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Context for a new disease: aspects of biomedical research policy in the United States before AIDS

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In the decade since AIDS was recognised in the United States, extraordinary public debate has surrounded the response of the medical establishment, especially the biomedical research enterprise, to the disease. Particular facets of this response have been considered by a number of authors. Gerald M. Oppenheimer, for example, has analysed factors involved in the epidemiological identification of AIDS at the Centers for Disease Control (CDC), and Daniel M. Fox has included biomedical research policy in his identification of a wider 'crisis of authority' in the United States health polity.[1] Lacking, however, has been an interpretation of the capacities, policies, opportunities and restraints that governed how and to what extent federal research organisations could respond to AIDS.[2]

Although such a full-scale evaluation is far too large for a single paper, we will examine two major policy issues and present two case studies that illuminate the context in which the emerging problem of AIDS was integrated into the existing framework of biomedical research sponsored by the National Institutes of Health (NIH).[3] The two policy issues are the structure of the NIH system for distributing grants and the emergence of targeted disease programmes and planning. The NIH grants system had been constructed carefully over three decades and, when confronted with the AIDS challenge, we will argue, functioned with adequate flexibility within its historic edifice. The agency's implementation of targeted research programmes and planning efforts provided an administrative context in which knowledge used to understand AIDS had been created and through which an AIDS research strategy was initially formulated.

The two case studies concern the formulation of guidelines for research on recombinant DNA and the 1976 epidemic of Legionnaires' disease. The former illuminates political concerns during the 1970s about the direction and control of science and, we believe, undergirded the agency's mandate to seek public advice in structuring AIDS advisory boards. The latter, which examines the roles of the

NIH and the CDC in response to another new disease, provides data for comparison with AIDS.

Research funding and NIH grants system

Although precedents for government patronage of medical research extend back to the late nineteenth century, the present system of federal support emerged after the Second World War, fuelled by wartime medical achievements, especially the development of antibiotics.[4] It was necessarily predicated on the assumption that practical results would soon follow the investment of public money, because creation of such a programme required that Americans suspend a deeply ingrained suspicion of government patronage for special groups.[5] Historically, Congress had preferred to support practical scientific endeavours over open-ended basic research, even when a lack of basic knowledge regarding the ventures undertaken resulted in wasted time, effort and money.[6]

The NIH grants system was modelled on the process for allocating scientific funds during the Second World War. Known as the 'peer review' system, its goal was to fund research on the basis of merit and of priorities determined by the granting agency. University-based investigators submitted research proposals, which were separated by the NIH according to subject area and referred to groups of non-federal scientists who were experts in each area – i.e. the peers of the proposers. After receiving ratings on their scientific merit from the review panels, the applications were reviewed a second time by the advisory councils for each institute. These bodies were comprised of physicians, scientists and laypersons, who considered the proposals from the perspective of each institute's mission, placing them in the context of nation-wide policy concerns about diseases and of the need for further research in selected areas. From the time an investigator submitted a proposal until the time funds were received, about eight or nine months elapsed, under normal circumstances. Grant monies were channelled to the principal investigators through the institutions with which they were affiliated.[7]

Studies of the peer review system began almost immediately after it was established. By 1976, some twenty-two studies had been conducted by congressional committees, by both Republican and Democratic administrations, by the scientific community and by NIH itself. Major issues discussed in these deliberations included conflict of interest, inability to provide adequate review in highly specialised areas, concern that the review groups were not representative of the current trends in science, fear of missing the unrecognised genius by funding only 'safe science', the volume of grants assigned to study section members and the burden for both applicants and reviewers imposed by new laws and regulations.[8] In the years just before AIDS was identified, the studies continued. Concerns about fairness, for example, surfaced in a 1977

appropriation hearing. A congressman queried NIH director Donald S. Fredrickson about allegations that the system was 'really an old boys' club' and that there was no 'provision for appeals'. Fredrickson noted that another committee had conducted yet another intensive review of the system and produced recommendations for establishing an appeals system and for reducing even further the possibility of cronyism or conflict of interest in awarding grants.[9]

Also of major concern in the late 1970s was the impact of economic forces on research funds awarded under the system. One measure of this was the increase in 'indirect costs' to support research. Indirect costs were defined as compensation to institutions for overhead expenses incurred in housing federally sponsored research. Heating and cooling, additional laboratory space and added maintenance costs fell into this category. The total cost of any grant represented the sum of direct and indirect costs. In 1947, when the first funds were awarded, indirect costs had been set at 8% of the direct costs of research. In 1955 Congress raised the indirect cost rate to 15% and by 1963, the rate had risen only to 16%.[10] Beginning with the oil crisis in 1974, however, indirect costs began to spiral upward, and by 1979 they had risen to 26.7%. The sharp increase in energy costs was the factor cited most frequently by recipient institutions as responsible for the increase. By the end of the 1970s, inflation had so increased the total cost of funding research that fewer grants could be supported. If the percentage of indirect costs for 1979 had been the same as the 1966 rate, for example, an additional $228 million would have been available in 1979 for research projects.[11]

During the years before AIDS was identified, the NIH grants system had become an elaborate, much-studied process designed to identify and support meritorious research through the judicious expenditure of taxpayer dollars. NIH and university administrators, Congress and biomedical scientists were most concerned with the impact of inflation on grants and with questions of accountability, fairness and scientific merit. Within this larger framework, as will be discussed below, the agency projected lines of research in annual plans and attempted to guide the course of research toward those health problems with which large segments of the public were concerned.

Managing the research enterprise: planning initiatives and targeted research

A second policy objective during the decade before AIDS was the refinement of existing policies to ensure progress in biomedicine toward specifically defined goals. In part, it was expressed through initiatives for planning programmes and for targeted research efforts. Both emerged after the grants programme had already functioned for more than a decade, and they represented a slight philosophical shift in management of the enterprise, which had been based on

two major premises: (1) that biomedical science would advance best by allowing individual scientists to propose lines of research and to follow up serendipitous observations, and (2) that a substantial investment in basic laboratory research was the method most efficient in the long term for producing practical clinical applications.[12] By the 1970s, however, these concepts had been modified after extensive study by Congress and outside groups.

Reliance on individual initiative to guide research came into question in 1965 when a blue ribbon panel appointed by President Lyndon B. Johnson stipulated that one of the most important organisational needs of NIH was 'strengthening of its capacity for long-term planning'. The next year a congressional committee investigation of the Department of Health, Education and Welfare (DHEW) pointedly noted 'the lack of effective planning procedures' as the 'most glaring deficiency' observed.[13] These studies did not negate the importance of the individual initiative concept but rather reflected the growing size and complexity of the research enterprise. Furthermore, they coincided with the introduction by the Johnson administration of a new budgeting system, called Planning–Programming–Budgeting (PPB), which sought to integrate agency planning and budgeting for greater administrative control and efficiency.[14] In response, the NIH elevated the Office of Program Planning within the administration and instructed it to place emphasis on working with individual institutes in developing long-range plans.[15]

A decade later the Assistant Secretary for Health launched another planning initiative, articulated in the 1974 publication, *Forward Plan for Health.* In this document the DHEW detailed activities to be supported by all of its agencies, including the NIH, for the fiscal years 1976–80. By 1977 individual agencies published their own annual planning documents separately. At the NIH, two major goals of the process were to identify research that spanned categorical institute lines and thereby promote co-ordination of effort and to integrate the planning process with both the budget and the legislative processes during each year. This integrated approach produced plans that included as many different scientific opportunities as possible.[16]

Closely allied with the concept of planning for research was an increasing emphasis on targeting specific diseases for intensified research. This initiative challenged the premise that free-ranging scientific inquiry into fundamental biological questions was the most direct route to clinical applications. By the waning years of the Johnson administration, the President and research lobbyists were calling for results from the investment in a quarter-century of basic research. Noting in 1966, for example, that 'a great deal of basic research has been done', Johnson stated that 'the time has come to zero in on the targets by trying to get our knowledge fully applied'.[17] This trend was continued and escalated during the administration of Richard Nixon with enactment of the

National Cancer Act that launched a 'War on Cancer' and with subsequent initiatives against heart disease and stroke.[18] Between 1971 and 1975, in fact, Congress passed seventeen public laws directing NIH to emphasise research on particular areas, including sickle-cell anaemia, Cooley's anaemia, multiple sclerosis, sudden infant death syndrome, diabetes, arthritis, Huntington's disease and epilepsy.[19]

Although research on specific diseases was to be emphasised in these programmes, considerable leeway existed in deciding how best to attack each malady. Much targeted money was utilised in projects that had broad implications, such as studies of a possible link between cancer and viruses, research on the immune system and improved techniques in molecular biology. In the decade before AIDS was identified, NIH research plans noted the high priority given to studies in these basic fields.[20] Funds designated for cancer research, for example, were utilised in support of immunology and virology, fields that had proved fruitful in the 1970s and had implications for many different diseases. In 1977 the National Cancer Institute (NCI) provided 48% of the total NIH investment in immunology and 69% of NIH support in virology.[21]

The planning and targeted research efforts reflected Congress's concern with assuring steady progress toward defined goals. Both of these initiatives arose outside the NIH, and implementation strategies reflect the agency's efforts to comply with congressional mandates. Neither introduced radical restructuring within the NIH; indeed, both had the effect of refining policies and procedures toward what Congress perceived as a more effective implementation of the agency's mission. The plans sought to identify and foster promising areas of research that might otherwise be missed and to minimise duplication of effort. Targeted research programmes raised the visibility of particular diseases with which substantial segments of the public were concerned. In concert with the modifications in the grants process, these management imperatives reveal the NIH in the pre-AIDS era as a mature institution, whose policies and procedures were directed at fine-tuning a broadly accepted and widely supported mission.

Policy making on the frontiers of science: recombinant DNA

In addition to responding to broad areas of policy concern in the 1970s, NIH addressed a number of issues concerning the ethics of science. These included investigation of fraud and misconduct in research, the ethics of research on human subjects and regulation of recombinant DNA research. The last provides an excellent case study for examining the emergence of new scientific techniques and the politics of biomedicine in the years preceding AIDS.

In 1974, a group of eminent scientists called attention to the potential hazards of newly discovered recombinant DNA techniques.[22] Their announcement sparked debates over control of this powerful new biological tool. These

occurred within a social climate sceptical of science. Discoveries in the 1960s about toxic side effects of antibiotics, the environmental dangers of chemical pesticides, carcinogens in food and the ethical dilemmas posed by manipulation of individuals in behavioural research had produced misgivings about the value and humanity of modern science and technology.[23]

In response to both scientific and lay concerns, the Secretary of the Department of Health, Education and Welfare chartered a Recombinant DNA Advisory Committee (RAC), headed by the director of intramural research at NIH and comprised of scientists and laypersons.[24] In February 1975 an international conference of molecular biologists convened at the Asilomar conference centre in California. Participants reached consensus about the appropriate levels of laboratory safeguards for experiments of differing potential risks and about the types of experiments that would be prohibited voluntarily until knowledge increased about the hazards or safety of the technology. Working from these findings, the RAC drafted guidelines that were promulgated in 1976.[25]

Some environmental activists complained that, in formulating the guidelines, the RAC had been dominated by 'technocratic' interests focused on safety alone to the exclusion of democratic debate on the ethics of recombinant experiments. A number of bills were introduced into Congress to legislate regulations for the research, but none was enacted. As the 1970s drew to a close, the highly vocal debate subsided, experience having demonstrated that biological disaster was unlikely. During the early 1980s, the controls were loosened, but the RAC was retained as a standing committee to evaluate research that broke new ground in recombinant DNA research.[26]

This case study illustrates several characteristics of federal biomedical research policy during the later 1970s. First, NIH leadership was expected by the larger biomedical community in dealing with such issues. Since recombinant DNA technology cut across disciplinary and geographic lines, no single professional scientific society could claim leadership, nor could any single institution. Second, the agency was implicitly charged by the scientific community with making the case for voluntary guidelines to Congress and thereby heading off legislative regulations that most scientists believed would be detrimental to research. Finally, in assuming leadership of the recombinant DNA discussions, the NIH had to respond to lay concerns about the potential social consequences of scientific decisions. The political benefits gleaned from lay participation in the RAC reinforced the wisdom of existing NIH practice to include lay members on major advisory committees.

Research and public health crises: Legionnaires' disease

The formulation of recombinant DNA guidelines raised broad questions about leadership and regulation in science. A second case study, focusing on the 1976

Table 1. *NIH and CDC initial expenditures on AIDS and Legionnaires' disease (dollars in thousands)*

	AIDS						
	Fiscal year						
	82	83	84	85	86	87	88
CDC	2,050	6,202	13,750	33,298	62,152	136,007	304,942
NIH	3,355	21,668	44,121	63,737	134,667	260,907	430,570
	Legionnaires' disease						
	Fiscal year						
	76	77	78	79	80	81	82
CDC	162	1,533	1,931	2,047	1,521	1,647	1,115
NIH	—	—	—	622	1,266	1,635	1,027

Sources: Office of Financial Management, CDC; NIH Data Book 1990, US Dept. of Health and Human Services, Public Health Service, NIH.

outbreak of Legionnaires' disease, provides insight into the functioning of well-established federal protocols. It also provides perspective on the respective roles of the CDC and the NIH in addressing an extraordinary public health problem in the pre-AIDS period.[27]

As many authors have detailed, in 1976 at an American Legion convention in Philadelphia, Pennsylvania, a mysterious respiratory malady struck 182 Legionnaires or members of their families. Twenty-nine of them died. The microbial cause of this epidemic eluded identification for some months, during which questions were raised about the ability of biomedicine to respond to unknown pathogens. Eventually, however, CDC microbiologists identified a gram-negative bacterium as the etiological agent. This organism, *Legionella pneumophilia*, had long been known to microbiologists. What had been unknown was its affinity for growing in modern air handling systems, which distributed the pathogen through the air to unwary victims. Subsequent studies of stored sera revealed that this organism also had been the cause of previous unsolved respiratory epidemics.[28]

Research on Legionnaires' disease was initially conducted by the CDC and, after October 1979, also by the NIH. As the first line of defence against epidemic outbreaks, the CDC launched an epidemiological investigation and utilised standard laboratory methodology in searching for the etiological agent. Once *Legionella pneumophilia* had been identified, the agency researched the biology, immunology and pathogenic microbiology of the organism. It also instituted serologic and pneumonic surveillance and investigated rapid diagnostic techniques. Research sponsored by the NIH fell into four categories:

clarification of the etiologic niche, elucidation of the mode of transmission, delineation of the pathology through the development of animal models and characterisation of different stains and surface antigens in order to develop diagnostic tests and possible vaccines.[29]

Legionnaires' disease was reminiscent of classic epidemics in that it struck rapidly, with considerable mortality, then waned just as rapidly. As the figures in Table 1 show, research expenditures by the CDC rose rapidly, peaked and then levelled off as the disease was understood. Those by NIH started later, and rose to a level comparable with those of CDC. Within a year, Legionnaires' disease had reaffirmed the belief that infectious disease problems were understood and controllable within the existing medical and scientific paradigm. The very success, moreover, of the CDC in identifying the cause of Legionnaires' disease and in developing diagnostic and preventive methods against it may have strengthened the expectation that other new diseases, including AIDS, would be quickly resolved through existing techniques.

Placing the NIH response to AIDS in context

This brief examination of the two issues and two case studies offers some insight to the historical context in which the NIH responded to AIDS. Broadly speaking, the NIH mission in the post-Second World War era had been defined by Congress as research, especially on chronic diseases, for which few or no medical interventions were effective. Steady progress toward specific goals, accountability and fairness in awarding grants were issues of primary concern. The advent of AIDS brought stress to the carefully built biomedical research system when political advocates suggested that it should have been structured to permit a more rapid response to the deadly new disease.

AIDS came as a surprise to the medical community. It was not just an outbreak of a well-known pathogen or even a new organism within a well-understood family of pathogens. Since no previous transmissible agent had been known that killed by undermining the immune system, research aimed at understanding such an agent had not previously been conducted, nor had it been contemplated in structuring plans for future research. In this sense, the research planning process was useless. By proposing support for lines of research in fruitful areas, however, such as molecular immunology and retrovirology, the planning process had fostered the new production of knowledge that proved useful in understanding the new disease. The 1981 NIH research plan, for example, which was prepared during the spring of 1981, before publications about AIDS had appeared, highlighted as promising areas new immunologic techniques, such as recombinant DNA technology and hybridoma cell fusion, and studies on interferon and other biological response modifiers – all fields that were utilised in research on AIDS.[30]

Once AIDS was identified, moreover, it was rapidly incorporated in the planning process as a promising area for research support. The plan written in 1982 contained two items of note with regard to AIDS. In the National Institute of Allergy and Infectious Diseases section, the institute proposed to redirect some funds during fiscal year 1983 (which began in October 1982) for new initiatives 'in response to unusual or emerging new opportunities, including acquired and inherited immunologic disorders'. Since AIDS was the only known 'acquired' immunologic disorder, this notation reflects the institute's interest in the new disease. Similarly, in the NCI section, 'Kaposi's sarcoma in homosexual men and concurrent viral infections' was specified as one area to be emphasised. These comments not only reveal institute awareness of AIDS as a research problem but also underscore the difficulty of formulating focused research programmes in the absence of knowledge about the etiological agent.[31]

Perhaps the single issue most assailed by critics of the NIH response to AIDS was the length of time between identification of a new disease threat and the receipt of the first grant dollars by university researchers who wished to investigate it. In *AIDS in the Mind of America*, for example, Dennis Altman asserted: 'There were two major problems in funding AIDS research, the first being the question of how much money would be available, the second involving the very cumbersome process whereby that money was made available to researchers.'[32] As we have seen, however, the question of whether the grants system could or should be a vehicle for rapid distribution of funds in response to public health emergencies had not been considered in studies of the process.[33] Given the history of the system and its many modifications, it could be compared to a vast ship laboriously constructed over many years. Critics who complained that the system did not distribute funds rapidly were denouncing the ship because it could not fly.[34]

Further, the impact of indirect costs had taken a severe toll on the number of new grants that could be awarded and on the percentage of approved grants, both new and continuing, that could be funded. During the time that AIDS emerged, the NIH leadership struggled to maintain a minimum number of new awards that would be funded each year in order to prevent further erosion in the number of investigators pursuing federally sponsored research.[35] The constrained situation, which was exacerbated by the budget-cutting policies of Ronald Reagan's administration, compromised the agency's flexibility to initiate new activities, including research on AIDS. Operating in a 'zero sum game' meant that, in the absence of new appropriations, substantial amounts of research support for new initiatives could be generated only by reducing or eliminating existing programmes or by transferring funds from one agency to another.[36]

In August 1982, just over one year after the first paper identifying AIDS had appeared, the NCI issued its first request for investigators to submit grant applications relating specifically to AIDS.[37] This formal request was designed to

bring into AIDS work those institutions that did not already participate in an NCI co-operative agreement, a funding mechanism similar to a grant, but one in which the awarding institute retained substantial programmatic involvement. Institutions already involved in co-operative agreements were eligible to apply for supplemental funds to inaugurate research on AIDS.[38] In addition, individual scientists could submit proposals relating to AIDS through the normal grants process, and recipients of grants whose work could be redirected towards AIDS were permitted to alter their projects if their home institutions agreed.[39] In April 1982 Bruce Chabner, director of NCI's Division of Cancer Treatment noted this flexibility in his testimony before California Representative Henry Waxman's Subcommittee on Health and the Environment during the first congressional hearing on AIDS: 'It is hard to account for the amount of money that they [NIH grantees] have invested through redirection of their grant support, but we feel it is considerable in view of the number of publications that have appeared.'[40]

Within the NIH intramural programme, flexibility to redirect research was considerably greater.[41] The first AIDS patient was treated in the NIH Clinical Center in June 1981, the same month that the initial publication about AIDS appeared.[42] During the ensuing year, a group of physicians and scientists redirected some or all of their research to explore the unusual disease and treat additional patients. One of them described the process: 'When we first started studying AIDS, just by word of mouth, there were a lot of people who wanted to look at various aspects [of the disease] . . . Very quickly we got a group of people . . . who didn't need an organized program because they all had a common interest.'[43] Another recalled that no one initially dropped existing projects to work on AIDS, 'they simply worked longer', into the evenings and on weekends.[44] In 1982 Robert C. Gallo, chief of the Laboratory of Tumor Cell Biology in the NCI, redirected his laboratory's research toward searching for the etiological agent after hearing evidence presented by James Curran, chief of the CDC's venereal disease branch, that AIDS was transmitted via blood and compromised the function of T-lymphocytes, white blood cells that were key components of the immune system. Curran's presentation suggested to Gallo that AIDS might be caused by an agent closely related to the retroviruses on which his laboratory was already working.[45]

These experiences of researchers in the intramural NIH programme reveals the existence of an informal network of investigators – inside and outside of government – in which information about AIDS was shared actively. In addition, internal correspondence files attest to official co-ordination and liaison efforts between agencies of the Public Health Service (PHS) within the Department of Health and Human Services (DHHS). In a memorandum dated 31 July 1981, for example, William H. Foege, director of the CDC, requested NCI co-operation in studying the 'outbreak' of Kaposi's sarcoma. Specifically, Foege asked that NCI augment the CDC's epidemiologic studies with therapy trials and with 'studies

designed to define possible microbiologic, immunologic, and/or toxic roles in oncogenesis'. Vincent T. DeVita, Jr, director of NCI, referred the memo to Bruce Chabner, then acting director of NCI's Division of Cancer Treatment, asking Chabner to arrange for 'someone to join in'. Chabner responded by organising a national conference in September 1981 aimed at developing a 'coordinated strategy regarding the etiology and treatment of Kaposi's sarcoma'. In January 1982 Edward N. Brandt, Jr, the Assistant Secretary for Health in DHHS, officially requested 'greater participation' in AIDS investigation by NCI, the National Institute of Allergy and Infectious Diseases and the National Institute on Drug Abuse to supplement epidemiologic work by the CDC. The directors of each institute reported on activities underway, and on 3 March the CDC hosted a conference on AIDS for PHS scientists. Further liaison activities continued, including the formation in July 1982 of an NIH 'working group' that co-ordinated efforts among institutes and provided agency representation on AIDS matters.[46]

The 1970s emphasis on targeted research made AIDS a candidate for earmarked funds as soon as it was established that the disease was no ordinary epidemic outbreak that would be quickly controlled. Expenditures on AIDS rose dramatically during the first three years after the disease was identified, and continued their exponential climb for years thereafter. The only parallel to this striking growth in funds for a single disease was the sharp rise in cancer funds after enactment of the 1971 National Cancer Act. Comparing funding patterns for AIDS and Legionnaires' disease underscores the magnitude of the difference. Figure 1 compares the overall pattern of research funding for Legionnaires' and AIDS during the years after each was first identified. Although some authors have suggested that public and political sentiment compelled a larger research effort for Legionnaires' disease, our analysis shows that spending on AIDS outstripped Legionnaires' research in overall magnitude and in acceleration of spending over time. Furthermore, NIH funding for Legionnaires' began only after the etiologic agent was identified. In the case of AIDS, however, NIH provided more funds for research than did the CDC within the first full fiscal year after the disease was recognised – two years before a retrovirus was accepted as the etiological agent. The differences in funding patterns for these diseases reflect early recognition of the differences between the diseases themselves. Legionnaires' disease proved to be a transient and limited disease event in sharp contrast to AIDS' relentless exponential growth.

The experience of developing guidelines for recombinant DNA research also had an impact on NIH's AIDS policy. Although there were important differences between recombinant DNA and AIDS – the former, though worrying, posed a hypothetical problem while the latter involved actual death and suffering – both confronted the biomedical community with critical issues relating to the

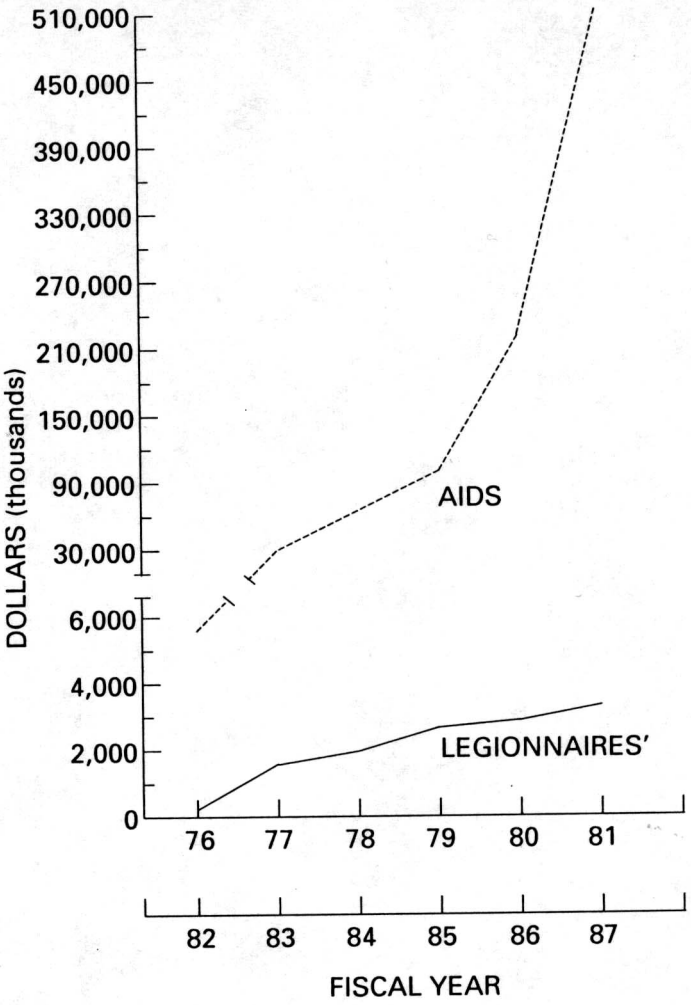

Figure 1 Initial PHS funding for AIDS and Legionnaires' disease

Sources: Office of Financial Management, CDC; NIH Data Book 1990, US Dept. of Health and Human Services, Public Health Service, NIH.

public health and welfare. The emergence of guidelines governing recombinant DNA research followed recognition of a theoretical but discernible risk. Response to AIDS was similar, once the magnitude of the risk had been ascertained. In 1980 and 1981, however, as unusual cases of what came to be known as AIDS were discussed between medical experts, the magnitude of the risk was not apparent. When epidemiological evidence mounted that it was a communicable disease with identifiable risk factors and that it was recognised in other countries as well as in the United States, both medical and lay communities mobilised to combat it.

Although it is impossible to pinpoint an exact moment when the enormity of this new disease became apparent, the evolution of phrases describing AIDS provides some clues. During the summer and autumn of 1981, the terms 'epidemic' – usually placed within quotation marks – and 'outbreak' were often used, sometimes in association with phrases such as 'dramatic increase'. By early 1982, the phrases 'accident of nature' or 'experiment of nature' appeared, indicating recognition of a problem that was larger than a limited 'outbreak'. During the next few months, however, the terminology escalated as appreciation increased about the scope of the disease and its lethal nature. In April 1982, Bruce Chabner of the NCI testified that AIDS was a 'new, complex, and very serious illness', which had become 'a public health problem of great magnitude'. At the same hearing, James Curran of the CDC suggested that known cases might be 'merely the tip of the iceberg', and that although the entire range of manifestations of the disease remained unclear, they were 'quite disturbing'. By mid-1982, epidemiological evidence had convinced many investigators that AIDS was caused not by an environmental agent but rather by an infectious pathogen, probably transmitted by blood as well as by sexual activity. This finding may well represent the turning point in medical understanding of AIDS because of its ominous implications. An environmentally caused disease might be limited geographically and/or controlled with existing public health methods, while an unknown, communicable pathogen would be much more difficult to identify, prevent and cure. Reflecting this realisation in his rhetoric, one investigator returning from a scientific meeting on AIDS in July 1982 strongly stressed the need for 'a most urgent response'.[47]

Internal NIH administrative structures for addressing AIDS also emerged parallel with funding increases as the scope of the disease became better understood. The NCI, concerned with the incidence of Kaposi's sarcoma, organised an informal 'working group' relating to AIDS in March 1982, four months before the agency-level group was established.[48] By 1985 all the NIH working groups had been consolidated and elevated into the NIH AIDS executive committee, and in 1987, the Secretary of the Department of Health and Human Services, chartered the AIDS Program Advisory Committee (APAC), with four of the thirteen appointed members designated as 'members of the general

public'.[49] To strengthen internal co-ordination further, an NIH Office of AIDS Research was created the following year.[50] The careful attention by NIH to lay involvement in the APAC was doubtless reinforced by the recent experience of constituting the RAC, as well as by earlier precedents of lay representation on advisory councils. Conversely, the demands of AIDS activists to participate in such official bodies reflected their assumption that power should be shared in making some medical decisions, an attitude that was in part an outgrowth of the experience with recombinant DNA.

In a 1989 article, historian Charles Rosenberg described social reaction to an epidemic as occurring in a predictable pattern like the acts in a drama.[51] In act three pressure is generated for decisive and visible community response. In the past, such ritualist actions have included quarantines and religious fasting or prayer. Large congressional allocations for research and the establishment of visible bureaucratic structures may be seen as a similar response in our secular, scientifically oriented society. Viewed in this light, much of the stridency directed against the federal biomedical research enterprise had its origin in the need to propel such an appropriate community response. The few issues addressed in this paper, however, suggest that considerable flexibility existed in the federal biomedical research response to AIDS even before external criticism appeared. They also indicate that careful attention to historic medical, scientific and organisational forces is indeed necessary to understand how the biomedical research community formulated and implemented its response to the deadly disease.

NOTES

1 Gerald M. Oppenheimer, 'In the eye of the storm: the epidemiological construction of AIDS', in Elizabeth Fee and Daniel M. Fox (eds.), *AIDS: The Burdens of History* (Berkeley, 1988), 267–300; Daniel M. Fox, 'AIDS and the American health polity: the history and prospects of a crisis of authority', in Ronald Bayer, Daniel M. Fox and David P. Willis (eds.), 'AIDS: the public context of an epidemic', special issue, *Milbank Quarterly*, 64 (suppl. 1) (1986), 7–33; reprinted in Fee and Fox (eds.), *AIDS: The Burdens of History*, 316–43. See also Stephen P. Strickland, *Research and the Health of Americans: Improving the Policy Process* (Lexington, Mass., 1978).

2 'Introduction', in Bayer, Fox and Willis (eds.), 'AIDS: the public context of an epidemic', 3.

3 The NIH is the research arm of the Public Health Service in the US Department of Health and Human Services. This department was created in 1980 out of the health and welfare programmes of the former Department of Health, Education and Welfare.

4 The two precedents for federal support of medical research by non-federal scientists were the grants given for research on yellow fever by the National Board of Health between 1879 and 1883 and those given for research on venereal diseases by the

Interdepartmental Social Hygiene Board between 1918 and 1921. See Peter Bruton, 'The National Board of Health', PhD dissertation, University of Maryland, 1974; Wyndham D. Miles, 'A history of the National Board of Health, 1879–1893', 2 vols., manuscript, National Library of Medicine, 1970. Within its own laboratories, first called the Hygienic Laboratory and later renamed the National Institute of Health, the US Public Health Service and its predecessor agencies had sponsored research since 1887. See Victoria A. Harden, *Inventing the NIH: Federal Biomedical Research Policy, 1887–1937* (Baltimore, 1986). Standard references on the emergence of the post-Second World War NIH include James A. Shannon, 'The advancement of medical research: a twenty-year view of the role of the National Institutes of Health', *Journal of Medical Education*, 42 (1967), 97–108; Elizabeth Brenner Drew, 'The health syndicate: Washington's noble conspirators', *Atlantic Monthly*, 220 (December 1967), 75–82; Stephen P. Strickland, *Politics, Science, and Dread Disease: A Short History of U.S. Medical Research Policy* (Cambridge, Mass., 1972); G. Burroughs Mider, 'The federal impact on biomedical research', in John Z. Bowers and Elizabeth F. Purcell (eds.), *Advances in American Medicine: Essays at the Bicentennial*, 2 vols. (New York, 1976), II, 806–71; Donald S. Fredrickson, 'The National Institutes of Health yesterday, today, and tomorrow', *Public Health Reports*, 93 (1978), 642–7; Daniel M. Fox, 'The politics of the NIH extramural program, 1937–1950', *Journal of the History of Medicine and Allied Sciences*, 42 (1987), 447–66; Stephen P. Strickland, *The Story of the NIH Grants Program* (Lanham, Md., 1989).

5 Alvin M. Weinberg, 'In defense of science', *Studium Generale*, 23 (1970), 797–807; reprinted in *Science*, 169 (1970), 141–5. On republicanism and suspicion of patronage for any special group, see Daniel T. Rodgers,'Republicanism: the career of a concept', *Journal of American History* 79 (1992), 11–38.

6 One of the earliest examples of this is found in efforts to survey and map the US coast. See A. Hunter Dupree, *Science in the Federal Government: A History of Policies and Activities* (Cambridge, Mass., 1957; reprint Baltimore, 1986), 29–33. Dupree also noted that in the nineteenth century, Congress created most scientific agencies through the appropriations process in order that they could be controlled – and, if necessary, terminated – by the simple act of withholding funding. Indeed, the organic legislation authorising the existence of the federal laboratory that became the National Institutes of Health was buried in a 1901 sundry civil appropriations act. See *ibid.*, 214–15; Harden, *Inventing the NIH*, 17.

7 Catherine Henley, 'Peer review of research grant applications at the National Institutes of Health 1: the assignment and referral processes', *Federation Proceedings*, 36 (1977), 2066–8; *idem*, 'Peer review of research grant applications at the National Institutes of Health 2: review by an initial review group', *ibid.*, 2186–90; *idem*, 'Peer review of research grant applications at the National Institutes of Health 3: review by an advisory board council', *ibid.*, 2335–8. On political questions relating to the peer review system, see Don K. Price, 'Endless frontier or bureaucratic morass?', *Daedalus*, 107 (Spring 1978), 75–92.

8 Major studies of the NIH peer review system are summarised in 'Selected studies, investigations, and recommendations related to the National Institutes of Health: an annotated bibliography', in Appendix D, 'Selected staff papers', of US President's Biomedical Research Panel, *Report of the President's Biomedical Research Panel*,

30 April 1976, 4 appendices, 4 suppl. (Washington, DC, DHEW Publication Nos. (OS) 76–500 through 76–509, 1976), 1–32.

9 US Congress, House Committee on Appropriations, *Departments of Labor and Health, Education and Welfare Appropriations for 1978: Hearings before a Subcommittee of the Committee on Appropriations*, part 3, 'National Institutes of Health' (Washington, DC, 1977), 56–7.

10 The rate set in 1963 was 20% of 'allowable' direct costs, which, because of the accounting methods used, resulted in a net rate of about 16% of total direct costs. See Kenneth T. Brown, 'Indirect costs of federally supported research', *Science*, 212 (1981), 411–18.

11 Brown, 'Indirect costs of federally supported research'; *Report by the Comptroller General of the U.S.: Indirect Costs of Health Research. How They are Computed, What Actions are Needed* (Washington, DC, General Accounting Office Publication No. HRD–79–67, 1979), esp. 9–10; Saunders MacLane, 'Total reporting for scientific work', *Science*, 210 (1980), 158–63. Because indirect cost rates were negotiated with individual institutions and because accounting practices in calculating direct and indirect costs varied among institutions, these figures represent overall trends.

12 These concepts have been discussed in most historical studies of the NIH grants programme. See, for example, *The Nation's Medical Research*, vol. 5 of US President's Scientific Research Board, *Science and Public Policy: A Report to the President*, by John R. Steelman, 5 vols. (Washington, DC, 1947), esp. 9, 27; Strickland, *Politics, Science, and Dread Disease*, 174; Shannon, 'The advancement of medical research', 105.

13 US President's NIH Study Committee, *Biomedical Science and its Administration. A Study of the National Institutes of Health*, Report to the President (Washington, DC, 1965), 1; US Congress, House Committee on Interstate and Foreign Commerce, *Investigation of HEW*, Report of the Special Subcommittee on Investigation of the Department of Health, Education and Welfare, 89th Cong., 2nd sess., 13 October 1966, House Rept. No. 2266 (Washington, DC, 1966), 110.

14 There is a large literature on this programme. Two review papers with useful citations are W. Ken Fisher, Jr, 'PPBS in proper perspective', *Federal Accountant*, 21 (1972), 22–32; B. H. DeWoolfson, 'Federal PPB: A ten year perspective', *ibid.*, 24 (1975), 52–61. In 1971 strict adherence to PPB format was abandoned as a requirement for submission of agency budgets, although many agencies continued to utilise its planning and programme analysis features.

15 The NIH did not implement the recommendation of the President's NIH Study Committee (known as the Wooldridge Committee after its chairman, physicist Dean E. Wooldridge) that a policy and planning council be formed to assist the NIH director in formulating programmes. The NIH position was explained in 'The initial NIH commentary, biomedical science and its administration, the Wooldridge Committee Report', staff paper, April 1965, Office of the Director central files, NIH (hereafter cited as OD central files, NIH).

16 US Congress, House Committee on Appropriations, *Departments of Labor and Health, Education, and Welfare Appropriations for 1975: Hearings before a Subcommittee of the Committee on Appropriations*, part 3, 'Department of Health, Education, and Welfare' (Washington, DC, 1974), 2–3; *Forward Plan for Health,*

FY 1976–80 (Washington, DC, 1974); US National Institutes of Health, *Forward Plan, FY 1979–83*, administrative document (Bethesda, 1977), copy in NIH Historical Office.

17 Johnson's remarks to medical and hospital leaders, 15 June 1966, quoted in *Research in the Service of Man: Biomedical Knowledge, Development, and Use*, proceedings of a conference sponsored by the subcommittee on government research (pursuant to S. Res. 218, 89th Cong.) and the Frontiers of Science Foundation of Oklahoma for the Committee on Government Operations, United States Senate, 24–7 October 1966 (Washington, DC, 1967), 5. See also Strickland, *Politics, Science, and Dread Disease*, chapters 9–10.

18 R. A. Rettig, *Cancer Crusade: The Story of the National Cancer Act of 1971* (Princeton, 1977); Natalie Davis Spingarn, *Heartbeat: The Politics of Health Research* (Washington, DC, 1976).

19 The specific initiatives with citations and appropriation amounts are listed in 'Congressional initiatives in biomedical and behavioral research', in Appendix D of *Report of the President's Biomedical Research Panel*, 36–8, 40.

20 See, for example, US National Institutes of Health, *Draft Research Plan, FY 1981–1983*, administrative document (Bethesda, 1979), copy in NIH Historical Office, 35–6.

21 *Ibid.*, 65. NCI also supported Robert C. Gallo's research in retrovirology during the 1970s. In 1979 Gallo announced his discovery of the first human retrovirus. See Robert Gallo, *Virus Hunting: AIDS, Cancer and the Human Retrovirus: A Story of Scientific Discovery* (New York, 1991), 99–115.

22 Stanley N. Cohen, Annie C. Y. Chang, Herbert W. Boyer and Robert B. Helling, 'Construction of biologically functional bacterial plasmids *in vitro*', *Proceedings of the National Academy of Sciences, U.S.A.*, 70 (1973), 3240–4. Paul Berg, David Baltimore, H. W. Boyer, Stanley N. Cohen, R. W. Davis, D. S. Hogness, D. Nathans, R. Roblin, J. D. Watson, S. Weissman and N. D. Zinder, 'Potential biohazards of recombinant DNA molecules', *ibid.*, 71 (1974), 2593–4. On the recombinant DNA controversy, see John Richards, *Recombinant DNA: Science, Ethics, and Politics* (New York, 1978); Nicholas Wade, *The Ultimate Experiment: Man-Made Evolution* (New York, 1977; rev. edn, 1979); David Archer and Stephen P. Stich, *The Recombinant DNA Debate* (Englewood Cliffs, NJ, 1979); Joan Morgan and W. J. Whelan (eds.), *Recombinant DNA and Genetic Experimentation* (New York, 1979); Sheldon Krimsky, *Genetic Alchemy: The Social History of the Recombinant DNA Controversy* (Cambridge, Mass., 1982). Initial research on recombinant DNA was supported by grants from the National Institute of Child Health and Human Development and the National Institute of General Medical Sciences.

23 On the anti-science movement, see Herbert Marcuse, 'The individual in the great society', in B. M. Gross (ed.), *A Great Society* (New York, 1968); Jacques Ellul, *The Technological Society* (New York, 1964); Theodor Roszak, *The Making of a Counter Culture* (New York, 1969); *idem*, *Where the Wasteland Ends* (Berkeley, 1972); Don K. Price, 'Purists and politicians', *Science*, 163 (1969), 25–31; Philip M. Boffey, 'AAAS convention: radicals harass the establishment', *Science*, 171 (1971), 47–9; Philip Handler, 'The federal government and the scientific community', *Science*, 171 (1971), 144–51; Harvey Brooks, 'Can science survive in the modern age?', *Science*, 174 (1971), 21–30.

24 Initially the committee was comprised primarily of experts on recombinant DNA technology, with few lay members, but, over the ensuing years, its composition changed to include a greater proportion of non-scientists.

25 Donald W. Fredrickson, 'Values and the advance of medical science', in *Integrity in Institutions: Humane Environments for Teaching, Inquiry, and Healing*, proceedings of a conference sponsored by the Association of Academic Health Centers, at the University of Texas Health Science Center, Houston, Texas, 25 May 1989 (in press), 18–23; quotation from 20. See also *idem*, *Decision of the Director, National Institutes of Health, to Release Guidelines for Research on Recombinant DNA Molecules* (Bethesda, Md., 1976); *idem*, 'A history of the recombinant DNA guidelines in the United States', in Morgan and Wheelan (eds.), *Recombinant DNA and Genetic Experimentation*, 151–60.

26 The guidelines were published in the *Federal Register*, 41, 131 (7 July 1976), part 2, 27902–943, and as National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules* (Bethesda, Md., 1976). For views of scientists on the guidelines, see, for example, Stanley N. Cohen, 'Recombinant DNA: fact and fiction', *Science*, 195 (1977), 654–7; for criticism, see David Dickson, *The New Politics of Science* (Chicago, 1984; 2nd edn, 1988), pp. 243–60; Wade, *Ultimate Experiment*, chapter 11. Principal regulatory bills were sponsored by Senator Edward M. Kennedy and Representative Paul G. Rogers. See Barbara J. Culliton, 'Recombinant DNA bills derailed: Congress still trying to pass a law', *Science*, 199 (1978), 274–7.

27 Before the Second World War, the NIH mission had included responding to epidemics of infectious diseases and monitoring incidence of mortality and morbidity. In the post-war era, as the federal health bureaucracy expanded, these responsibilities were assumed by the newly created Centers for Disease Control, whose initials, CDC, originally stood for Communicable Disease Center. See Elizabeth Etheridge, *Sentinel for Health: A History of the Centers for Disease Control* (Berkeley, 1992); Fitzhugh Mullan, *Plagues and Politics: The Story of the United States Public Health Service* (New York, 1989), 128–65.

28 Gary L. Lattimer and Richard A. Ormsbee, *Legionnaires' Disease* (New York, 1981), 1–8, quotation from 1. On the history of this epidemic, see also Gordon Thomas and Max Morgan-Witts, *Trauma: The Search for the Cause of Legionnaires' Disease* (London, 1981); *idem*, *Anatomy of an Epidemic* (Garden City, NY, 1982); Paul Clinton, comp., *Legionnaires' Disease: A Bibliography* (London, 1989). For an evaluation of the biomedical response to the epidemic, see also Barbara J. Culliton, 'Legion fever: postmortem on an investigation that failed', *Science*, 194 (1976), 1025–7; *idem*, 'Legion fever: "failed" investigation may be successful after all', *Science*, 195 (1977), 469–70.

29 Information on funding was supplied by the Financial Management Offices, CDC and NIH. Information on areas of NIH research, which included both intramural and extramural projects, was supplied by the Research Documentation Section, Information Systems Branch, Division of Research Grants, NIH.

30 US National Institutes of Health, *Draft Research Plan, FY 1984*, administrative document (Bethesda, 1982), copy in NIH Historical Office.

31 *Ibid.*, 66, 116.

32 Dennis Altman, *AIDS in the Mind of America* (Garden City, NY, 1986), 48.

33 The only report in which we have found concern about the speed of the process was a General Accounting Office study of grants made by the National Cancer Institute, which complained about 'significant delays' in the funding process. See US General Accounting Office, Comptroller General of the United States, *Administration of Contracts and Grants for Cancer Research, National Institutes of Health, Department of Health, Education, and Welfare B–164031(2)* (Washington, DC, 1971), 2–3. The National Cancer Act of 1971 (and later the National Heart, Blood Vessel, Lung, and Blood Act) authorised those institutes to award grants up to $35,000 without review by the institute advisory councils. These small grants, however, were not exempted, as the General Accounting Office report had recommended, from peer review by scientific panels.

34 In 1983 Representative Theodore S. Weiss of New York utilised the ship metaphor in a slightly different argument. He stated that 'persuading NIH to pay greater attention to the AIDS epidemic is like rerouting a luxury liner that takes ten miles to turn'. See US *Congressional Record*, House, 3 May 1983, 2587.

35 Donald S. Fredrickson, 'Communal resources, community responsibilities', *Clinical Research*, 29 (1981), 239–47.

36 Donald S. Fredrickson, 'Biomedical research in the 1980s', *New England Journal of Medicine*, 304 (1981), 509–17.

37 National Cancer Institute, 'Request for cooperative agreement applications: RFA NIH–NCI–DCT–CTRP–82–13. Studies of AIDS (Kaposi's sarcoma and opportunistic infections)', *NIH Guide for Grants and Contracts*, 11, 9 (13 August 1982), 3–7.

38 William D. DeWys to Michael A. Friedman, 18 November 1981, file 'Kaposi's sarcoma', Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland (hereafter cited as DCT, NCI).

39 US Public Health Service, *Grants Policy Statement* (Washington, DC, DHEW Publication No. (OS) 77–50,000 (Rev.), 1 October 1976), 36. Grantees must discuss changes in the scope of their research with their home institution, which receives and distributes NIH grant funds. This provision in grants policy provides one of the essential differences between the grant and the contract instruments for funding research.

40 US Congress, House Committee on Energy and Commerce, Subcommittee on Health and Environment, *Kaposi's Sarcoma and Related Opportunistic Infections: Hearing before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce*, 97th Cong., 2nd sess., 13 April 1982 (Washington, DC: Government Printing Office (Serial No. 97–125), 1982), 32. In preparing for the testimony, Chabner's office had identified twenty-seven existing grants and contracts 'with some applicability to the subject' of Kaposi's sarcoma and estimated that $433,000 of the 1981 funding for these projects might be utilised in studying the new disease. See 'National Cancer Institute, Kaposi's sarcoma', table with attachments, 6 Apr. 1982, file 'Kaposi's sarcoma', DCT, NCI.

41 Intramural investigators do not have to apply for grant funds to support their research. Their work is reviewed by their administrative superiors and, periodically, by each institute's board of scientific counsellors, comprised of non-federal scientists who are experts in fields supported by the institute. Within this structure

and within the limitations of budgets, intramural scientists can redirect their research at any time if they believe a new direction is more promising.

42 Victoria A. Harden and Dennis Rodrigues, interview with Thomas Waldmann, 14 March 1990, Bethesda, Maryland, copy in NIH Historical Office. Dr Waldmann was the admitting physician for this patient.

43 Victoria A. Harden and Dennis Rodrigues, interview with Henry Masur, 22 November 1989, Bethesda, Maryland, copy in NIH Historical Office.

44 Victoria A. Harden and Dennis Rodrigues, interview with Robert B. Nussenblatt, 25 April 1990, Bethesda, Maryland, copy in NIH Historical Office.

45 Gallo, *Virus Hunting*, 134–5. Gallo's account of his decision to investigate AIDS is representative of the approach taken by many scientists. Most investigators, whether on the staff of the intramural programme on the Bethesda campus or supported by grants at universities, were committed to particular research projects on a long-term basis. Seeing the research through to its conclusion and publishing experimental findings were prerequisites for continued funding and for status among scientific peers. A serendipitous finding could lead research projects in new directions, but most investigators were wary of jumping from topic to topic. A decision to redirect research towards AIDS was usually made only after it became clear that a laboratory's existing expertise could be utilised to illuminate some aspect of the disease. See comments on this in Alan N. Schechter, 'Basic research related to AIDS', in Victoria A. Harden and Guenter B. Risse (eds.), *AIDS and the Historian: Proceedings of a Conference at the National Institutes of Health 20–21 March 1989* (Washington, DC, NIH Publication No. 91–1584, 1991), 45–50.

46 William H. Foege to Vincent T. DeVita, Jr, memorandum re 'Kaposi's sarcoma and opportunistic infections', 30 July 1981; DeVita to Bruce Chabner, n.d., handwritten note on same memorandum; Chabner to Foege, memorandum re 'Kaposi's sarcoma conference', 6 August 1981; Vincent T. DeVita, Jr, to Edward N. Brandt, Jr, memorandum re 'Current work on Kaposi's sarcoma', 18 February 1982; William H. Foege to Bruce A. Chabner, 23 February 1982, all in file 'Kaposi's sarcoma', DCT, NCI; Edward N. Brandt, Jr, to Vincent DeVita, Richard Krause and William Pollin, memorandum re 'Kaposi's sarcoma', 7 January 1982; Richard M. Krause to Edward N. Brandt, Jr, 15 January 1982; James B. Wyngaarden to BID Directors, memorandum re 'Working group on epidemic of acquired immunosuppression, opportunistic infections, and Kaposi's sarcoma', 13 July 1982, all in file 'Kaposi's sarcoma, January 1982', Intramural Research 5–15, OD central files, NIH.

47 The words 'epidemic' and 'outbreak' are found in numerous early documents; Chabner and Curran testimony from the April 1982 hearing on *Kaposi's Sarcoma and Related Opportunistic Infections* (see n. 40), 34, 10; Arthur S. Levine to Vincent T. DeVita, Jr, memorandum re 'Update on the epidemic of acquired immunodeficiency sarcoma-opportunistic infection', 2 July 1982, file 'Kaposi's sarcoma, July 1982', Intramural Research 5–15, OD central files, NIH.

48 Associate Director for Field Studies and Statistics, DCCP, NCI to William Blattner, Mark Greene, James Goedert, Robert Biggar, Dean Mann, Robert Hoover and Deborah Winn, memorandum re 'Epidemiology working group on Kaposi [*sic*] sarcoma', 8 March 1982, file 'Intramural research 5–15, March 1982', OD central files, NIH.

49 Documentation of the creation of the NIH AIDS executive committee is in Director, NIH to Acting Assistant Secretary for Health, memorandum re 'NIH coordination of AIDS research', 15 October 1985, file 'Intramural research 5–15, October 1985', OD central files, NIH. On creation of the APAC, see Otis R. Bowen, 'Formal determination', 21 August 1987; 'Charter, acquired immunodeficiency syndrome program advisory committee', 21 August 1987; and 'Amendment to the charter of the acquired immunodeficiency syndrome program advisory committee', 23 November 1987, copies in files of the NIH Office of AIDS Research.

50 Statutory authorisation for the NIH Office of AIDS Research is in the Omnibus Health Bill, PL 100–607, 4 November 1988, US *Statutes at Large*, vol. 102, 3076.

51 Charles E. Rosenberg, 'What is an epidemic? AIDS in historical perspective', in 'Living with AIDS', special issue, *Daedalus*, 118 (Spring 1989), 1–17.