine-derived, carries the risk of causing poliomyelitis. Although thought to be relatively unstable in the environment, there is little documentation as to how long these viruses actually persist.[8] The assumption has been that once all regions of the world have been certified as polio-free for about two years, vaccination would be stopped completely. It has been noted that this polio-free definition is narrowly limited to wild polioviruses. It does not include the oral vaccine live virus that is shed from vaccinated individuals which can mutate to virulence at or near wild virus levels.[9]

The history of poliovirus research not only illustrates the relationship between biomedical research and an eradicable disease, but more generally illuminates how societal outcomes are tied to particular research paths. The potential to eradicate poliovirus was probably apparent even as the first doses were being distributed in the 1950s.[10] If this theoretical potential was not a convincing enough reason to pursue eradication efforts, the results of early vaccination efforts in the United States certainly were: poliovirus virtually disappeared from the United States. The last wild cases were reported in 1979; since then, all paralytic polio in the United States arose from imported poliovirus or as vaccine-associated cases.[11] Subsequent vaccination efforts

were so successful that, in May of 1988, the World Health Assembly, the governing body of the World Health Organization, judged it possible "to eradicate polio from the world by the year 2000."[12] Although that goal was not met, it is now believed by WHO and others working toward the eradication of poliovirus that the next deadline of 2005 is feasible.[13] For only the second time in history, the causative agent of an infectious disease of human beings almost certainly will become extinct in the wild as a result of purposeful human intervention. Along with the eradication of variola, the smallpox virus, the eradication of polio will stand as one of the great achievements in the global improvement of public health.

The possibility of eradication brings with it several compelling public policy issues, particularly if the cessation of vaccination were to accompany eradication. Ease of use of live (OPV) vaccine and its ability to interrupt outbreaks have been cited as the reasons for continuing its use, but the small possibility remains that such vaccinated individuals will acquire vaccine-associated paralysis remains.[14] In the United States, the switch to IPV for the first two vaccinations has already been made. Still, individuals who have been vaccinated exclusively with IPV can act as carriers of wild virus.[9] While significant cost savings would result from ending routine immunizations (nearly $270 million in the US[15]), the cost of responding to a reintroduction of the virus would likely be far greater. Surveillance will need to continue at high levels for the first several years following vaccine withdrawal. If vaccine withdrawal really is to occur, then these decisions (switching to IPV world-wide, surveillance plans, intervention plans should a polio case crop up) need to be made quickly. Nonetheless, arriving at the point of near-eradication, even if this state needed to be maintained by continuing population-wide vaccinations indefinitely, is a significant achievement.

Several threads of research had to come together to ensure this success. *In vitro* culture of the virus, the understanding of the differences in the immune response provoked by each of the vaccines, and the ability to understand how a virus can be eradicated can all be attributed to research that we would recognize, in a modern sense, as "basic biomedical research"—that is, research investigating basic biological processes, but informed by the strategic effort to cure disease. As with smallpox, eradication also required the surveillance capabilities and social institutions that could deliver vaccines when and where necessary. Eradication, in other words, is a triumph of biomedical science, but it is also a triumph of social organization ranging from brute human force (simultaneously vaccinating millions of children on one day[16]) to the most delicate, complex diplomacy ("Days of Tranquility;" the cessation of hostilities in several regions of a country to allow workers to carry out vaccinations and epidemiological surveillance[17]). These multiple successes were possible for several reasons, but perhaps the most compelling is the overall coordination of the effort by the World Health Organization. Critical was the design of vaccination efforts, leading to centralized epidemiological data that allowed vaccinologists and policy-makers to understand how to best distribute vaccines, and which vaccine formulations would be best to use in particular regions.[18] As the recent experience with AIDS drugs painfully demonstrates, the existence of a physical technology is only a part of the solution to an

epidemic. The (near) eradication of poliovirus is a testament to the necessity of intertwining scientific knowledge with policy knowledge.

There is no argument that by 1961, effective vaccines to prevent poliovirus infection were available. It would take many years for either vaccine to be readily available for much of the world, but in the developed nations, within a year or so of the introduction of Sabin's vaccine, new poliovirus infections would drop essentially to zero.[11] It would also be almost a decade before federal support for research on the poliovirus (mostly through the National Institutes of Health) began to grow significantly. And while funding for such research never came close to levels provided for diseases like human immunodeficiency viruses or breast cancer, it did approach levels of funding for other, major diseases such as malaria and schistosomiasis. In this context, how is the post-vaccination commitment to polio research best understood?

Research Paths are Chosen

The optimism that poliovirus could be eradicated was widely shared, including (perhaps especially) among scientists working on the virus itself, even as they knew that such research would of necessity be stopped (or made extremely difficult) by a bona fide eradication. Why would researchers dedicate their careers to a path that might be suddenly blocked? The most obvious explanation is simply that good scientists thought that poliovirus was a worthy candidate for fundamental research. Among these workers were James Darnell and David Baltimore, and after that many of their students. Baltimore had a significant role in determining the outlines for future work in many areas of virology,[19] perhaps most interestingly in poliovirus biology, beginning his work just after the introduction of Sabin's vaccine.[20] His work particularly provides many examples of elegant, important, undirected contributions to the understanding of basic biological mechanisms, as were many of the contributions of workers in virology around this time. This early work set the stage for a rapid increase in funding and effort in virology in the mid- to late 1980s, followed by the explosion of research on HIV.

This explanation is incomplete, however. Insights could have emerged from research on another virus so the choice of polio was neither necessary nor sufficient for Baltimore's success. Poliovirus was not an entirely random choice, as researchers benefited from the *in vitro* culture work and were able to grow large amounts of the virus robustly. But many viruses could be handled with relative ease at that time, including influenza virus, for which there is still no straightforward vaccine or treatment. Indeed, Baltimore's biographer notes that his early work was (at that time) not only of no interest to the public, but also of little if any interest to biologists.[20]

Poliovirus nonetheless became of more interest to researchers as time passed. To better understand trends in federally funded polio research, and as a case study of how science progresses generally, we looked closely at projects funded by the National Institutes of Health (NIH), the primary agency responsible for funding health-related research in the United States. Much research performed with NIH funds comes through a peer-reviewed, investigator-initiated mechanism (sometimes referred to as an "R01

grant," although this is just one of several categories of investigator-initiated research). This funding is administered through discipline-specific study sections made up of peer scientists, who conduct reviews for scientific merit. In contrast, broad, strategic research priorities are set by the agency, the administration, and Congress, through the federal budgeting process. Mediating between these two mechanisms are the National Advisory Councils, charged with representing both the research community and the public. But because the Councils nearly always take the recommendations of study sections, scientific merit remains the main, if not only, criterion for grant success.

Once proposals have been peer-reviewed and approved, investigators are given nearly absolute freedom, within ethical and safety boundaries, to conduct the research as they and their collaborators see fit. Successful execution of such research projects, as measured for the most part by the number and quality of publications, frequently leads to multiple renewals of grants. This peer-review infrastructure is widely accepted as yielding uniformly high levels of scientific productivity and excellence.

In order to characterize one aspect of the federal government's selection and funding of research on various aspects of poliovirus biology, we catalogued and classified investigator-initiated projects paid for by the NIH. The NIH's Computer Retrieval of Information on Scientific Projects (CRISP) database[21] comprises biomedical research conducted within the Department of Health and Human Services. In addition to all extramural research funded by NIH, it includes NIH intramural research and relevant (biomedical) research funded by the Centers for Disease Control and Prevention, the Food and Drug Administration, the Health Resources and Services Administration, the Substance Abuse and Mental Health Services Administration, and the Agency for Healthcare Research and Quality. The database contains abstracts from 1972 to the present; funding information for extramural research is available from 1992 to the present from the Office of Extramural Research.[22] Additional extramural grant information was obtained courtesy of Robert Moore, NIH.

We used CRISP to investigate various types of federally-funded grants related to poliovirus research of any kind. Searching in CRISP permits identification of abstracts both through the text of the abstract itself, and through thesaurus terms. Thus, even if the abstract itself did not contain a mention of polio in any form, abstracts could still frequently be identified by thesaurus terms (i.e., polio appears elsewhere in the grant). We identified every project containing any reference to *poliovirus*, *polio*, or *poliomyelitis*. The quality of that search was checked in a variety of ways to insure that it was thorough. These checks included search for thesaurus words that should appear with the main search words (e.g., *picornavirus*), by searching for authors known to have worked with poliovirus, and by searching for variations on the search terms (e.g., misspellings). The dataset that we assembled is thus comprehensive, or nearly so.

The CRISP database was last searched 1 October 2001. A simple search of the database (all years, all grant types) yielded 1366 individual entries, each entry corresponding to one grant-year. These abstracts include both intramural and extramural research. We then re-worked the data from CRISP for easier manipulation[a] and identified 332 unique grants, many of which were active over multiple grant-years.[23] We eliminated grants that were for conferences, meetings, or books, and high

a. All datasets discussed in this paper are available from the corresponding author.

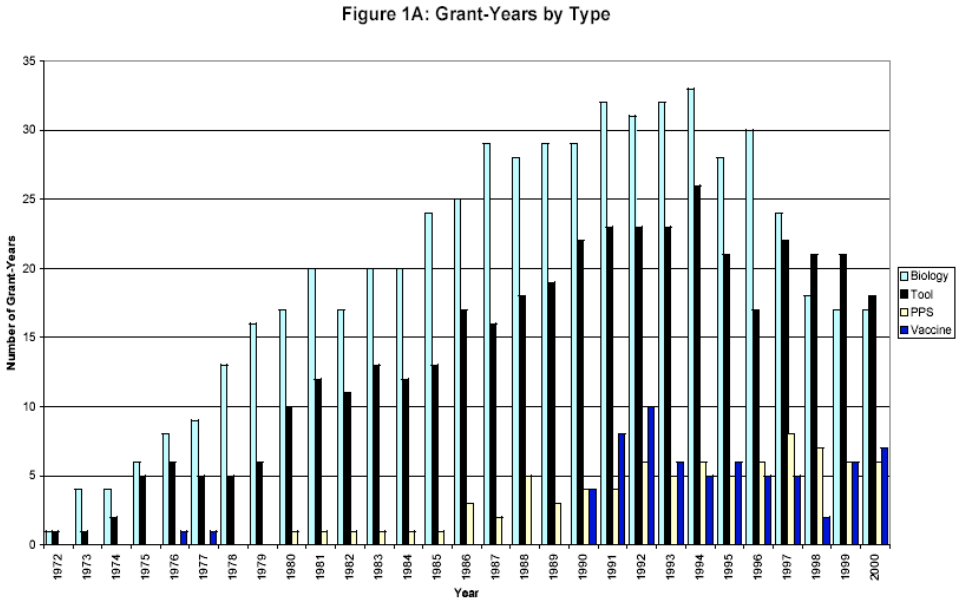
school training grants (9 unique grants totaling 19 grant-years). We then subdivided the remaining 323 unique grants, corresponding to 1347 grant-years, according to the nature of the research with respect to poliovirus as follows:

(1) Research directed at the nature of the virus itself: 87 grants (483 grant-years).
(2) Research directed at some aspect of polio vaccines: 32 grants (66 grant-years).
(3) Research using the virus (or parts of the virus) as a tool, including for vaccines for other diseases: 91 grants (352 grant years).
(4) Research directed at post-polio syndrome: 23 grants (88 grant-years).
(5) Research neither about nor using the virus, but invoking poliovirus studies as at least a partial rationale for the grant in question: 56 grants (181 grant-years).
(6) Grants mentioning poliovirus or the disease in passing, but not invoked as a specific rationale for the proposal: 49 grants (144 grant years).

This categorization accounts for 338 grants. This is higher than the number of unique grants, because a subset of grants had one goal in some years, and a different one in later years. (In general that sort of shift occurred following a competing grant renewal.) In total, this is 1314 grant-years. It is lower than the number of grant-years as calculated from the initial CRISP list because we eliminated grants where the goal of the project was not unambiguously interpretable.

To check these calculations, and to look at the numbers and distributions of grants in more detail, we broke out the information by year. This analysis includes intramural grants, which are not considered in the funding analysis below (Figures 1A and 1B: grant years). In total, we recognized 1138 grant-years, which compares well with the 989 recognized simply by scanning abstracts from categories 1-4, above. (We eliminated categories 5 and 6 for this analysis as their importance is in understanding the "cultural" influence of poliovirus research on other research programs, discussed below.) This discrepancy is for the most part accounted for by grants that did not have abstracts or thesauri available but that were clearly part of a renewal series picked up in this actual physical count of grant-years. These data, plotted in Figure 1A, show a trend of steadily increasing grant years, peaking in the mid-1990s. The total grant years for these types of polio research are shown in Figure 1B. Research on post-polio syndrome, which will linger for decades after the last case of polio, is more or less flat during the period of most rapid increase in research grant-years.

This is not an extraordinary number of grants compared to, for example, research on human immunodeficiency virus (HIV), for which nearly 16,000 grant-years are listed in CRISP (and which is research that does not even appear until 1986, compared with the first listings for poliovirus in 1972, the first year available in CRISP). Nonetheless, several aspects of the distribution of research on and using poliovirus are notable. While some increase in the number of grants might be expected based only on the increase in the NIH budget over time, because this is a vaccine-controllable disease, one might more strongly expect the number of grants to decrease. Yet the number of grants focused on the virus increased progressively for two decades. Further, the number of researcher avenues that use poliovirus as a tool to understand another system (category 3, above) continues to increase, despite the fact that the call for eradication is coupled to a requirement to eventually destroy stocks of the virus. In this context, increases after 1988 (the year that the World Health Organization issued its eradication goals) are especially striking.



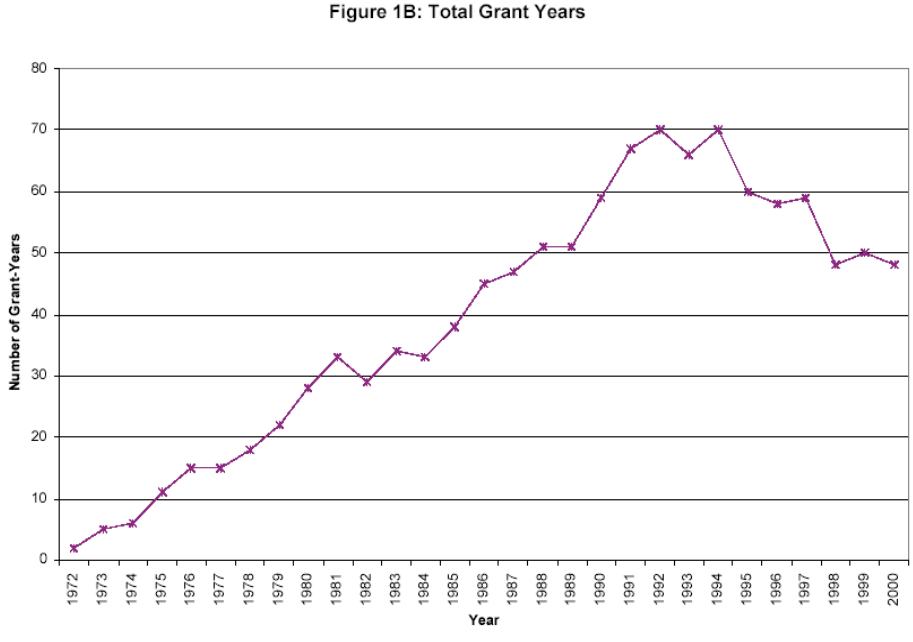
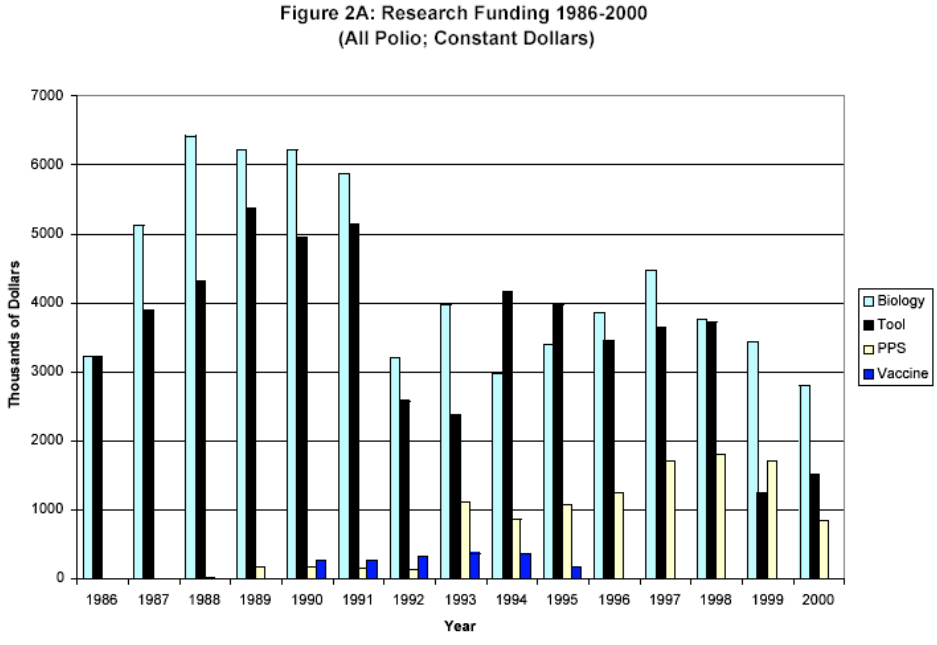


Figure 1. Overview of grants by type and by total, by year

Figure 1A illustrates the number of grant-years for each broad type of research conducted under a variety of funding mechanisms. One grant-year is one year of funding for one project as defined by the grant identification number. Thus, e.g., a three-year initial grant followed by a five-year renewal would comprise eight grant-years. **Figure 1B** shows the cumulative number of grants by year.

In both figures, note the broad peak in the mid-1990s, decades after the introduction of a robust vaccine.



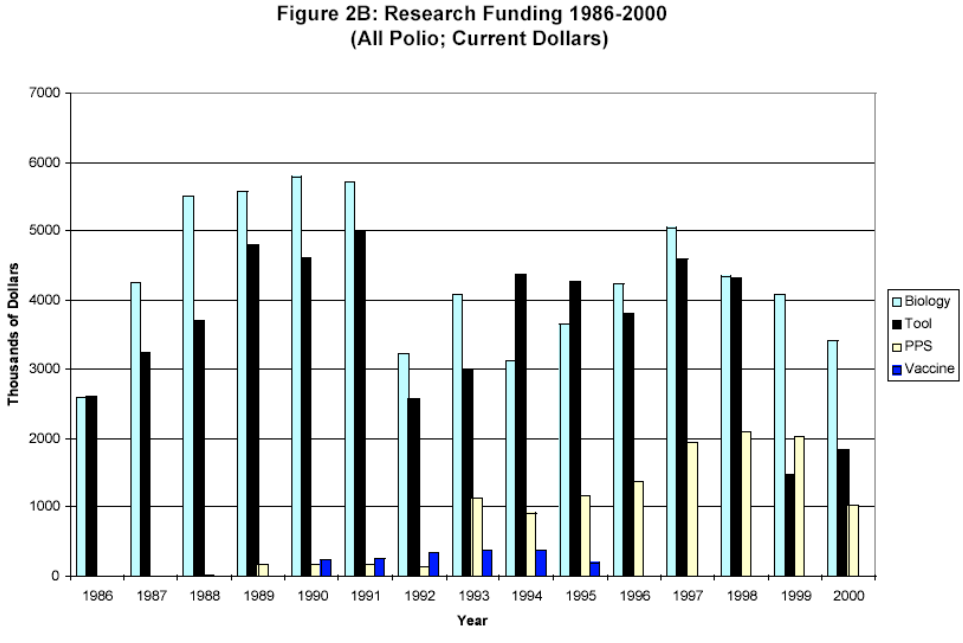


Figure 2. Overview of funding of poliovirus-related research, constant and current dollars, by year

Figure 2A: Constant (1992) dollars

Figure 2B: Current dollars

Note that only very late into the 1990s is any drop-off in funding apparent.

But the number of different grants is only one part of the story; the amount of money that has been spent on this research is significant as well. We examined NIH expenditures on research for understanding or using poliovirus, dating from 1986, for the purpose of trying to understand the types of research programs that are being undertaken despite the preventability of disease, and despite the fact that researchers must be prepared to drop their programs in time.[b]

As illustrated in Figure 2A (constant dollars) and Figure 2B (current dollars), polio research funding was dominated by projects from categories 1 (fundamental investigations on the virus itself) and 3 (using the virus as a tool). Funding for this work peaked in the late 1990s, and has since leveled off, with category 3 work showing a significant decline over the last 2 years for which information was available. Total expenditures, in constant (1992) dollars for all polio research peaked in the period from 1988-1991, at approximately $9-10.5 million/year. After a dip in the mid-1990s, there was another small peak of around $9.5 million in 1997, and then a slow drop off to the year 2000 funding level of almost $5 million. Research on post-polio syndrome and vaccines, however, has increased over the past decade, though they are still funded at a considerably lower level than "basic research." Certainly, this kind of research was never restricted to the public sector: private concerns (for-profit and non-profit) have made significant contributions, particularly in vaccine research. In all cases, though, resources for conducting research are strained, and tradeoffs are constantly made to assemble the "best" research portfolios; the underlying goal is to improve health. Has this happened with the federal poliovirus research enterprise?

Poliovirus Research and Health Outcomes

The major benefit to society from research on poliovirus was derived from the introduction of the polio vaccines (Salk's in 1955 and Sabin's in 1961). While much is now understood about the vaccines, the vast majority of publicly funded research on vaccines has been on general safety issues (preservatives, contaminants) and on assuring that batches of vaccine can be effectively tested for efficacy. These are not minor issues, but they are not special to poliovirus; rather, they are general issues of vaccinology. Research on the single issue unique to poliovirus, the paradigmatic difference between Salk's killed and Sabin's oral vaccines, has yielded useful information about vaccine-associated paralytic polio, which was important in establishing policy: in the United States, once the oral vaccine stocks are depleted, only the inactivated version will be used. Beyond this type of research applied to a practical problem (Can the number of vaccine-associated paralytic polio cases be lowered

b. Extramural grant funding information was totaled by year (grant amounts are available at http://grants.nih.gov/grants/award/state/state.htm for 1992-present. 1986-1991 inclusive, courtesy Robert Moore, NIH. Funding information not readily available prior to 1986.) We looked at grants through the year 2000, the last year for which complete information is available. For constant-dollar ("inflation-adjusted") calculations, we used the Office of Management and Budget's Gross Domestic Product (GDP) Deflator Table (available in the Fiscal Year 1999 Budget as Table 10.1) which sets the year 1992 as 1.00 for GDP deflation.

without compromising the robustness of coverage?), we wanted to analyze the types of research being conducted that can be used to describe the linkages between basic research and the reduction of disease burden.

In order to more rigorously evaluate the nature of the connection between NIH-funded poliovirus research and health, we looked again at the abstracts, and identified statements pertaining to the goal of the work in regard to health. All proposals require a definitive statement of "health relatedness" (*sic*) in the abstract. Even in older abstracts, before this requirement was made explicit, it is often possible to identify such rationales. For all proposals where abstracts were available, the presence or absence of a health-relatedness statement was noted. Initially, we strove to be as generous as possible in identifying these statements, as it is counterintuitive to many scientists, and difficult in many cases, to state a presumptive application from their research.[24] Further, in many of the cases where no abstract was available a general health goal could be deduced from a combination of the title and the thesaurus terms.

Of the 323 unique grants (including intramural), 30 had no abstract. We divided the remaining 293 into five general goal categories:

(1) Research directed toward understanding poliovirus per se: 112 grants. Forty-two of these were concerned with the biology of poliovirus exclusively; 33 dealt with poliovirus as part of a larger research program, usually including other viruses; 37 were on the safety and efficacy of polio vaccines.
(2) Research directed toward preventing, treating, or understanding other microbial diseases (including vaccines): 91.
(3) Research on improving or understanding the health of those with post-polio syndrome: 26.
(4) Studies concerned with non-microbiological issues: 63. Of these, 25 were directed toward understanding normal cellular metabolism or organ function, and 38 toward nonmicrobial diseases generally.
(5) Could not be characterized: 1.

This categorization is very liberal, in that we categorized the abstracts based on a generous interpretation of how "health relatedness" would be indicated. A more literal re-reading of the abstracts led to the elimination of 49 projects where there was only a mention of polio, poliovirus, or poliomyelitis, as we did not want to include health relatedness statements from unrelated research. Of the remaining 244, we found that 51 of the abstracts (for both extramural and intramural projects) in fact contain no statement of or allusion to how the work will be relevant to human health. After eliminating those 51 abstracts we then studied the pool of 193 in more detail. By our analysis, 128 articulate an implicit link between the proposed research and human health, for example, by labeling poliovirus as a "human disease virus" but with no further explanation as to the benefits to human health that would be derived from the project.

Of those 65 remaining abstracts that stated a clear link between the course of the study and improved human health, 28 studied vaccine safety and/or efficacy; 6 were

techniques for detecting or treating food or blood contamination; 25 were concerned with chronic diseases and aging (including clinical trial designs for studying these issues); and 6 were studies of the biology of poliovirus itself, or the use of the virus as a tool to eventually alleviate human suffering.[c]

By the community's own accounting, research carried out on poliovirus has led to a sophisticated understanding of the molecular mechanisms that confer pathogenicity during poliovirus infection. But whether the uncovering of the mechanisms of poliovirus infection has led to improved health is unclear. Some results of the research have been applied to assuring that the vaccine supply is safe and effective.[25] Further, the connection between poliovirus research, including poliovirus vaccine research, and HIV/AIDS research, has been explicitly acknowledged,[26] although, as indicated below, the impact of this connection for improved health is difficult to document. Finally, using poliovirus as a tool has allowed a better understanding of both normal and abnormal cellular metabolism, including during infections by other microbes.

Here as well the link from poliovirus research to a societal outcome of better health is difficult to determine. Although a "linear model" of research has been clearly discredited as the major way in which science advances,[27] scientific leadership has been successful using this model as an argument for more funding for "unfettered" research.

Policy Implications

1. The rationale for more polio research

What are the implications of the post-vaccine polio research agenda for research policy? The seminal results of Baltimore's early work on polio could have emerged from research on other viruses. Over the past 30 years there has been little demand for more or better understanding of the virus with regard to human health. Post-polio syndrome remains a problem even in developed countries, but that problem will fade as poliovirus is eradicated and no new cases emerge (although our analysis shows that post-polio syndrome has attracted relatively little research attention). There is no demand from those implementing vaccination programs for better or different vaccines, and understanding the basic biology of polio will not improve or speed up polio eradication.

Justification for continued research on poliovirus must therefore be grounded in the argument that additional fundamental understanding of polio contributes to a more

c. This last set of six includes statements such as:

"The health relatedness of this proposal derives from its contribution to the understanding of molecular mechanism[s] of viral pathogenesis and to the basis of host protection by poliovirus vaccines." (1986)

"The implications of this work for human health are difficult to predict, since there is little understanding of how any mammalian virus kills its host cell. Thus many of the answers sought in this study will break entirely new ground. If novel cytotoxicity genes can be identified, then novel antiviral agents may suggest themselves." (1994)

general reservoir of knowledge whose future utility is unpredictable. In other words, there is little that is sufficiently special or unique about the polio virus to suggest that research on it will make a more valuable contribution to the reservoir of knowledge than research using other viruses or non-viral microbes. The point here is not that research on polio did not or cannot yield valuable insights, but that criteria for choosing polio over other viruses cannot have been legitimately rooted in either the claim that more research was necessary to ensure eradication, or that poliovirus was uniquely suited to fundamental exploration of other microbiological systems like viruses.

Moreover, while undirected research is often justified by the valid assertion that useful results can derive unpredictably or serendipitously from investigations motivated only by the quest for new knowledge, the polio case illustrates that such a justification can be logically and practically perverse. Say, for example, that a scientist wants to investigate cellular metabolism, and that he or she can choose to carry out this investigation using one of several viruses. It is true that each virus has a different impact on the cell—some subtle, some dramatic—and in some cases poliovirus might be the very best choice. But, as discussed below in detail, each research choice (at the level of the individual experiment up through the level of funding of Institutes and Centers at NIH) has an opportunity cost. In the case of a potential research path such as the cellular metabolism experiment mentioned above, the potential for unforeseen or serendipitous contributions to health outcomes is by definition unknown. On the other hand, any fundamental investigation will add not only to general understanding, but also to knowledge of how the particular subject virus behaves. In the case of polio, this knowledge will not contribute to curing the disease, since it is already on the verge of eradication. But research on a different, uncured disease virus offers not only the equal possibility of unexpected or serendipitous application, but also the additional possibility of direct contribution to finding a cure related to that specific virus. The quest for fundamental knowledge is not compromised, but the likelihood of a more direct contribution to better health is increased.

The clarity of hindsight obscures this argument by revealing a chain of causation that was not knowable in advance. The result of "basic research" is, legendarily, a contribution to a reservoir of knowledge that can be drawn upon to solve problems, and to frame more research as well. The early work on poliovirus structure and metabolism is echoed in much research on many animal viruses now, so Baltimore's choice of poliovirus may seem prescient. At the same time, however, while similarities pervade across virus types, each microbe is unique enough that contributions to a reservoir of knowledge may not be broadly applicable to other diseases. While the possibility exists that an experiment on or using poliovirus will be absolutely critical to treating or curing another disease, in the absence of understanding that can only emerge after the research has been conducted, that possibility is no greater than it is for an experiment in another system.

The reservoir model of basic knowledge,[28] as articulated, for example, by NIH and various other organizations representing science and scientists, suggests that research on polio need not be carried out with a given application in mind. Although the foundation for this thinking has been subject to much valid criticism,[27] it is important

here to note that many federal funding agencies, including the NIH, still frame their research within the reservoir/linear model.[29] New knowledge about polio will become part of a larger reservoir of knowledge that can be drawn upon to support applications to other human health problems. An obvious candidate for such cross-fertilization would be the acquired immune deficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV). Indeed, HIV/AIDS researchers frequently use a comparison to the amount of research done on poliovirus as a way of emphasizing how much research has been done on HIV ("Experts say no virus, even polio, has been more thoroughly studied than H.I.V."[30]), while the nature of the trials of the first polio vaccines is evoked as both a negative and positive comparison (depending on one's agenda) to HIV vaccine trials.[31] The power of Salk's name (and the multidisciplinary institute that bears his name) draws, among others, HIV/AIDS researchers, especially vaccine researchers; polio frequently is a prototype for their research and to some degree for their politics. It should not be unreasonable, then, to expect that federally-funded research should exploit some of the power derived from our deep understanding of poliovirus.

To investigate this hypothesis, we searched the CRISP database from 1985-2001 using the search terms "*human immunodeficiency virus* and *poliovirus*," "*human immunodeficiency virus* and *polio*," "*HIV* and *poliovirus*," and "*HIV* and *polio*." We identified 39 unique grants and 42 principal investigators (including 9 intramural grants, 8 principal investigators) that included those search terms. We categorized these as follows:

(1) *Poliovirus cited as example* (where something learned from poliovirus might be applied to understanding HIV): 7 grants
(2) *Poliovirus to be used directly for HIV vaccine research:* 5 grants (including 2 large multi-disciplinary, multi-center, multi-investigator grants)
(3) *Poliovirus as a tool* (for studying HIV/AIDS but not directly in vaccines): 3 grants

Thus we identified 8 grants employing poliovirus either as a tool for any HIV research (including vaccine) and 7 invoking previous knowledge of poliovirus as a rationale for the grant. The total pool of "HIV grants" can be measured in a number of ways. A search of CRISP for the period 1985-2001 yielded 12816 grant years in the category "research grants" alone (with an additional 1957 grant years intramural). Even looking at a specific sector of the research in a limited time period is telling: the Treatment Action Group carried out a detailed analysis of NIH-funded HIV vaccine research. For the year 1998 alone, they identified 647 unique grants.[32] Whatever the basis for comparison, the number of grants where prior poliovirus research seems to have had any impact (either material or intellectual) is minimal. While it is possible that evidence of an influence of poliovirus research would appear in the full body of the grant, and while it is true that HIV research also occurs without federal funding and thus was not fully captured by our analysis, the cross-fertilization from polio to HIV research is surprisingly weak, given the presentation of the poliovirus story as a potential model for the development of HIV vaccines.

It might be argued that it would be more fruitful to compare a virus more biologically related to poliovirus in order to assess cross-fertilization opportunities. A scan of the CRISP database (1972-2001) for abstracts containing "poliovirus" and "hepatitis C virus" yielded 41 grant-years (13 unique grants, 11 principal investigators). Again, while some of this research might be taking place through non-governmental grants, this result points toward a general lack of contribution from "basic research" on a "solved" problem (polio) to an unsolved one (hepatitis C).

2. How researchers choose

In a "standard model" of investigator-driven research, questions lead to experiments, leading to more questions and more experiments.[33,34] This process, however, is rarely unmediated. Sometimes there is social pressure to pursue certain diseases, or the problems of particular populations.[31] This pressure is most publicly apparent during hearings for the various appropriations committees of the United States Congress, where representatives of disease-specific action groups, including celebrities, have testified. But sometimes research decisions reflect the social structure of the research community itself, with no exogenous pressure.[35,36] For example, specific sets of experiments may be chosen because a close colleague has elegantly developed it and can relay tacit knowledge about the techniques involved. And, in the expected manner of choosing a research path based on prior knowledge or availability, researchers tend to work on what they worked on before—and what their graduate advisors worked on still earlier. The expectation—and practical necessity—that at least some people will continue to work in fields where they received graduate or, more frequently, post-doctoral training is the basis for at least some of the structure of the entire research community. Does this continuity become inertia?

Because NIH grants contain only the name of the principal investigator, we utilized the National Library of Medicine's PubMed database of publications to investigate this question. Entries in PubMed date to 1966 and are essentially comprehensive for biomedical journals. Each entry contains the name of all authors on any paper, thus allowing us to tease out some of the relationships between the investigators identified in CRISP and their students and collaborators. By doing a simple forward scan of the database, we found that around 1/3 of the workers studying basic poliovirus biology or using it as a tool (43 of 125) "map" to three researchers: David Baltimore, James Darnell, and Igor Tamm. Specifically, using PubMed, we were able to determine an initial set of relationships between Baltimore, his students, and his early collaborators, and then two more generations hence. This was repeated for Darnell and Tamm. We chose this foundational group based on a nascent understanding of the history of research on animal viruses.[20] Selection of this foundation group is somewhat arbitrary and could be expanded in several ways, for example, by identifying all workers publishing in a certain time period. However, we chose to start with those workers for whom historical documentation of their initial contributions (in addition to scientific documentation such as abstracts) is available.[20]

We know, however, that this 1/3 figure does not express the full population of workers who were "offspring" of Baltimore, Darnell, and Tamm. It is likely, for

example, that additional names on our CRISP-generated list of NIH researchers could be connected back to these investigators, but in a more indirect manner. For example, some names on the CRISP list are researchers who initiated the use of polio *de novo* based on the strength of research from Baltimore and his intellectual progeny. (The progeny of this set of researchers would not have been recognized on our scan unless they had coincidentally been in a direct line from Baltimore.) At the same time, the PubMed list generated names from, for example, non-US researchers, who would not have had US federal grants. (Their progeny, if NIH funded, would have been recognized in our PubMed scan.)

Even so, the degree of genealogical continuity is considerable, and it helps to explain how, in a research system driven in large part by the decisions of individual investigators, research on polio continued to be a vibrant field for several decades after it ceased being a serious health problem. Ironically, however, we note that none of the seven workers that were identified in our CRISP search as engaged in research on post-polio syndrome, nor on vaccine research, were identified in the "genealogy" of poliovirus researchers working on fundamental problems (categories 1 and 3, above). Thus, the problem that perhaps deserves the most attention in poliovirus research (i.e., post-polio syndrome) is not receiving attention from a pool of researchers that have been very successful at understanding and using the poliovirus: the intersection of category 1 and 3 grants and post-polio syndrome "health-relatedness" is small, a mere 5 grants. Again, while it is of course never predictable where advances will come from, there is an intrinsic inelegance to a system where intellectual resources do not move into fundamental research on those aspects of a disease that represent an ongoing health threat.

3. Opportunity costs

Any choice entails an opportunity cost, and in the case of polio research, one cost is in research foregone on other viruses or diseases. As a strict accounting matter, these costs are relatively minor. Funding for polio research that can be characterized as aimed at understanding the fundamental biology (our category 1 only) of the virus was about $3 million in FY 2000 (constant dollars), a mere 0.016% of the total NIH budget for that year. On the other hand, the National Institute of Allergy and Infectious Disease (NIAID), the NIH institute primarily responsible for infectious disease research, provided funding for poliovirus research at nearly 10% of malaria research funding from about 1996-1999, and nearly 25% of malaria research before that.[37]

Seven hundred twenty three polio cases worldwide (caused by wild virus) were identified in the year 2000, and the number per year is dropping rapidly. Yet 18 million people are currently infected with *Onchocerca volvulus* (the cause of onchocerciasis); 270,000 of them are blind.[38] Schistosomiasis, second only to malaria in terms of public health and socioeconomic impact in the tropical regions, currently infects 200 million people, 10% of whom suffer severe consequences, ranging from anemia to bladder cancer.[39] Even guinea worm disease (dracunculiasis), which itself may be eradicated relatively soon, had 1 million reported cases in 1989, the first year of good surveys; even in this year's accounting 80,000 were thought to be infected.[40]

A recent evaluation of NIH-funded research on these helminth-caused diseases pointed out a distressing decrease in both the numbers of grants aimed at those diseases, and on overall funding for that research.[41] Looking at the years 1985-2000, the number of helminth-related grants decreased 27% (from 74 to 54) and funding (adjusted dollars) decreased 16% (from about $18 million to $15 million, adjusted dollars) for research funded through the NIAID. In this same period, "direct" poliovirus research alone (our category 1) totaled about $65 million, or, on average, $4.3 million/year, from roughly 50 unique grants during this period. This is one-fourth of the yearly expenditure and a similar effort (as measured by the numbers of grants) on all helminth diseases, which threaten and kill far more people. Given these types of numbers, it is not unreasonable to suggest that the marginal benefit of a reallocation of polio research funds to one or more other diseases would be high.

The standard investigator-initiated, peer-reviewed process for allocating research funds at NIH does not easily allow explicit trade-offs between competing lines of investigation.[42] But it is still well worth considering the implications of a research-priority-setting protocol that assigns to a disease that is almost eradicated a more-or-less equal priority level as it does to diseases that cause thousands or millions of deaths annually. As we have seen, the persistence of significant funding for fundamental research on polio to some extent may reflect a sort of genealogical inertia in the research community. This inertia is reinforced by peer-review criteria that focus almost exclusively on scientific merit. The awkward logical implications of the specific criteria defining "successful research" exempt leaders from ethical responsibility for their choices. Overall, the bottom-up character of the research funding allocation process, combined with the broad acceptance of a stochastic model of how science yields social benefit, means that assessment of opportunity costs cannot form the basis for actions aimed at improving the social value of research. Such assessments must come from a politically higher level (i.e., anywhere, from program managers to politicians), and must incorporate a more complex model of how science contributes to society. The interconnectedness of what were once widely scattered global communities, and the suffering of vast numbers of individuals throughout the world indicate that such a model must include international concerns, even if such concerns do not appear to be immediately relevant to developed nations that are providing most research funding.

4. Implications of polio eradication

Polio research continues to receive federal funding occurs in spite of the fact that polio may soon be eradicated. At the same time researchers who are studying polio continue to claim that their work offers important potential health benefits for society. This tension forces attention to the basic philosophical tenets of the individual investigator research model: an avenue of investigation that scientists continue to choose for its scientific promise may soon be foreclosed because of decisions out of the control of the research community. Specifically, although problems have arisen with finalizing global eradication of wild poliovirus (and regardless of the end game of vaccine withdrawal)

the demand to destroy laboratory stocks has grown. What then becomes of the argument that using poliovirus in research is the "best" way?

Another issue arises here as well, with both practical and symbolic implications. What does it mean to continue to dedicate resources to what is essentially a solved problem? That kind of approach to research, to continue along successful lines, is not necessarily a bad thing. But the reasons for it should be clearly articulated, particularly for federally-funded research where taxpayers rightfully expect payoffs for their investments, including the advancement of knowledge for unsolved problems.

Conclusions

The history of research with respect to the use and understanding of poliovirus provides a useful model for understanding many aspects of the biomedical research enterprise. Poliovirus is one of the most well understood of the medically important microbes, and has certainly provided a model for many laboratories to follow for their experiments in unrelated systems. At the same time it is critical to keep in mind that the current research environment is one of limited resources. Strategic allocation of assets, including human resources, is a perpetual issue in biomedical science, whether this concern is addressed explicitly or not. The freedom to follow interesting research paths using well-understood tools is a crucial aspect of scientific advancement. With that freedom comes the need for responsibility from leaders to consider overall societal needs. The framework for biomedical research in the United States is both strong and flexible, with an enormous capacity to pursue research goals suggested by societal needs and desires. Policymakers, legislators, citizens, and scientists can all contribute to balancing research portfolios to accommodate both scientific and societal needs. The history of poliovirus in the human population, including its imminent eradication, provides a rare opportunity to extract concrete research policy lessons. Measles is the next virus slated for eradication. If lessons from poliovirus research in an era of approaching eradication can be used to speed the demise of measles by, for example, focusing resources toward an already-attainable goal, that will be a useful contribution indeed.

Acknowledgments: The authors thank Robert F. Moore, Director of the Division of Statistics and Analysis, Office of Reports and Analysis, Office of Extramural Research, National Institutes of Health (retired) for providing budget data for 1986-1991 and for clarifying some aspects of funding mechanisms. We also thank Anne Smith for research support, and Richard Nelson and Leo Slater for insightful critiques.

REFERENCES

1. Smith, J.S. (1990) *Patenting the Sun: Polio and the Salk Vaccine*, Anchor Books (Doubleday, New York).
2. Centers for Disease Control and Prevention. (2001) *Epidemiology and Prevention of Vaccine-Preventable Diseases 6th Edition*, Centers for Disease Control and Prevention (Department of Health and Human Services, United States). Also available at http://www.cdc.gov/nip/publications/pink/polio.pdf (accessed 10 January 2002).
3. March of Dimes. (2001) *After Effects of Polio Can Harm Survivors 40 Years Later*, http://www.modimes.org/About2/PressReleases/2001/PolioCanHarm.htm (accessed 10 January 2002).
4. World Health Organization, Global Programme for Vaccines and Immunization. (1998) *Report of the Technical Review Group Meeting*, Geneva, Switzerland.
5. Seavey, N.G., Smith, J.S. and Wagner, P. (1998) *A Paralyzing Fear*, TV Books, Inc. (New York).
6. Blume, S. and Geesink, I. (2000) A Brief History of Polio Vaccines, *Science* **288**: 1593-1594.
7. Sutter, R.W., Cochi, S.I. and Melnick, J.L. (1999) Live attenuated Polio Vaccines. In: Plotkin, S.A. and Orenstein, W.A., eds. *Vaccines 3rd Edition*, W.B. Saunders Company, Philadelphia (Pennsylvania).
8. Dowdle, W.R., Cochi, S.L., Oberste, S. and Sutter, R. (2001) Preventing Polio from Becoming a Reemerging Disease, *Emerging Infectious Diseases* **7** (Supplement): 549-550.
9. Dove, A.W. and Racaniello, V.R. (1997) The Polio Eradication Effort: Should Vaccine Eradication be Next? *Science* **277**: 779-780.
10. Gladwell, M. (2001) Annals of Public Health: The Mosquito Killer, *The New Yorker*, 2 July.
11. Centers for Disease Control and Prevention (1997) Paralytic Poliomyelitis—United States, 1980-1994, *Morbidity and Mortality Weekly Report* **46**: 79-83.
12. World Health Assembly of the World Health Organization. (1988) *Resolution WHA41.28*, Geneva, Switzerland.
13. World Health Organization. (2000) On Track for a World Certified Polio-Free in 2005, But Intensified Efforts Needed, *Press Release WHO/***33**.
14. Centers for Disease Control and Prevention. (1999) Recommendations of the Advisory Committee on Immunization Practices: Revised Recommendations for Routine Poliomyelitis Vaccination, *Morbidity and Mortality Weekly Report* **48**: 590.
15. Lee, J.W. (1995) Ending Polio—Now or Never? In UNICEF, *The Progress of Nations: Action on Polio*, http://www.unicef.org/pon95/heal0002.html.
16. World Health Organization. *National Immunization Days: Calendar*, http://www.polioeradication.org/nidcalendar.htm (accessed 10 January 2002).
17. World Health Organization. (1997) Global Polio Eradication Campaign: WHO and UNICEF To Broker "Days of Tranquility" in Afghanistan, *Press release WHO/***9**. Available at http://www.who.int/archives/inf-pr-1997/en/pr97-09.html (accessed 10 January 2002).
18. World Health Organization (2002) *Polio Case Count*, http://www.who.int/vaccines/casecount/case_count.cfm (accessed 10 January 2002).
19. National Science Foundation (2000) *Twelve Pioneering Researchers Will Receive the 1999 National Medal of Science*, http://www.nsf.gov/od/lpa/news/press/00/pr0003.htm (accessed 20 June 2003).
20. Crotty, S. (2001) *Ahead of the Curve: David Baltimore's Life in Science*, University of California Press, Berkeley.
21. National Institutes of Health *Computer Retrieval of Information on Scientific Projects*, http://crisp.cit.nih.gov/ (accessed 20 June 2003).
22. National Institutes of Health, *Office of Intramural Research Grants* http://grants.nih.gov/grants/oer.htm (accessed 10 January 2002).
23. National Institutes of Health. (2001) *Activity Codes, Organization Codes, and Definitions Used in Extramural Programs*, User Support Branch, Division of Extramural Information Systems, Office of Extramural Research. Also available at http://grants.nih.gov/grants/funding/ac.pdf

24. National Academy of Public Administration. (2001) *A Study of the National Science Foundation's Criteria for Project Selection*, Washington. Also available at http://www.napawash.org/napa/nsfreport.pdf (accessed 10 January 2002).
25. Chen, R.T. and Hibbs, B. (1998) Vaccine Safety: Current and Future Challenges, *Pediatric Annals* **27**: 445-455.
26. National Academy of Sciences. (1996) *Colloquium: Genetic Engineering of Viruses and Viral Vectors.*
27. Stokes, D.E. (1997). *Pasteur's Quadrant: Basic Science and Technological Innovation*, Brookings Institution Press, Washington, District of Columbia.
28. Bush, V. (1945) *Science, The Endless Frontier: A Report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development*, United States Government Printing Office, Washington (District of Columbia). Also available at http://www1.umn.edu/scitech/VBush1945.html (accessed 10 January 2002).
29. Office of the Director, National Institutes of Health. (Undated) *Setting Research Priorities at the National Institutes of Health, Section II, "How Science Works."* Available at http://www.nih.gov/news/ResPriority/priority.htm (accessed 10 January 2002).
30. Kolata, G. (2001) *On Research Frontier, Basic Questions*, The New York *Times* (5 June). Health Section Front. Also available at http://www.nytimes.com/2001/06/05/health/05FRON.html (accessed 10 January 2002).
31. Epstein, S. (1996*) Impure Science: AIDS, Activism, and the Politics of Knowledge,* University of California Press.
32. Gonsalves, Gregg (2000) *NIH-Funded AIDS Vaccine Research: A Critical Review*, http://www.aidsinfonyc.org/tag/science/vaccines.html.
33. Kuhn, T.S. (1970) *The Structure of Scientific Revolutions*, The University of Chicago Press, Illinois.
34. National Research Council (1998*) Assessing the Value of Research in the Chemical Sciences*, National Academy Press, Washington.
35. Kitcher, P. (1995) *The Advancement of Science: Science without Legend, Objectivity Without Illusions*, Oxford University Press, Oxford.
36. Merton, R.K. (1973*) The Sociology of Science: Theoretical and Empirical Investigations*, University of Chicago Press, Illinois.
37. Fauci, A.S. (1998) *Global Health: The United States Response to Infectious Diseases*, Testimony before the U.S. Senate Labor and Human Resources Subcommittee on Public Health and Safety. Available at http://www.niaid.nih.gov/director/congress/1998/0303/posters/poster8.htm (accessed 10 January 2002).
38. World Health Organization. (2000) *Onchocerciasis (River Blindness)*, Fact Sheet Number 95. Available at http://www.who.int/inf-fs/en/fact095.html (accessed 10 January 2002).
39. World Health Organization (1996) *Schistosomiasis*, Fact Sheet Number 115. Available at http://www.who.int/inf-fs/en/fact115.html (accessed 10 January 2002).
40. World Health Organization. (1998) *Dracunculiasis Eradication*, Fact Sheet Number 98. Available at http://www.who.int/inf-fs/en/fact098.html (accessed 10 January 2002).
41. Colley, D.G., LoVerde, P.T. and Savioli, L. (2001) Medical Helminthology in the 21st Century, *Science* **293**: 1437-1438.
42. Garfinkel, M.S. (2000) Biomedical Gerrymandering, *Recent Science Newsletter* **2**: 4-7.