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"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9203115
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

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FROM: DUBOCOVICH, Margarita: NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 10/05/92

SUBJECT: SHE IS WRITING TO SOLICIT DR. BROMLEY'S ASSISTANCE IN ENSURING THE CONTINUED PARTICIPATION OF THE NATIONAL INSTITUTES OF HEALTH IN THE FEDERAL DEMONSTRATION PROGRAM.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: William Raub

ACTION REQUIRED: AS NECESSARY

STAFF ACTION: AS NECESSARY

****

SENDER'S DUE DATE:

OSTP DUE DATE: 10/29/92 STAFF DUE DATE 10/29/92
DATE COMPLETED: DATE COMPLETED/DEPT: 11/25/92

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COPIES TO: D. Allan Bromley

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WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:

REMARKS: Dr. Raub responded to this letter as well as one addressed to him.

OSTP RECEIVED: 10/19/92 DEPT RECEIVED: 10/20/92
FILE: P-LIFE SCIENCES

CENTRAL FILES:

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

November 25, 1992

Dear Dr. Dubocovich:

Thank you for your letters to Dr. D. Allan Bromley and me regarding the decision by the National Institutes of Health (NIH) to discontinue its participation in one of the activities of the Federal Demonstration Project (FDP), i.e., the trial of a simplified application procedure for noncompeting continuation grants. Your disappointment at this turn of events is understandable, for the procedures by which agencies of the federal government handle noncompeting renewal awards undoubtedly include unnecessary and unproductive administrative requirements and therefore are an appropriate focus for an FDP initiative. Nevertheless, having discussed the matter at length with some of my NIH colleagues, I recognize that their decision, made in conjunction with higher-level officials of the Department of Health and Human Services (DHHS), has a strong supporting rationale.

As I understand the issue, the crux of the problem is that the streamlined FDP procedure for noncompeting renewals has failed to win strong support among the NIH funding units. My colleagues report widespread concern among program- and grants-management staff because the noncompeting renewal procedure now being tested does not generate all the information they believe they need to fulfill their stewardship responsibilities. This conclusion in turn has reinforced misgivings that senior DHHS policy officials have held since this particular trial first was proposed. Whereas many of us hoped that real-world experience with the streamlined procedure might allay the early concerns, the opposite has proved true.

Under the circumstances, with so many key staff at several different levels of DHHS disinclined to endorse the streamlined renewal process, I see no chance that the Department will adopt it as standard policy. Further pursuit of this particular FDP activity as currently designed therefore is likely to be an unproductive expenditure of energy, resources, time, and good will. Regrouping and reassessing the issue in the light of the concerns generated by the trial seems the better course.

I view this setback as unfortunate but far from lethal for FDP. The NIH decision neither tarnishes the other FDP achievements nor diminishes the importance of our fundamental goals. For my part, I will continue to be an advocate for FDP, as will many of my colleagues. That will include searching for a broadly acceptable way to address anew how we might make the noncompeting renewal process more efficient for both parties without an actual or perceived compromise of stewardship.

Sincerely yours,

Bill Raub

William F. Raub, Ph.D.
Special Assistant for Health Affairs

Margarita L. Dubocovich, Ph.D.
Associate Professor of Pharmacology
Northwestern University Medical School
303 East Chicago Avenue
Chicago, Illinois 60611

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9203034
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

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FROM: YOUNG, James B.: NORTWESTERN UNIVERSITY MEDICAL SCHOOL

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 10/05/92

SUBJECT: HE IS SOLICITING ASSISTANCE TO ENSURE CONTINUED PARTICIPATION OF NIH IN THE NONCOMPETING CONTINUATION OF THE FEDERAL DEMONSTRATION PROJECT.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: William Raub

ACTION REQUIRED: AS NECESSARY

STAFF ACTION: AS NECESSARY

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SENDER'S DUE DATE:

OSTP DUE DATE: 10/22/92 STAFF DUE DATE 10/22/92
DATE COMPLETED: DATE COMPLETED/DEPT: 11/25/92

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COPIES TO: D. Allan Bromley

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WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:

REMARKS: Dr. Raub responded to this letter as well as one addressed to him.

OSTP RECEIVED: 10/07/92 DEPT RECEIVED: 10/08/92
FILE: P-LIFE SCIENCES

CENTRAL FILES:

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

November 25, 1992

Dear Dr. Young:

Thank you for your letters to Dr. D. Allan Bromley and me regarding the decision by the National Institutes of Health (NIH) to discontinue its participation in one of the activities of the Federal Demonstration Project (FDP), i.e., the trial of a simplified application procedure for noncompeting continuation grants. Your disappointment at this turn of events is understandable, for the procedures by which agencies of the federal government handle noncompeting renewal awards undoubtedly include unnecessary and unproductive administrative requirements and therefore are an appropriate focus for an FDP initiative. Nevertheless, having discussed the matter at length with some of my NIH colleagues, I recognize that their decision, made in conjunction with higher-level officials of the Department of Health and Human Services (DHHS), has a strong supporting rationale.

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Under the circumstances, with so many key staff at several different levels of DHHS disinclined to endorse the streamlined renewal process, I see no chance that the Department will adopt it as standard policy. Further pursuit of this particular FDP activity as currently designed therefore is likely to be an unproductive expenditure of energy, resources, time, and good will. Regrouping and reassessing the issue in the light of the concerns generated by the trial seems the better course.

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Sincerely yours,

Bill Raub

William F. Raub, Ph.D.
Special Assistant for Health Affairs

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Searle Building 3-489
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Chicago, Illinois 60611-3008

TYPE: . INFORMATION DOCUMENT NUMBER: 9203170
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
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FROM: BELL, George: LOS ALAMOS NATIONAL LABORATORY

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 10/02/92

SUBJECT: HE IS FORWARDING A COPY OF HIS LETTER TO FLORIDA GOVERNOR LAWTON CHILES REGARDING THE REBUILDING OF HOMESTEAD AIR FORCE BASE.

****
DIRECTORATE ASSIGNED: STAFF ASSIGNED:

ACTION REQUIRED: STAFF ACTION:

****
SENDER'S DUE DATE:
OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES

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WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS:

OSTP RECEIVED: 10/15/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

3170

Los Alamos
NATIONAL LABORATORY

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October 2, 1992

Governor Lawton Chiles
The Capitol
Tallahassee, Florida 32399-0001

Dear Governor Chiles,

I met you during the exciting early days of the Human Genome Program and more recently have followed the distress of your State with Hurricane Andrew and its aftermath. The rebuilding of so much of South Florida will be a tremendous task, but with disasters sometimes come opportunities, and I venture to make a suggestion in this instance.

It occured to me while hearing of a proposal to rebuild Homestead Air Force Base, which the commentator claimed was of relatively little interest to the Defense Department. Rather, I suggest what should be built is an Institute of Tropical and Infectious Diseases, which would study infectious diseases of greatest concern for developing countries but of growing importance for the United States, develop vaccines and drugs for disease control and provide training to health care workers.

Some background: In the developing world, it is clear that Infectious Diseases such as Malaria and Hepatitis are terrible problems; organisms have become resistant to pesticides and drugs that once controlled them. The challenge of Malaria is set forth in attachment 1, and in the Institute of Medicine Report referenced therein. Problems due to various hepatitis strains, cholera and dengue epidemics are further reminders of the public health problems of developing countries. Accordingly, I recommend that a small portion of our foreign aid budget, say $300M/yr, support the research and training that such an Institute would provide.

Even in the United States, it has recently become clear that infectious diseases can no longer be thought of as scourges of the past. The AIDS pandemic is the clearest counterexample but tuberculosis is on the increase in this country and elsewhere, and many strains of virulent bacteria have become resistant to the most common antibiotics. Growing

urban populations and ease of worldwide travel are also factors that enhance the liklihood of further worldwide epidemics. The issue of Science Magazine of 21 August 1992 was devoted to a series of articles on these problems and I enclose copies of two, on Tuberculosis and on plagues in general. I understand that the Institute of Medicine is about to come out with a report, "Microbial Threats to Health", confirming the seriousness of these problems. I believe that the National Institutes of Health are in agreement concerning the renewed importance of infectious diseases, but given all the budget constraints, it is difficult for them to respond quickly. Hence the suggestion to tap the foreign aid budget for operating costs and perhaps construction as well.

So there you have it. I cannot claim to be an expert in this field, but I strongly feel that the tools of molecular biology and biotechnology should be brought to bear on these major public health problems and that this country should exert the moral and technical leadership. I am confident that any number of hearings, panels or workshops could be assembled to support the importance of the proposed research and training.

These are my own opinions and do not reflect any position of the Los Alamos National Laboratory.

Sincerely yours,

George I. Bell, Ph.D.

cy Pete Domenici w. att.
Jeff Bingaman w. att.
George Bush w. att.
Bill Clinton w. att.
Alan Bromley w. att. ✓

Attachments: (1) Miller, L. H., The Challenge of Malaria , *Science* 257:36-37, 1992.
(2) Bloom, B. R. and C. J. L. Murray, Tuberculosis: Commentary on a Reemergent Killer, *Science* 257:1055-1064, 1992.
(3) Krause, R. M., The Origin of Plagues: Old and New, *Science* 257: 1073-1078, 1992.

The Challenge of Malaria

Louis H. Miller

Plasmodium falciparum, like the human immunodeficiency virus (HIV), causes a major disease in the tropical world that will become worse in the years ahead, with no guaranteed solution at hand. This threat is highlighted most dramatically by a recent Institute of Medicine (IOM) report on malaria (*1*). In this Perspective, I have developed what I see as the research priorities to develop new tools for reducing mortality and for control and eradication of malaria.

Malaria is one of the few diseases for which we can estimate past mortality rates on the basis of today's gene frequencies. These estimates depend on the assumption that the mutation in the β chain of hemoglobin A that generates hemoglobin S, common in Africa, and in the red cell membrane protein band 3, common in Southeast Asia (*2*), were selected because such mutations, when heterozygous, confer resistance to severe malaria. Given this assumption, the mortality from malaria can be predicted from the frequency of these genes with the use of the Hardy-Weinberg equation (see figure). The mortality in recent years has been less because of the widespread use of the antimalarial drug chloroquine.

In Africa south of the Sahara, where methods that are conventionally used to control the mosquito vector have not proved feasible, the spread of chloroquine resistance is rapidly eliminating this primary tool to reduce morbidity and mortality. The impact was documented at a hospital in Zaire where a sudden increase in admissions and mortality from malaria was precipitated by the appearance of chloroquine-resistant *falciparum* malaria in the region (*3*). Resistance is also developing to the affordable, alternative drug combination: pyrimethamine-sulfadoxine.

Research to lessen the impact of malaria immediately is focused on evaluating the effectiveness of insecticide-impregnated bed nets, drugs that are far along in development such as ginghaosu derivatives (*4*), and better ways to apply the less-than-perfect, currently available tools. The United States should continue to contribute to this research aimed at mitigating the effects of malaria in the short term, but I believe that our most valuable and unique contribution would be to find better tools to apply against *P. falciparum* and its vectors.

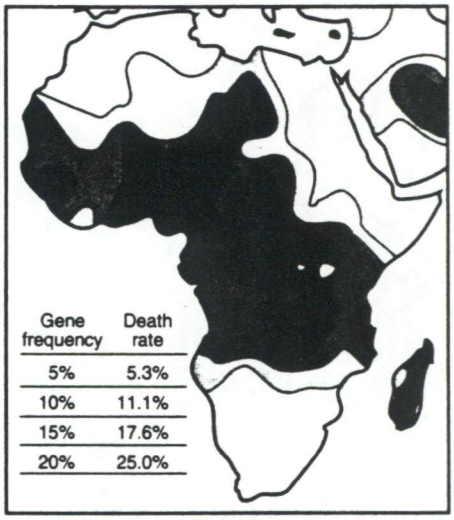
Laboratory of Malaria Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892.

What longer term research approach is likely to have the earliest and most dramatic impact on disease and deaths? It is my opinion that vaccines are in this category (*5*)—specifically, an effective vaccine against the asexual erythrocytic parasite. First, this is the only stage in the life cycle that causes disease. Even partial vaccine-induced immunity, which controls an evolving infection by decreasing parasite density in the blood, will lessen mortality. Second, immunity eventually does develop in older children and adults after repeated infections. Third, vaccines have been successful in every animal model of malaria, including *P. falciparum* in New World monkeys. For example, purified antigens from parasites effectively induce protection against otherwise lethal malarias (*1*, *5*). I do not wish to minimize the difficulties development of a successful vaccine must overcome, which include parasite evasion mechanisms, the reluctance of industry to become involved in malaria vaccine development, and the inherent difficulties in testing vaccines against asexual blood stages for efficacy in humans. If we could involve industry in the development process even though large profits cannot be expected, then I trust that the application of modern biology could solve the scientific problems. In the past, science has had a great impact on health through making available clean water supplies, pasteurization of milk, chemotherapy, insecticides, and viral and bacterial vaccines. I would like to believe that an equivalent contribution today would be the development of a malaria vaccine.

Of lesser priority, but still of great importance, would be the development of vaccines that would interrupt transmission at the sporozoite or sexual stages. Such vaccines may, in combination with other methods of control, eradicate malaria from regions of low to moderate transmission such as Sri Lanka. For travel to malaria-endemic areas where chloroquine is no longer effective in protecting against malaria, sporozoite vaccines offer great promise.

Attack against the mosquito vector has always offered the only hope for eradication of the parasite. It is only through eradication that we would no longer have the continual concern about emergence of drug- and vaccine-resistant parasites. To appreciate the potential of this approach, it is only necessary to remember the dramatic effect the insecticide DDT had on reducing or eliminating malaria from many parts of the world. It is also important to note that malaria is a serious problem in Africa because of the high rates of transmission—a direct result of the *Anopheles gambiae* complex of mosquitoes, the most efficient vectors in the world (*6*). It is not surprising, then, that when *An. gambiae* was introduced into other parts of the world such as Brazil and Egypt, epidemics occurred where malaria was previously easy to control (*7*). The problem was eliminated when *An. gambiae* itself was eradicated. The eradication of *An. gambiae* is out of the question in Africa, at least with the technology that we can envision.

There is a new program at the World Health Organization, with support by foundations such as the MacArthur Foundation and the Wellcome Trust, to alter the capacity of mosquitoes to transmit malaria. The program focuses on factors in the mosquito that kill the parasite or block the parasite's development (*8*) and on methods to introduce genes for these factors into vector populations. Two observations make me optimistic about the feasibility of such an undertaking. It has been assumed that the parasite is able to mutate to escape any barrier in the mosquito that we may introduce, as if the parasite's adaptability is unlimited. This may not be the case. Mammalian malarias are transmitted only by *Anopheles* mosquitoes. Although *Culicine* mosquitoes regularly bite malaria-carrying humans, none is involved in the transmis-



Hemoglobin S gene in Africa. The most intense maroon areas have a frequency of 14% or more, with decreasing frequencies radiating from there. (**Inset**) Risk of death from malaria in hemoglobin AA children calculated from the equilibrium frequency of the hemoglobin S gene. Map adapted with permission © from W. F. Bodmer and L. L. Cavalli-Sforza, *Genetics, Evolution, and Man* (Freeman, San Francisco, 1976).

sion of the infection. There must be some block to the development of the parasite in *Culicine* mosquitoes that the human parasite is unable to overcome.

Introduction of genes encoding refractoriness into field populations of mosquitoes remains a major obstacle to implementation of such control strategies. A transposable element, the P element, first appeared in *Drosophila melanogaster* around 1950 and spread in a non-Mendelian fashion to flies of this species around the world (*9*). We might use an analogous transposable element of mosquitoes in a cassette with genes for refractoriness to malaria to introduce these genes into vector populations.

The third leg of basic research aimed at developing new tools is the identification of biochemical pathways unique to the malaria parasite and subsequent development of poisons specific to the parasite. One such area is hemoglobin digestion. The parasite, after digestion of hemoglobin, reorganizes heme into a nontoxic compound, hemozoin pigment. The polymeric structure of hemozoin pigment has recently been identified, and the polymerizing enzyme activity is blocked by chloroquine and other related antimalarial compounds (*10*). Furthermore, the locus for the chloroquine resistance gene (*11*), which encodes a drug-efflux mechanism (*12*) unrelated to the polymerase, has been identified. Understanding the structure and function of the polymerase and efflux mechanism should open the way for drug design to reverse chloroquine resistance.

Malaria, unlike AIDS, is not a major health problem for citizens of the United States; it is a problem of the unseen sick and dying in the villages of the tropical world. Our goal must be to develop tools and ways of delivering these tools to limit disease and to prevent malaria at a cost that is affordable and sustainable in these populations with limited resources. Success will demand continual support of basic scientists and involvement of industry. Can we ignore this challenge?

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13. I thank D. Alling, T. Wellems, R. Gwadz, and C. Plowe for suggestions on the manuscript and the figure.

Mosquito Molecular Genetics: The Hands That Feed Bite Back

Anthony A. James

Mosquitoes are the most important vector of human parasitic diseases. Every year they transmit over 250 million new cases of malaria, filariasis, and viral disease. It is therefore surprising that only recently has mosquito molecular genetics been pursued with the same rigor and zeal characteristic of other aspects of parasitic disease control and treatment. In the last few years, research efforts funded by the John D. and Catherine T. MacArthur Foundation and the National Institutes of Health here in the United States, and by the Wellcome Trust in Great Britain, have catalyzed a renaissance of interest in the vectors of parasitic diseases. New knowledge of the molecular bases of vector-parasite interactions and population structure in mosquitoes should ultimately lead to novel ways to control disease transmission.

A workshop (*1*) sponsored by the MacArthur Foundation brought together vector molecular biologists with scientists who have made significant progress in other, well-studied organisms, most notably *Drosophila melanogaster*. Together, these two groups assessed the state of mosquito molecular biology and molecular genetics.

Many of the investigators are working toward developing strains of mosquitoes that are refractory or resistant to parasites. These strains will be released to control the transmission of disease by replacing the existing populations. Better diagnostic methods will help these efforts by defining those species or strains that should be the targets of genetic control.

In Africa there are six described members of the *Anopheles gambiae* complex, three of which overlap in their geographical range. Different members of a complex can coexist in a single locale, but only one may be actually transmitting the parasites. Members of the *An. gambiae* species complex have been differentiated by their polytene chromosome banding patterns (*2*), and the derived maps are as detailed as those available for *Drosophila*. However, these maps have yet to lead to techniques that would allow quick and accurate identification of large numbers of animals in the field. At the workshop, various molecular approaches for species identification were presented. Ribosomal (F. H. Collins, Centers for Disease Control–Atlanta) and mitochondrial (A. Cockburn, U.S. Department of Agriculture–Gainesville) DNA variation potentially can provide sensitive measures of species differentiation. The ribosomal RNA genes of mosquitoes have the typical structural features of the eukaryotic rDNA cistrons. Included in the intergenic spacer regions (IGS) are sequences of DNA that vary among populations (*3*). Regions of the IGS were scanned for two base-pair sequence polymorphisms among the members of the species complexes. Polymerase chain reaction (PCR) primers containing two 3′-terminal nucleotides that overlap the polymorphisms can distinguish among members of the complex. Only those animals with an exact match to the primers amplify a product. Mitochondrial DNA variability is also being evaluated in the *An. quadrimaculatus* species complex of the Americas, but probes have yet to be developed. PCR techniques with random amplified polymorphic DNA (RAPD) sequences (C. Louis, Institute of Molecular Biology and Biotechnology–Crete) are being investigated, but it remains to be seen whether they are generally applicable.

Another necessary step in developing strains of mosquitoes that are resistant to parasites is the identification of the gene or genes required for disease transmission. For example, certain genetic variants of *An. gambiae* and *Aedes aegypti*, the yellow fever mosquito (see figure), have reduced capacity to transmit the pathogens responsible for parasitic diseases, including malaria and filariasis. In order to identify the genes responsible for this reduced transmission, certain technological achievements must be made. The three central workshop topics—genome mapping, transposable elements, and transformation strategies—point to the challenges facing molecular biologists working with mosquitoes, notably, a lack of ability to transform mosquitoes at useful frequencies and an inability to isolate genes

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tence, and transmission of drug-resistant organisms. Surveillance systems that are more sensitive and timely can provide information in making critical public health decisions.

Many of the above methods to reduce antimicrobial resistance focus on curative medicine, that is, preserving the ability to treat the ill or infected individual. Curative medicine is, in a sense, a failure of preventive medicine. As antimicrobial resistance increases, health efforts need to be focused on preventing transmission and infection rather than on treating the illness once it has occurred. A very effective mechanism for dealing with the emergence of antimicrobial resistance would be the development of vaccines to prevent diseases that are difficult to treat. There is also a variety of opportunities to disrupt transmission. In hospitals, infection control practices can be enhanced; in the community, hygiene and sanitation can be improved; and on the farm, a number of agricultural and animal husbandry practices can reduce the transmission of organisms between animals and eventually decrease their transmission to humans. The increasing frequency of resistance indicates the need for a stronger partnership between clinical medicine and public health. Unless currently effective antimicrobial agents can be successfully preserved and the transmission of drug-resistant organisms curtailed, the post-antimicrobial era may be rapidly approaching in which infectious disease wards housing untreatable conditions will again be seen.

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Attach 2

Tuberculosis: Commentary on a Reemergent Killer

Barry R. Bloom and Christopher J. L. Murray

Tuberculosis remains the leading cause of death in the world from a single infectious disease, although there is little knowledge of the mechanisms of its pathogenesis and protection from it. After a century of decline in the United States, tuberculosis is increasing and strains resistant to multiple antibiotics have emerged. This excess of cases is attributable to changes in the social structure in cities, the human immunodeficiency virus epidemic, and a failure in certain major cities to improve public treatment programs. The economic costs of not adequately addressing the problem of tuberculosis in this country are estimated from an epidemiological model.

In an interview on acquired immunodeficiency syndrome (AIDS) earlier this year with the Director of the National Institute for Allergy and Infectious Diseases (NIAID), a distinguished television newscaster asked, "How is it that we have conquered most infectious diseases but are unable to find a cure for AIDS?" The question reveals misperceptions that are costly to the public in both human and economic terms, and it is not a misapprehension solely of the general public. In 1969, the U.S. Surgeon General testified to Congress that it was time to "close the book on infectious diseases" (*1*). In fact, infectious diseases have not been eradicated but remain the largest cause of death in the world today, greater than cardiovascular disease or cancer (*2*). The World Health Organization (WHO) estimates that in 1991 there were still 4.3 million deaths in children from acute respiratory infections, 3.5 million from diarrheal diseases, 0.88 million from measles, and about 1 million from malaria (*3*). To that, one must add an estimated 1.5 million cumulative deaths worldwide from AIDS.

The stark reality, largely overlooked, is that among infectious diseases, tuberculosis (TB) is the leading cause of death (*4*). Each

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year, there are an estimated 8 million new cases of TB and 2.9 million deaths from the disease (5). Approximately one-third of the world's population harbors *Mycobacterium tuberculosis* and is at risk for developing the disease. In global terms, TB accounts for 6.7% of all deaths in the developing world, 18.5% of all deaths in adults aged 15 to 59, and 26% of avoidable adult deaths (4). The steadily declining incidence of TB in the United States since 1882 has been reversed since 1985 (6), with 26,283 cases reported in 1991. To the trend of increasing incidence one must add the ominous emergence of drug-resistant strains that threaten our capability of controlling the disease. One-third of all cases tested in a New York City survey in 1991 were resistant to one or more drugs (7). The case fatality rate for TB resistant to two or more major antibiotics (multidrug resistance) is 40 to 60%, equivalent to untreated TB (8). Last year, cases of TB were reported to the Centers for Disease Control (CDC) by all 50 states, and drug-resistant TB was noted in at least 36 states, the District of Columbia, and Puerto Rico (9). Our aim here is to adumbrate the context and a few scientific challenges of TB and to highlight some economic implications of the failure to adequately address the problem.

A Brief History of Time—Forgotten

Tuberculosis was almost certainly the leading cause of death in Europe and the United States in recorded history, although because of the multifarious forms of the disease, it was often confounded with other maladies (*10, 11*). Probably described first in Indian texts, pulmonary TB was known from the time of Hippocrates (*12*) as phthisis, which is derived from the Greek for "wasting away." The swollen glands of the neck were described as scrofula, and because newly crowned kings of England and France were believed to have special healing powers, the most desired treatment of this "King's Evil" was being touched by kings. TB of the skin was known as lupus vulgaris and that of bone as Pott's disease, characterized by vertebral fusion and deformity of the spine, which enabled historians to establish the existence of TB from mummies dating from 2000 to 4000 B.C. From contemporary descriptions, bills of mortality, and records of the dispensing of the royal touch, estimates suggest that consumption (TB) was responsible for 20% of deaths in London in 1651, reached rates of 700 cases per 100,000 people in 1801, and declined thereafter. Consecutive autopsies by G. L. Bayle and R. T. H. Laennec in the early 19th century indicated that TB may have probably accounted for a third of all deaths in Paris at that time. Upon introduction into new locales, TB assumed an epidemic form; for example, the Pacific Islands had a prevalence of TB in children reaching 81% (*13*).

Franciscus Sylvius in 1679 described the characteristic lung nodules as "tubercula" (small knots), observing their evolution to cavities (lung ulcers), but virtually all of the great pathologists, including Rudolf Virchow, believed the disease to be constitutional, a form of tumor or abnormal gland, rather than infectious. H. Fracastoro included phthisis in a work on contagion in 1546, but the first credible speculation on the infectious nature of TB was made by Benjamin Marten, who proposed in 1722 that the cause of TB was "animaliculae or their seed . . . inimicable to our Nature" that can be transmitted by "a Breath [a consumptive] emits from his Lungs . . . that may be caught by a sound Person" (*12*). It was Robert Morton in 1689 who used the term "consumption" specifically to denote TB, and it took until 1819 for Rene Laennec, inventor of the stethoscope, to first recognize the unity of manifestations of TB. Although the 17th century anatomists A. M. Valsalma and G. B. Morgagni enjoined their students not to perform autopsies on tuberculous cadavers, the first public health edict to prevent transmission of TB was the Decree of Lucca, promulgated in Italy in 1699, that required physicians to notify the General Sanitary Council of the names of patients with phthisis and to destroy their belongings after death (*12*).

The formal demonstration that TB was contagious was made in 1865 by Jean-Antoine Villemin, who successfully transferred pus and fluid from human and bovine lesions to rabbits that then developed TB (*14*). This monumental finding was ignored by his contemporaries and unappreciated by R. Koch, who in 1882 astonished the world by isolating and culturing *M. tuberculosis* from crushed tubercles (*15*). The lessons from the discovery of the anthrax and tubercle bacilli were now generalized into Koch's Postulates: "To prove that tuberculosis . . . is caused by the invasion of bacilli and conditioned by the growth and multiplication of bacilli it was necessary: [i] to isolate the bacilli from the body; [ii] grow them in pure culture; and [iii] by administering the isolated bacilli to animals, reproduce the same morbid condition. . . ." Although a primary inoculation of guinea pigs with tubercle bacilli in the skin produced a nonhealing ulcer, Koch noted that reinoculation of the animals after several weeks produced only a firm, red nodule that eventually healed (the Koch phenomenon), which first suggested the existence of immunity to infection. Unfortunately, in 1890 he also announced that culture filtrates cured the disease, a claim that was promptly discredited. At a time when intellectual property rights were hardly a burning issue, Koch refused to divulge the nature and preparation of the curative material—an action imputed by some to assure a monopoly for the German government and an institute for himself—and this great scientist brought discredit upon himself (*16*). Nevertheless, those filtrates, later partially purified, became the principal means to establish infection, the tuberculin skin test.

Four historical intervention strategies are noteworthy. The lack of effective treatments prompted Hermann Brehmer in Europe in 1854 to establish the first sanatorium in the belief that exercise and altitude would serve to cure TB. Based on his own recovery from TB in New York's Adirondack mountains, Dr. Edward Livingston Trudeau in 1882 established the first sanatorium in the United States and initiated a public health movement featuring community participation, emphasis on the outdoor life, and ordinances to improve sanitation and slum housing (*17*). Another was the application of pasteurization to cows' milk, reducing the possibility of *M. bovis* being a cause of human TB. In 1908, Albert Calmette and Camille Guerin, seeking to overcome the problem of bacillary clumping associated with mycobacteria, grew bovine tubercle bacilli in dispersed culture that contained ox bile. A morphological variant was observed on the 39th passage that was avirulent in many animal species and provided protection against challenge with virulent *M. tuberculosis*. In the 231st passage, this variant was first used to immunize a child whose mother died in childbirth of TB (*18*). This vaccine, BCG (bacille Calmette-Guerin), is currently the most widely used vaccine in the world (*19*). Finally, the introduction of antibiotics, streptomycin in 1947 (*20*), isoniazid, first synthesized 1912 but allowed to sit on the shelf for 40 years, and then *p*-aminosalicylic acid led to an effective chemotherapy that dramatically reduced mortality from TB. Thus ended the sanatorium era.

"The Captain of All These Men of Death" (*21*)

As in many communicable diseases, it is important in TB to distinguish between infection and disease. There are two basic clinical patterns that follow infection with *M. tuberculosis* (*22*). In the majority of individuals, inhaled tubercle bacilli ingested by phagocytic alveolar macrophages are either directly killed or grow intracellularly to a limited extent in localized lesions called tubercles. Infrequently, in children and in immunocompromised individuals, there is early hematogenous dissemination

with the formation of small miliary (millet-like) lesions or life-threatening meningitis. More commonly, within 2 to 6 weeks after infection, cell-mediated immunity develops, and infiltration into the lesion of immune lymphocytes and activated macrophages results in the killing of most bacilli and the walling-off of this primary infection, often without symptoms being noted by the infected individual. Skin-test reactivity to a purified protein derivative (PPD) of tuberculin and, in some cases, x-ray evidence of a healed, calcified lesion provide the only evidence of the infection. Nevertheless, to an unknown extent, dormant but viable *M. tuberculosis* bacilli persist. The second pattern is the progression or breakdown of infection to active disease. Individuals infected with *M. tuberculosis* have a 10% lifetime risk of developing the disease (*23*). In either case, the bacilli spread from the site of initial infection in the lung through the lymphatics or blood to other parts of the body, the apex of the lung and the regional lymph node being favored sites. Extrapulmonary TB of the pleura, lymphatics, bone, genito-urinary system, meninges, peritoneum, or skin occurs in about 15% of TB patients. Although many bacilli are killed, a large proportion of infiltrating phagocytes and lung parenchymal cells die as well, producing characteristic solid caseous (cheese-like) necrosis in which bacilli may survive but not flourish. If a protective immune response dominates, the lesion may be arrested, albeit with some residual damage to the lung or other tissue. If the necrotic reaction expands, breaking into a bronchus, a cavity is produced in the lung, allowing large numbers of bacilli to spread with coughing to the outside. In the worst case, the solid necrosis, perhaps a result of released hydrolases from inflammatory cells, may liquefy, which creates a rich medium for the proliferation of bacilli, perhaps reaching 10^9 per milliliter (*24*). The pathologic and inflammatory processes produce the characteristic weakness, fever, chest pain, cough, and, when a blood vessel is eroded, bloody sputum.

The case fatality rate of untreated TB wherever studied hovers between 40 and 60% (*23, 25*). The introduction of antibiotics rendered TB a disease that could be cured. There have been many prescribed treatment regimens; the one currently most favored is combinations of isoniazid, rifampicin, and pyrazinamide given over a period of 6 months. This treatment is referred to as short-course chemotherapy (SCC) and, in patients who complete it, produces cure rates of >90% (*26*). For individuals recently infected with conventional *M. tuberculosis* and converting to PPD positivity, chemoprophylaxis with isoniazid has been about 90% effective in preventing the disease (*27*).

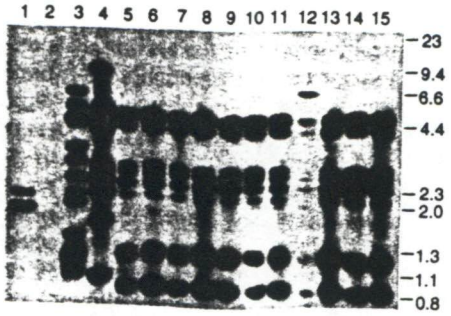


Fig. 1. Restriction fragment length polymorphism analysis of clinical *M. tuberculosis* isolates from residents of an HIV congregate living site in San Francisco. Patients 1 and 2 were receiving chemotherapy when they entered the facility, and their isolates have different banding patterns from 11 patients whose isolates have the same banding pattern. [Reprinted from (*39*), *New England Journal of Medicine*]

The course of TB in individuals infected with the human immunodeficiency virus (HIV) is dramatically different (*28*). Tuberculosis is a sentinel disease for AIDS because, in contrast to most opportunistic infections, it is frequently the first indication of HIV infection. In the United States, the risk of developing TB (reactivation) for individuals who have positive tuberculin skin tests (PPD^+) and then seroconvert to HIV positivity is about 8% a year, in contrast to the 10% lifetime risk for PPD^+ healthy individuals (*29, 30*). Although patients with minimal immunodeficiency may show a normal pattern of the disease, extrapulmonary disease—for example, miliary TB, lymphadenitis, and meningitis—that coexists with pulmonary infection is a more common form of TB in patients with advanced immunodeficiency. Diagnosis is often difficult because PPD reactivity may be compromised in AIDS patients, and x-rays may show only diffuse patterns of infiltration, too often resulting in delayed diagnosis (*31*). Significantly, cure rates with the appropriate regimen appear to be as high for HIV-positive patients as cure rates with standard SCC are for seronegative individuals (*32*).

A Wealth of Ignorance

In few infectious diseases is knowledge of both the pathogen and the host responses to it so essential to understanding of the pathogenesis as in TB. Mycobacteria are daunting organisms to study (*33*). In contrast to the most commonly used organism for molecular biological studies, *Escherichia coli*, which produces a visible colony (10^7 bacilli) in about 8 hours, *M. tuberculosis* requires 3 to 4 weeks to yield a comparable colony. It has a formidable waxy coat comprised of multiple complex lipids and carbohydrates that renders it impermeable to many common drugs. The bacilli tend to form clumps, which makes working with them and quantitation of them difficult (*34*). Because of its pathogenicity and transmission by aerosols, current biosafety regulations require that work with *M. tuberculosis* be carried out under high-level biological containment that is expensive and not widely available. Hence, research on the pathogen is slow and demanding. Although the study of microbial genetics developed over 40 years ago, little beyond the size of its genome and its DNA content was known about *M. tuberculosis* until the last 5 years (*35*). In that short time, methods that enable gene transfer in mycobacteria and selection for recombinants that contain introduced genes and that permit expression of foreign genes have been developed. Perhaps the basic strategy that made molecular study feasible within a lifetime was development of shuttle vectors that allow mycobacterial genes to be manipulated efficiently in *E. coli* and then shuttled into mycobacteria for expression (*36*). These molecular tools, though limited, have made it possible to introduce and express genes for foreign antigens in BCG vaccine strains to create multivalent recombinant BCG vaccines capable of immunization experimentally against multiple protective antigens of several different infectious pathogens simultaneously (*37*).

Individual isolates or strains of *M. tuberculosis* have several repetitive DNA elements with distinct banding patterns in DNA fingerprinting analysis (*38, 39*) (Fig. 1). When multiple isolates from different patients exhibit the same DNA fingerprint pattern, it is highly suggestive that each derives from a common source. This molecular epidemiology can be used to track sources of infection and transmission of individual strains, including drug-resistant organisms. The commonly used diagnostic methods for TB, aside from staining for bacilli in sputum (which is relatively insensitive), require 2 to 8 weeks. With the use of *M. tuberculosis*–specific repetitive or single-copy DNA sequences, the polymerase chain reaction potentially could provide specific and sensitive diagnosis in a few hours (*40*), although it is not yet clear how readily the technology, which is expensive and technically demanding, will be applicable to routine diagnosis. It is disquieting that the current methodology for assessing patterns of antibiotic resistance and susceptibility of strains requires from 3 to 12 weeks for completion.

Our ignorance of the molecular basis of virulence and pathogenesis is great. As W. R. Jacobs, Jr. (*41*), has suggested, molecular evidence analogous to Koch's postulates is required—that is, the establishment of avirulent strains, the identification and cloning

of putative virulence genes of the pathogen, and the demonstration that virulence can be conveyed to an avirulent strain by those genes. Although avirulent strains of *M. bovis* and *M. tuberculosis* exist (*17, 42*), the nature of the mutations is unknown. Not a single gene involved in the pathogenesis of TB has been defined. The molecular bases of invasion of host cells, intracellular survival, growth, spread, or tissue tropism are not known (*43*). None of the targets of existing drugs has been characterized at a molecular level, and the mechanism of resistance to any drug has not been defined; no new mycobacterial target for drug development has been characterized in 20 years. Nonetheless, it is gratifying that although the Human Genome Project did not initially entertain proposals on any human pathogens, *M. tuberculosis* and *M. leprae* have recently been included. With appropriate support, in 3 to 5 years the entire DNA sequence of these pathogens should be known, empowering prediction of every protein, every enzyme, every drug target, and every antigen—a farsighted scientific investment.

After decades of controversy, the rapid course of TB in HIV-seropositive individuals has compellingly established that immunity plays a major role in restricting TB infection in immunocompetent hosts. T cells rather than antibodies are involved, but the precise nature of protective immunity is not known. There are ample data that indicate that the BCG vaccine protects against disseminated TB and meningitis in children (*44*). It is puzzling, however, that BCG's protective efficacy against pulmonary TB in adults has varied from 0 to 77% in different trials (*45*) and that, even in trials with a high percentage of efficacy, skin-test reactivity did not correlate with protection (*46*); thus, surrogate end points for protection are badly needed.

Cell-mediated immunity is required for protection in experimental TB but may also be responsible for much of the tissue damage in the disease (*47*). For example, the most destructive tissue lesions—that is, cavities of the lung—occur only in PPD^+ individuals. Lymphokines produced by T cells are involved in activating macrophages to kill or inhibit the growth of *M. tuberculosis*. Although *M. tuberculosis* can grow extracellularly, it survives predominantly in macrophages. It is resistant to generally cytocidal reactive oxygen intermediates, such as hydrogen peroxide and hydroxyl radical, but is susceptible to reactive nitrogen intermediates (RNI), particularly nitric oxide (NO) (*48*). Activated mouse macrophages and human endothelial cells produce NO, but it is unclear whether human monocytes can do so. The lymphokines required to activate murine macrophages to produce RNI are interferon-γ and tumor necrosis factor–α (TNF-α). TNF-α is critically important for walling off infection and preventing dissemination (*49*) and has been identified in tuberculous pleural fluids (*50*). But TNF and other products of activated macrophages—for example, radicals, proteases, and cytokines—are toxic molecules that can contribute to tissue damage (*51*). Cytotoxic lymphocytes, $CD4^+$, $CD8^+$, γ,δ T cells, and natural killer cells may participate in killing infected macrophages that harbor the bacilli (*52*). Although over a dozen somatic and secreted antigens of *M. tuberculosis* have been cloned (*53*), it is not known which are important for engendering protective immunity. Because killed mycobacteria are far less protective in animal models than live bacteria, current hopes for protective antigens center about secreted molecules (*54*). Fundamental questions remain about the nature of immune responses required for protection, the antigens that engender them, and the extent to which pathogenesis in TB is the price we pay for protection.

Can I Catch TB from Riding the Bus?

The principal risk behavior for acquiring TB infection is breathing. Yet, the idea that microbes exist in sufficient concentration in air to represent a significant source of disease transmission was counterintuitive, and the importance of airborne infection was not established until the first quarter of this century. Careful observations established that coughing, sneezing, and speaking release organism-bearing particles (*55*). For example, a sneeze may contain over a million particles <100 μm in diameter, the mean being about 10 μm. Two types of organism-bearing particles have been found: droplet nuclei and dust-associated particles. After ejection from the nose and mouth, an aerosol droplet rapidly begins to evaporate. The evaporation continues until the vapor pressure of the droplet equals atmospheric pressure. The residue of a droplet that contains any organism is the droplet nucleus, which settles very slowly (12.2 mm per minute) and essentially remains suspended on small air currents until removed by ventilation. The second and less efficient mode of airborne transmission is from rapidly sedimented organisms associated with dust, which can be transiently resuspended by disturbance in air motion and which can serve as a reservoir for the bacilli.

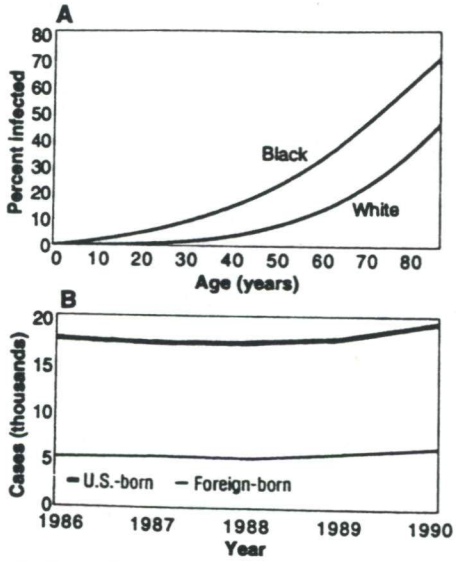


Fig. 2. (**A**) Prevalence of previous infection with *M. tuberculosis* by age for whites and blacks in the United States during 1990. (**B**) Number of cases of TB in U.S.– and foreign-born individuals in the United States from 1986 to 1990. Cases of unknown origin have been proportionately distributed.

In experimental studies in rabbits, droplet nuclei were found to be the major source of *M. tuberculosis* infection (*55*). The number of tubercles in the lungs was approximately equivalent to the number of live bacilli inhaled on droplet nuclei of a settling velocity of 9.14 mm per minute. Only 6% of the bacilli that were inhaled on larger particles reached the alveoli and produced tubercles; the majority settled in the upper respiratory mucosa where they were expelled by ciliary action. Oral infection is far less (10^{-4}) efficient in transmission of TB than inhalation of droplet nuclei, partially because mycobacterial viability is reduced by stomach acidity (*56*). Droplet nuclei were shown to be important in transmission of TB by the passage of air from the ventilating system of a hospital ward with patients with advanced TB through a large exposure chamber in which 71 out of 156 guinea pigs acquired infection (*57*). However, when half the air taken from the ward was vented to a duct where it was exposed to strong ultraviolet (UV) irradiation before passing through the chamber with the guinea pigs, none of the animals became infected, thus establishing the effectiveness of UV in killing tubercle bacilli on droplet nuclei. UV, if properly employed, remains an inexpensive means to decontaminate droplet nuclei (*58*). The number of bacilli present in the source case is a critical variable. The number of bacilli in solid nodular lesions varies between 10^2 and 10^4, whereas in cavitary lesions, the number of organisms is on the order of 10^7 to 10^9 (*24*). Animal studies indicate that as few as one to ten bacilli in droplet nuclei are sufficient to cause infection.

Clearly, there is no simple answer to the question posed above (*59*). TB infection is a stochastic process, and there appears to be

no threshold of organisms required to produce infection. The main determinants of individual risk are the concentration of organism-bearing particles exhaled by the source, their aerodynamic characteristics, the rate of ventilation, and the duration of exposure. Although large outbreaks of infection have been traceable to exposure to a single infected source case (60), epidemiological findings support the likelihood that the majority of patients infected with TB have acquired infection from nonintimate contacts (61).

The Changing Epidemiology of TB

The widespread use of skin tests with tuberculin PPD to detect past or present infection with M. *tuberculosis* has been developed into a valuable tool for epidemiological monitoring of the disease. A body of surveys provides direct measurements on the prevalence of past infection in children and adolescents throughout the world (62). In the 1960s, statistical methods were developed that used survey data on the prevalence of infection by age to estimate the annual risk of being infected with the bacillus each year (63). The most recent regional estimates for the annual risk of infection in the developing world (Table 1) show that the highest risks are in sub-Saharan Africa, where up to 2% of the population may be infected each year (4). Social and economic consequences of the enormous burden of TB morbidity and mortality are only magnified by the concentration of TB in young adults in the developing world. As BCG vaccination also produces skin-test reactivity to PPD, the value of the PPD test will diminish as the number of children vaccinated with BCG increases.

The annual risk of infection also provides a framework for understanding the epidemiological trends over this century. With the use of data on the prevalence of infection in army recruits each year, trends in the annual risk of infection in the Netherlands since the turn of the century have been reconstructed (63, 64). Before effective chemotherapy, the annual risk of infection in the Netherlands and other industrialized countries is believed to have decreased at a rate of 5 to 6% per year because of social and economic changes and the possible quarantine effect of the sanatorium movement. Since 1950 and the widespread use of chemotherapy, the annual risk of infection has been declining at a rate of nearly 10% per year.

The prevalence of positive PPD skin tests of U.S. Navy recruits has been used to estimate the annual risk of infection in the United States for whites as 0.1% in 1970 and 0.04% in 1990 (65). On the basis of these data as well as more recent data on Navy recruits (66) and taking into account methodological differences (67), we have estimated the prevalence by age of ever being infected (Fig. 2) (68). This methodology allows us to estimate that the total population currently living that has ever been infected with M. *tuberculosis* in the United States is 19 million (69).

Reflecting the declining annual risk of infection in the United States, the number of reported cases in the United States decreased every year but one from 1953, the beginning of national reporting, until the mid-1980s. Since 1985, TB cases have increased 18% nationwide. To delve deeper into the causes of this resurgence, we have disaggregated TB cases into four types: (i) reactivation of distant infections and new cases, estimated from annual risk of infection data, (ii) cases in foreign-born individuals, (iii) cases that are a result of HIV and TB co-infection, and (iv) cases in specific risk groups that result from increased active transmission. We estimated the number of cases expected to occur each year since 1978 from the prevalence of infection by age and breakdown rates (Fig. 3) (70). Cases beyond this number are defined as excess cases that can be attributed to immigration, HIV, or increased active transmission.

Several researchers have attributed a significant portion of the past and recent incidences of TB outbreaks to immigrants who enter the country with a greater prevalence of infection than the general U.S. population (6, 71). The CDC has followed cases in foreign- versus U.S.-born individuals for selected areas in the United States since 1979 and for the country after 1985. From 1986 to 1990 (the last year completed in its study), the proportion of total cases in foreign-born individuals in the United States has increased from 22.8 to 24.8%, although the largest share of the increased cases is among U.S.-born individuals (Fig. 2B). Of the excess cases in 1990 (calculated below), only 31% can be attributed to foreign-born individuals, which is only

Table 1. Estimated annual risk of TB infection, new cases, and deaths from TB for the developing world, 1985–1990 (4).

Area	Annual risk of TB infection	New cases per year	Deaths per year
Sub-Saharan Africa	1.5 to 2.5%	1,313,000	586,000
North Africa and western Asia	0.5 to 1.5%	323,000	91,000
Asia	1.0 to 2.0%	5,102,000	1,825,000
South America	0.5 to 1.5%	356,000	111,000
Central America and the Caribbean	0.5 to 1.5%	185,000	80,000
Total developing world		7,280,000	2,692,000

Table 2. Percentage of patients completing 12 continuous months of chemotherapy from 1976 to 1985 and the percentage of patients completing 6 continuous months of chemotherapy from 1986 to 1990 for the United States and selected cities within it. Figures shown are the average of annual percentage for those years with data. The number of areas reporting chemotherapy continuity data each year varies substantially. Within those areas that do report, the number of cases diagnosed each year that are included in the treatment completion database is substantially less than 100%. For the United States as a whole, the percentage of diagnosed cases included in this database has increased from 28% in 1975 to 64% in 1989. As these numbers are averages of a variable number of observations for each city, they should be taken only as indicative of the situation. Blank spaces indicate that no data were reported during that entire period. It is interesting to note that data for Los Angeles are not available for almost all years.

Years	Patients completing chemotherapy by location (%)										
	United States	Chicago	New York	District of Columbia	New Orleans	Detroit	Miami	Atlanta	San Francisco	Dallas	El Paso
1976–1980	82.6%	36.2%	59.7%	50.7%	29.2%		74.7%		83.3%	91.3%	93.5%
1981–1985	81.9%	39.8%	59.6%	60.4%	71.4%	71.1%	82.0%	84.7%	88.2%	95.2%	96.0%
1986–1990	83.7%	57.8%	53.6%	59.9%	81.3%	68.3%	82.5%	84.2%	96.5%	93.3%	99.2%

slightly more than expected in light of their share of total cases.

We estimate the number of excess cases from 1985 to 1991 that resulted from co-infection to be 18,000 (*72*). Although the number of individuals with TB who are also HIV-positive may be higher, the component that is due to active transmission among the same groups that have high HIV seropositivity is difficult to measure. A more refined understanding of the interaction between TB and HIV, including the prior prevalence of TB infection, is needed.

The presence of active transmission beyond that predicted by the small and declining annual risk of infection would cast the resurgence of TB in a different light. Increased active transmission is a sensitive indicator of the failure of a control program to promptly detect and institute effective treatment for infectious cases of TB. Several studies and routine data hint at the importance of active transmission in certain risk groups. Clear evidence of active transmission has been provided for residents of homeless shelters (*73*) and prisons (*74*) and for health-care workers (*75*). A prospective study showed that the annual risk of PPD conversion in initially negative intravenous (IV) drug abusers was 6.7% (*29*), considerably higher than for the general population in the poorest developing countries. Even more worrisome is the possibility that active transmission has been spilling out of high-risk groups into the general population. The number of cases of TB in U.S.–born children under the age of 5 has increased 34% from 1987 to 1990. Because all of these infections must have occurred in the last 5 years, this implies an increase of more than 10% per year in the risk of infection—except for those few cases that are a result of HIV infection in infants and children. In an attempt to quantify the possible role of heightened active transmission, we attributed the excess cases that cannot be explained by HIV infection or by the expected cases from past infection and the declining risks of infection to active transmission (Fig. 3) (*76*). From 1985 to 1991, this excess totals 13,700 cases.

Five possible factors could explain the reversal of the nearly century-long decline in the annual risk of infection: (i) the HIV epidemic; (ii) an increasing homeless population with high potential for transmission and breakdown through adverse living conditions; (iii) increasing numbers of IV drug users with similar living conditions; (iv) the concentration of all three of these risk factors in the same individuals or population subgroups, such that those at high risk for breakdown are at a high risk for transmission; and (v) at a time when the needs for TB control have increased, many city and state governments have been unable to

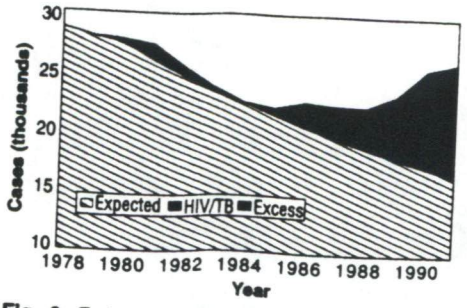


Fig. 3. Estimated cases of TB in the United States from 1978 to 1991, disaggregated into cases expected on the basis of trends in the risk of infection, cases of HIV and TB co-infection, and excess cases.

maintain or improve their TB treatment programs (*77*).

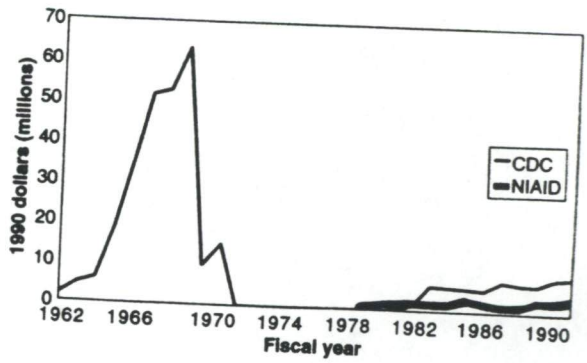
With depreciating infrastructure, declining real recurrent budgets, and a patient population that is more difficult to treat, programs to treat TB patients in a group of major cities had poor results. Table 2 summarizes the treatment results for the United States and a sample of cities with more than 100 cases of TB a year (*78*). During the time period in which treatment completion data have been collected by CDC, a number of cities have had very poor performance, whereas others have had excellent programs. The apparent failure of a number of urban programs to ensure a continuity of therapy for a higher percentage of their patients is difficult to ascribe to poverty or to general social conditions when other countries such as Mozambique, Tanzania, and Malawi are able to achieve high cure rates (*79*). With the use of CDC definitions, treatment completion in Malawi from 1984 to 1988 was 96% and in Tanzania from 1982 to 1988 was 86%. The experience of these and other developing countries illustrates that high rates of treatment completion have been achieved in the most difficult social, political, and economic circumstances. A common denominator of success has been investment in guaranteeing compliance through hospitalization or direct supervision of ambulatory treatment.

Compliance, Complacence, and Drug Resistance

From the earliest studies, it became app ent that resistance to any single antibio developed readily, and combinations of a tibiotics were necessary to prevent t emergence of resistance (*80*). The proble in effectively treating sensitive M. *tuberc losis* has been patient compliance with lo drug regimens (*81*). After 2 to 4 weeks treatment, the debilitating symptoms of T wane, and without active interventic more and more patients drop out of ther py. Many of those who fail to complete a adequate course of chemotherapy will re lapse and require retreatment if they ar diagnosed. Such circumstances create th conditions for the selection of drug-resis tant organisms. For example, in New Yor from 1982 to 1984, although 9.8% of iso lates from untreated patients were resistan to one or more drugs, 52% of isolates fron relapsed cases were resistant (*9*). The low compliance and lack of immunological re sistance mechanisms in some groups o HIV-seropositive cases have allowed the selection of multidrug organisms refractory to virtually the entire pharmacopoeia of effective drugs. Although the numbers remain too small to be certain, the case fatality rate of multidrug-resistant TB may be between 40 and 60% (*8*). In HIV-positive individuals, the case fatality rate may be higher than 80%, and the time from diagnosis to death may be dramatically accelerated; in one case series, it ranged from 4 to 16 weeks (*82*).

Case numbers tell only part of the story; the resurgence of TB is severely complicated by emerging drug resistance. Because isoniazid and rifampicin are microbicidal and the most effective drugs, resistance to both drugs is a very serious clinical and public health problem. A CDC survey of drug resistance from 1982 to 1986 showed that isolates from 9% of patients who were never previously treated were resistant to one or more drugs and that 22.8% of isolates from previously treated patients were resistant (*83*). In new cases in that

Fig. 4. Federal funding of the CDC for grants to the states for TB control and to NIAID (NIH) for research on TB.



survey, resistance to both isoniazid and rifampicin was 0.5% and in recurrent cases was 3.0%. The most recent data from the CDC, based on a set of reporting areas, indicate that for the first quarter of 1991, 14.4% of isolates were resistant to one or more drugs, whereas 3.1% of new and 6.9% of recurrent cases were resistant to isoniazid and rifampicin (9). These increasing rates of drug resistance challenge previous suggestions that drug-resistant bacilli are less infectious. Drug resistance is a much larger problem in certain cities, most notably New York (7); a study of all isolates in April 1991 showed that in new cases 23% were resistant to one or more drug, and 7% were resistant to isoniazid and rifampicin. In previously treated patients, 44% of isolates were resistant to one or more drug, and 30% were resistant to isoniazid and rifampicin. Experience from the developing world illustrates that programs with good results have comparatively low rates of drug resistance (84).

The Costs of Inaction

According to the simple model outlined above, about half of the increase of the occurrences of TB was unavoidable, a consequence of the natural history of TB and HIV co-infection. Many of the excess cases that resulted from increasing active transmission, however, could have been avoided through effective treatment programs in certain major cities. What has been the cost of our lack of vision in the 1980s when we did not act to strengthen these programs? The direct treatment costs of the excess cases since 1985 that were a result of increased active transmission equal $340 million (85). To this sum, we should add the human suffering quantified as 4,400 discounted years of healthy life lost and the economic indirect costs of lost productivity and social contribution, all totaling $300 million (86).

Predicting the course of the TB resurgence is difficult. Case numbers in this model that result solely from the increased breakdown rate from HIV infection will remain roughly constant at 4000 to 5000 new cases per year in the United States over the next decade. If there were no increased transmission between groups at high risk for HIV and TB because of dramatically improved treatment programs in the major cities, then case numbers in the United States could peak and begin declining again by the middle of this decade. However, we know from outbreak studies that there is a continuing risk of increased active transmission among these groups and into the general population. This threat is only heightened by drug resistance, because of which the treatment of cases and the reduction of transmission potential will be more difficult. In a worst-case scenario, total TB cases might continue to rise at the same rate as in the period of 1985 to 1991 (87). This would mean an excess of 86,000 cases in the United States that were a result of active transmission before the end of the decade. The direct treatment costs of these cases would total $2.2 billion, and the indirect costs would total $1.9 billion. These figures do not include infrastructure costs, which would be considerable—for example, for construction of isolation and negative-pressure facilities and for additional personnel required for directly observed therapy.

Where There is No Vision, the People Perish

Current recognition of the global importance of TB and renewed interest in addressing the problem derive, curiously, not primarily from public health institutions but from the World Bank. In a farsighted and comprehensive review of health problems of developing countries, it concluded that the impact of TB on development had been largely overlooked (88). The World Bank has recently made substantial loans to China and Bangladesh for TB control. But the hero of the piece is the International Union Against Tuberculosis and Lung Diseases (IUATLD) (89) that, on an annual budget of $4 million, has established control programs that detect approximately two-thirds of all cases, treat 65,000 cases, and provide cure rates of 80 to 85% in seven developing countries, including Tanzania, Malawi, Mozambique, and Nicaragua. From their detailed control program data, it was possible to estimate the burden of the disease and establish the cost-effectiveness of providing SCC (79). The WHO over the previous 15 years tragically allowed its Tuberculosis Unit to decline to the point that a single professional remained in 1989. Fortunately, WHO has recently initiated a new program in TB to both provide technical expertise requested by developing countries and develop an international research program that, if given appropriate resources, could make a significant impact (90). It is to be hoped that the considerable expertise of the Tropical Disease Research Programme and other WHO scientific programs will be engaged to strengthen the TB research effort.

In the United States, a generation of expertise has been lost. NIH support for research dwindled in the 1970s and, though now rising, is inadequate to address the scientific challenges of TB (91). Although drug resistance has been emerging unnoticed overseas, the importance to the United States of NIH engagement in research on international health problems has never been adequately appreciated or funded. The CDC receives federal funds to disburse through cooperative agreements with states and locales to control TB (Fig. 4). Additional special funding for HIV and TB demonstration projects in the United States, of particular importance for confronting TB drug resistance in AIDS patients, currently amounts to $10.8 million. It is hoped that these funds will double in the 1993 U.S. federal budget (92), although the proposed $35 million in grants to states is less than the request from New York City alone. With the loss of $340 million in the past 5 years attributable to excess cases of TB and the projected loss of more than $2.2 billion by the end of the decade, it is unlikely that the present resources will be adequate. It is essential to determine the true costs required to stem the increase of TB in this country.

In the world of infectious diseases, there is nothing from which we are remote and no one from whom we are disconnected. We will continue to be challenged by emergent threats to health, new agents and vectors, and new evolutionarily selected and man-made variants. The United States spends 12% of its gross national product on health care, although one wonders how much is spent to prevent disease rather than to treat it. We know how to cure and prevent conventional TB; we must quickly develop the capacity to prevent the spread of drug-resistant TB. If we do not learn from the current epidemic of TB and if we do not develop new scientific tools to diagnose, prevent, and treat the disease, the tragedy unfolding in New York City could be repeated in any city in America that has homeless people, AIDS, prisons, hospitals, and nursing homes. The fundamental principle of infectious disease control that we have yet to apprehend was best articulated in 1513, not by a physician but by the political scientist Machiavelli (93):

> It happens then as it does to physicians in the treatment of Consumption, which in the commencement is easy to cure and difficult to understand; but when it has neither been discovered in due time nor treated upon a proper principle, it becomes easy to understand and difficult to cure. The same thing happens in state affairs; by foreseeing them at a distance, which is only done by men of talents, the evils which might arise from them are soon cured; but when, from want of foresight, they are suffered to increase to such a height that they are perceptible to everyone, there is no longer any remedy.

Note added in proof: The first molecular target for any antituberculosis drug, isoniazid, has recently been defined (94).

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improved diagnostics, $0.18 million.

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The Crisis in Antibiotic Resistance

Harold C. Neu

The synthesis of large numbers of antibiotics over the past three decades has caused complacency about the threat of bacterial resistance. Bacteria have become resistant to antimicrobial agents as a result of chromosomal changes or the exchange of genetic material via plasmids and transposons. *Streptococcus pneumoniae, Streptococcus pyogenes*, and staphylococci, organisms that cause respiratory and cutaneous infections, and members of the *Enterobacteriaceae* and *Pseudomonas* families, organisms that cause diarrhea, urinary infection, and sepsis, are now resistant to virtually all of the older antibiotics. The extensive use of antibiotics in the community and hospitals has fueled this crisis. Mechanisms such as antibiotic control programs, better hygiene, and synthesis of agents with improved antimicrobial activity need to be adopted in order to limit bacterial resistance.

The stunning success of the pharmaceutical industry in the United States, Japan, the United Kingdom, France, and Germany in creating new antibiotics over the past three decades has caused society and the scientific community to become complacent about the potential of bacterial resistance. There are countless antibiotics: more than 50 penicillins, 70 cephalosporins, 12 tetracyclines, 8 aminoglycosides, 1 monobactam, 3 carbapenems, 9 macrolides, 2 new streptogramins, and 3 dihydrofolate reductase inhibitors (*1*). Despite all these antibiotics, a person could die in a hospital in New York, San Francisco, Paris, Barcelona, Tokyo, or Singapore as a result of a resistant bacterial infection.

Antibiotics are available that effectively inhibit bacterial cell wall synthesis, protein synthesis, and DNA replication (Fig. 1 and Table 1). Bacteria can resist antibiotics as a result of chromosomal mutation or inductive expression of a latent chromosomal gene or by exchange of genetic material through transformation (the exchange of DNA), transduction (bacteriophage), or conjugation by plasmids (extrachromosomal DNA) (*2*). Conjugation with plasmid transfer of DNA is particularly common among the *Enterobacteriaceae*, *Pseudomonas*, and anaerobic species (*2, 3*). In addition to conjugative plasmids, bacteria may possess transposons, the so-called jumping genes, that have the ability to enter transmissible plasmids or chromosomes (*4*). Resistance can be transferred horizontally by plasmids or chromosomally located conjugative transposons that spread the resistance to other species. It has been postulated that *Escherichia coli* transferred the ability to produce β-lactamase enzymes that destroy compounds with a β-lactam nucleus (Fig. 2) in *Haemophilus influenzae* by initially infecting *Haemophilus parainfluenzae* (*5*). Intergeneric spread of resistance can occur between Gram-positive species such as staphylococci and enterococci and between *Enterobacteriaceae* and *Pseudomonas* or anaerobes such as *Bacteroides* (*6*). Gram-positive species can transfer resistance to Gram-negative species but the reverse is uncommon.

Antimicrobial agents are rendered inactive by three major mechanisms: (i) inactivation of the antibiotic by destruction or modification, (ii) prevention of access to the target, and (iii) alteration of the antibiotic target site (*3*). Some examples of inactivation are β-lactamase and aminoglycoside inactivating enzymes (*7, 8*) (Table 2). The alteration of permeability or efflux of the agent occurs for β-lactams, aminoglycosides, and tetracyclines (*9*), and a single amino acid change in an enzyme alters the sensitivity of the targets for β-lactams, macrolides, and folate synthesis antagonists (*3, 10*).

Staphylococci

In 1941, virtually all strains of *Staphylococcus aureus* worldwide were susceptible to penicillin G, but by 1944 *S. aureus*

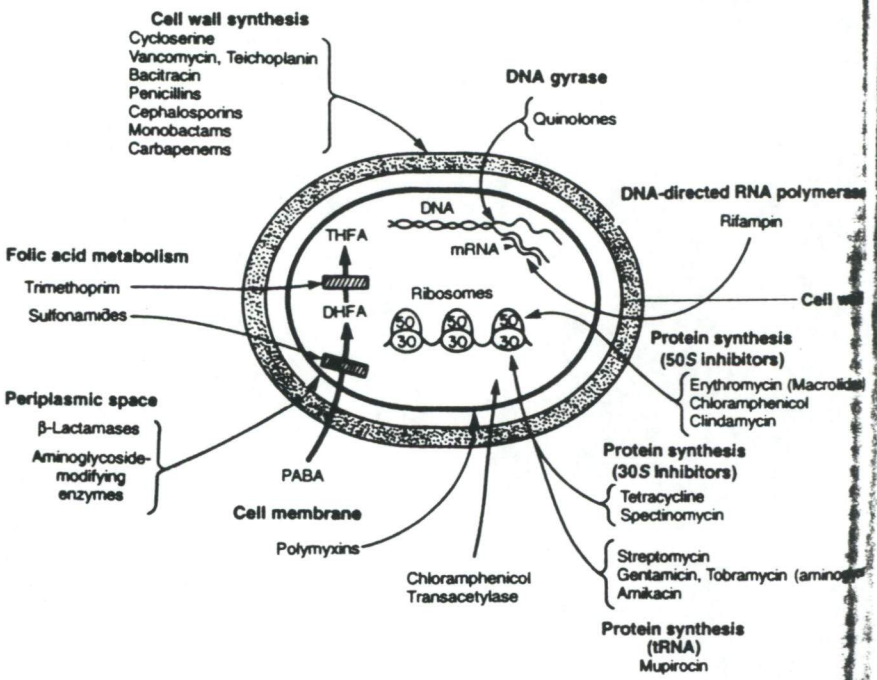


Fig. 1. Sites of action of various antimicrobial agents; mRNA, messenger RNA; tRNA, transfer RNA; PABA, *p*-aminobenzoic acid; DHFA, dihydrofolic acid; THFA, tetrahydrofolic acid.

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The Origin of Plagues: Old and New

Richard M. Krause

Viruses and bacteria emerge in new and old forms to cause disease epidemics. Some microorganisms recur when changing life-styles (including increased international travel) offer new opportunities; others arise from new genetic variations. These various epidemics connect the future with the past, offering lessons for guarding the health of generations to come—lessons learned from diseases such as tuberculosis, toxic shock syndrome, Lyme disease, streptococcal infection, influenza, and acquired immunodeficiency syndrome (AIDS). The public must be vigilant to the possibility of new epidemics, learn more about the biology and epidemiology of microbes, and strengthen systems of surveillance and detection.

Acquired immunodeficiency syndrome is the most contemporary example of human vulnerability to the microbial world, and there is genuine concern that another "new" microbe, or a genetic variation of an old one, can and will "go global" as AIDS has done. A new epidemic may be incubating even now in the crowded, unsanitary mega-cities of the developing world, or in remote jungles in Africa, South America, or Asia—once sparsely inhabited regions that have recently been altered by modern civilization (*1–4*).

AIDS is not the only case of a microbial threat to human beings in the late 20th century. Since the 1970s, a series of unanticipated outbreaks of microbial diseases startled inhabitants of the United States. Legionnaires' disease, toxic shock syndrome, and Lyme disease all happened before the recognition of AIDS in 1981.

In addition to these threats within the United States, strange epidemics have been occurring elsewhere in the world. In Africa, outbreaks of the deadly Ebola virus took the lives of 50% of the people who became infected. A majority of the doctors and nurses who treated these patients also died of the disease. After fatal but localized outbreaks of Ebola fever, the disease failed to become a worldwide epidemic. At the same time, however, the AIDS virus, human immunodeficiency virus (HIV), was spreading from the rural communities of Africa to the towns and cities, infecting thousands of people in Central Africa alone. After a few years, HIV, which has a long latency period, manifested itself when those who were infected developed the medical symptoms of full-blown disease. By that time, AIDS had spread from Africa to the United States, Europe, Asia, and elsewhere.

Many factors interact and contribute to the reemergence of old infectious diseases or the emergence of new ones. More often than not, epidemics occur because of changes in the patterns of human behavior, social organization, urbanization, and agriculture. However, the most important factor is the spread of microbial organisms from points of origin as a result of the migration and travel of their human hosts (*5*).

In ancient times, infectious diseases spread slowly but steadily along caravan routes throughout the Roman and Asian world (*6, 7*). From A.D. 165 to 180, measles was spread along the caravan routes, and from A.D. 251 to 266 smallpox was carried. One-third of the population died. Such a catastrophe did not recur until the bubonic plague spread from Asia to Europe in the 13th and 14th centuries. This occurred when the horsemen of the Mongol armies raced across the steppes of Asia, transmitting the disease from the point of origin in northern Burma. They carried fleas infected with plague bacillus. From there the plague moved farther eastward via the caravan routes to Europe and elsewhere. After 1492, the oceans became highways that further extended the dispersal of disease agents. It became possible for plagues such as smallpox and measles to circle the globe within a year. The oceans remained the predominant route of transmission until the present era of mass air travel. Today, airborne travelers incubating infections can reach any point on the globe within 24 hours. As a consequence, worldwide exposure to a highly infectious virus, such as influenza, occurs in a matter of weeks.

However, microbes are not idle bystanders, waiting for new opportunities offered by human mobility, ignorance, or neglect. Microbes possess remarkable genetic versatility that enables them to develop new pathogenic vigor, to escape population immunity by acquiring new antigens, and to develop antibiotic resistance.

For these reasons, it is necessary to be prepared for new epidemics caused by old

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microbes as well as those caused by new microbes that appear as a consequence of evolutionary events. Examples of early and recent epidemics are described here to illustrate the principles that govern the occurrence of plagues.

Old Microbes, New Epidemics

Tuberculosis. Although tuberculosis (TB) is discussed elsewhere (8), it is useful to recall the epidemic of TB in the 18th and 19th centuries. In the tragic story of TB (9), it becomes clear that the slums of the big industrial cities were cauldrons for the incubation of TB; the disease then spread to the upper classes and rural communities until it threatened "the very survival of the European race" (9). As McNeil has noted, quoting from *Piers Plowman*, "A fair field full of folk makes a [fertile] feeding ground" for microbes (7). Tuberculosis is again advancing, into populations that have been rendered susceptible to antibiotic-resistant strains by poverty, malnourishment, and infection with HIV.

Toxic shock syndrome. Nosocomial infections and surgical and trauma wound infections are frequently caused by *Staphylococcus aureus*. However, an unexpected occurrence in 1980 was the epidemic of toxic shock syndrome (TSS) caused by this organism. Changes in human behavior also preceded this epidemic, which occurred among young, primarily white women, with an onset during menstruation (10). A strong correlation was found between TSS and the presence of *S. aureus* in vaginal or cervical cultures of affected patients. A series of studies identified TSST-1 toxin as the most frequent cause of this syndrome (11). The pathogenesis of TSS involves the establishment of a toxin-producing strain in an individual not immune to TSS under conditions that favor the formation of the toxin. Such conditions prevailed with the introduction of certain brands of hyperabsorbent tampons. Their prolonged intravaginal use enhanced the aerobic surface area in the vagina, which favored the growth of intravaginal *S. aureus* and the production of TSST-1.

Public education and removal of the hyperabsorbent tampons from the market resulted in a marked decrease in the number of TSS cases in menstruating females (Fig. 1). This disease, as a complication of tampon use, has now almost disappeared. Sporadic cases of TSS have occurred before and since this epidemic, when penetrating or surgical wounds in individuals lacking immunity to TSS become infected with toxin-producing strains of *S. aureus*. TSS also persists as a threat to patients receiving hemodialysis.

Over 100 years ago, the Scottish surgeon

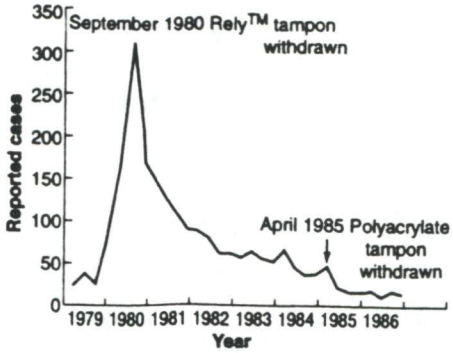


Fig. 1. Reported cases of toxic shock syndrome by year; passive surveillance, United States, 1979 to 1986 (11).

Sir Alexander Ogsden proved that *S. aureus* was a frequent cause of surgical wound sepsis. Mortality was very high because of unsanitary conditions but was greatly diminished with the introduction of sterile surgical techniques and, later, antibiotics (12). However, *S. aureus* is very adept in developing resistance to multiple antibiotics (13). For this reason, infections of surgical and trauma wounds are frequently difficult to treat. For reasons that are still unclear, a "new" strain of *S. aureus* arose in the 1950s that caused frequent outbreaks of severe infections in nurseries for the newborn and pediatric wards of hospitals in most countries of the world; however, these outbreaks subsided a decade later.

Future outbreaks of TSS might be caused by changes in medical practices or by possible alterations in the epidemiology and bacteriology of *S. aureus*. It is conceivable, for example, that *S. aureus* will acquire the genetic capacity to produce a "new" TSS toxin to which most humans are not immune. For all of these reasons, immunological approaches to the control of staphylococcal disease should be promoted that include the development of both active and passive immunization against the toxin or toxins and the surface carbohydrate antigens (12).

Lyme disease. Lyme disease is another bacterial infection whose outbreak startled the public. The disease emerged from obscurity as a result of changes in the habits of people and as a result of the ecological relation between the tick vector and its animal host. The illness is an old disease that recurred sporadically during the 19th century; it was then of unknown cause, but became known as Lyme disease in the mid-1970s as a result of an epidemic of arthritis that occurred in the village of Old Lyme, Connecticut (14). Since then, the number of cases has increased substantially. More than 10,000 cases were reported this past year.

Interest in Lyme disease was heightened with the discovery that chronic infection with the spirochete resulted in chronic inflammatory arthritis similar in many respects to rheumatoid arthritis. For this reason, the illness has become a model for the study of rheumatic diseases in humans. Lyme disease is a generalized infection; additional complications include cardiac inflammation and neurological abnormalities that resemble multiple sclerosis and neurosyphilis (15).

In 1982, the disease-causing spirochete, which was subsequently named *Borrellia burgdorferi*, was discovered (16). The reservoir of the spirochete in the northeastern United States is the white-footed mouse, on which the deer tick feeds and then becomes infected. This tick, *Ixodid dammini*, transmits the disease to humans. The adult-infected ticks mate in the fur of white-tailed deer (15) and then populate the landscape to which humans are exposed.

Lyme disease has become the most prevalent vector-borne disease in the United States (17). Although initially identified primarily in New England and Wisconsin, it has spread to other regions. An important factor in the spread of this epidemic has been the rapid increase in the deer population in the eastern United States, which has led to a large increase in the tick population. According to wildlife biologists, deer had almost disappeared in the northeastern United States by the end of the 19th century. Since then, the deer population has increased steadily, and by 1985 there were an estimated 13 million white-tailed deer in the United States. As the range of the deer spread, so did the range of the infected deer tick. During this time, the urban population moved to the suburbs; some people acquired second homes in rural areas, and outdoor recreation enthusiasts were exposed to and frequently bitten by infected ticks. Events were on a collision course.

This epidemic will continue until people follow the recommended precautions to prevent and avoid tick bites, until people seek prompt diagnosis and treatment with antibiotics after receiving a tick bite in an endemic region, and until the serological tests to detect infection are more reliable than current methods. An early first step in containing this epidemic is the formulation of an experimental vaccine that protects mice from illness produced by direct injection of spirochetes (18) or by infected tick bites (19).

Only recently has a satisfactory explanation for the occurrence of several hundred cases of Lyme disease in California and other western states been presented (20). The dusky-footed woodrat serves as the spirochete reservoir, but the transmission requires a two-cycle pattern involving two ticks distinct from the northeastern United States tick, *I. dammini*. The spirochete-

infected tick, *I. neotomae*, only bites the dusky-footed woodrat, and this rat maintains the reservoir. Another tick, *I. pacificus*, bites both the rat and the human and is responsible for transmission of the disease to humans. It is too early to know what events might enhance the "bi-cycle" transmission of Lyme disease in the western United States and whether the disease will become as prevalent as in the northeastern United States.

Old Viruses, New Epidemics

There are numerous examples of old viruses that have caused new epidemics as a consequence of changes in human practices and social behavior. Epidemic poliomyelitis emerged in the first half of this century when modern sanitation delayed exposure of the virus until adolescence or adulthood, at which time it produced infection in the central nervous system and severe paralysis. Before the introduction of modern sanitation, polio infection was acquired during infancy, at which time it seldom caused paralysis but provided lifelong immunity against subsequent polio infection and paralysis in later life. Thus, the sanitation and hygiene that helped prevent typhoid epidemics in an earlier era fostered the paralytic polio epidemic.

An outbreak of dengue hemorrhagic fever became an epidemic in southeast Asia in the 1950s, and more recently in Central and South America. This has occurred as a consequence of ecological changes that have resulted in the proliferation of the mosquito vector *Aedes aegypti*. The inadvertent introduction and wide dissemination of a second mosquito vector, *Aedes albopictus*, from Asia into the United States, has set the stage for a possible epidemic of dengue in this country. These and numerous other examples of new epidemics caused by old viruses are discussed in recent reviews (*2*, *3*).

The Genetic Origin of New Microbes

Although people have influenced the distribution of microbes and the occurrence of epidemics, microbes have been more than simple opportunists. They have also been great innovators and have developed, through genetic versatility, new vigor for survival and species dominance. Examples of such genetic versatility for both bacteria and viruses are described below.

New Bacteria, New Epidemics

It is likely that many human bacterial infections, such as leprosy and TB, have survived successfully for hundreds of years, if not millennia. Nevertheless, genetic events can alter the antigenic characteristics of bacteria so that they can elude herd immunity, enhance pathogenicity by the acquisition of virulence factors, and result in the acquisition of antibiotic resistance.

Mutations comprise one source of such new properties. Of greater interest, however, has been the discovery that these new characteristics are acquired within a bacterial species or transferred between species by genes that are carried on extrachromosomal elements such as plasmids or on the DNA of bacterial phages. The genes associated with such elements are transferable from organism to organism by conjugation and transduction or by transformation. The genetic events involved in the appearance of antibiotic resistance among microbes are discussed elsewhere (*13*, *21*).

A sudden epidemic outbreak of an infectious disease can be the consequence of microbial genetic events. For example, an outbreak of diphtheria occurred in Manchester, England, because the resident nontoxin-producing diphtheria microbe (which did not produce disease) was converted to a toxin-producing, virulent form (*22*). The origin of this conversion was traced to a child who returned by airplane to Manchester from Africa and who had become infected with a pathogenic, toxin-producing diphtheria bacillus. This organism contained the phage that carried the diphtheria toxin gene. Because multiple infections allowed toxigenic diphtheria bacilli to comingle in the community with nontoxic diphtheria bacilli, the toxin gene was spread to the latter by phages that possessed the toxin gene.

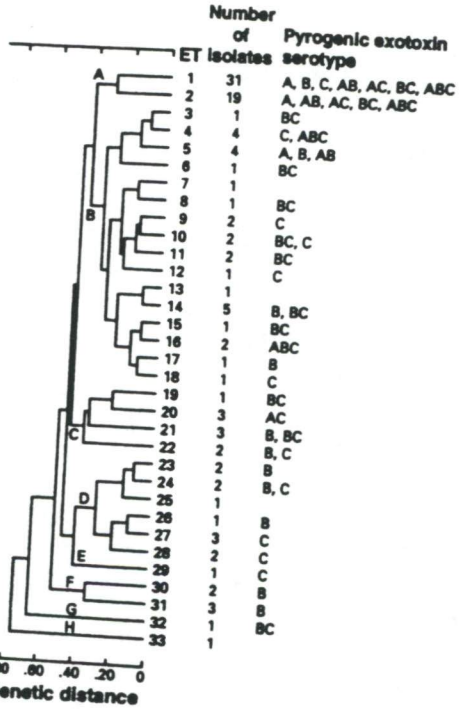


Fig. 2. Dendrogram showing estimates of genetic relations among 33 electrophoretic types (ETs) of 108 isolates of *Streptococcus pyogenes* group A, based on allele profiles at 12 enzyme loci. Eight major lineages are identified by letters A to H. Pyrogenic exotoxin serotypes of the isolates of each ET are indicated (*24*).

"New" streptococcal infections. There was a sense of disbelief among the general public when the media reported the unexpected death of the popular TV puppeteer Jim Henson. The disbelief arose because he died from a presumably ordinary streptococcal infection that is readily treatable with penicillin and normally resolves without complications. However, the infection progressed rapidly to a fulminating fatal pneumonia and irreversible shock, despite treatment with penicillin.

Although there is not an entirely satisfactory explanation for the occurrence of this virulent form of streptococcal disease [termed toxic shock-like syndrome (TSLS) because of its resemblance to *S. aureus* TSS], the evidence suggests that it is caused by certain strains of group A streptococci that produce potent "erythrogenic toxins." This severe form of streptococcal infection from which Jim Henson died made its appearance in the mid-1980s and was reported in Europe and throughout the United States. In one study of 30 patients, six died (*23*). Death from common streptococcal infections, including streptococcal sore throat, is very rare.

Streptococci are known to produce three distinct erythrogenic toxins: types A, B, and C. These toxins produce the rash of scarlet fever and possess powerful inflammatory and cytotoxic properties. In the early part of this century, streptococcal infections frequently resulted in a severe form of scarlet fever and toxic shock. Death was common. The streptococci cultivated from these patients produced the particularly potent toxin A. In contrast, modern strains that produce toxin types B and C are less likely to cause these lethal complications.

It now appears that the toxic streptococcal strains that more commonly produce the potent type A toxin have reemerged and are associated with TSLS. A relatively high frequency of exotoxin A among streptococcal isolates recovered from TSLS patients has been reported (*24*). Toxin A was produced by 28 of 31 strains isolated from patients with TSLS. In contrast, toxin A was produced by only 14 of 77 strains isolated from patients with streptococcal infections of the usual severity.

Multilocus enzyme electrophoresis was performed to further elucidate the genetic diversity and relations among the 31 TSLS and 77 non-TSLS streptococcal isolates (*24*). Thirty-three electrophoretic types

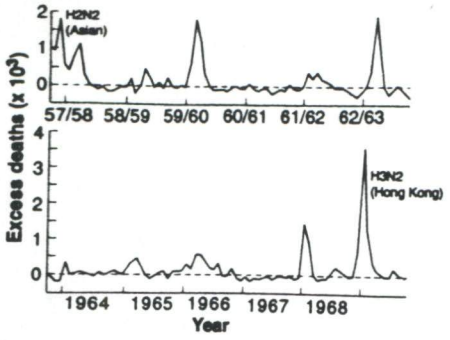


Fig. 3. Excess pneumonia and influenza mortality (than would have been predicted for a nonepidemic year), by 4-week periods, from 122 U.S. cities during periods of prevalence of A influenzas [modified from (*27*)]. The 1957 to 1958 Asian (H2N2 virus) and the 1968 to 1969 Hong Kong (H3N2 virus) influenza pandemics were due to "new" viruses that arose by genetic reassortment. The epidemics between the pandemics were due to mutants of the Asian influenza virus that had undergone point mutations in the antigenic genes. H2 and H3, hemagglutinin antigens 1 and 2, respectively. N2, neuraminidase 2.

(ETs) representing distinctive multilocus clonal genotypes were identified. More than two-thirds of the cases of TSLS were caused by strains of two related clones, ET-1 and ET-2 (Fig. 2). Recent pathogenic European isolates were also classified as ET-1 or ET-2. Nearly identical nucleotide sequences were found for the exotoxin A structural gene of six isolates from five ETs of diverse phylogenetic lineages. This finding suggests that the gene has been transferred from clones ET-1 and ET-2 and distributed horizontally among other clones, presumably by bacteriophage-mediated transfer. This supports the hypothesis that toxin A is a major factor in the pathogenesis of TSLS, although it is also conceivable that a product of a gene tightly linked to exotoxin A is involved in the pathogenesis of this severe disease.

The streptococcal strains from patients with serious disease may consist of a unique recent clone (*25*). Whether the streptococcal strains that cause TSLS are "new" or recurring strains is a complex question. In addition to phage-mediated genetic change, as noted above, other variables such as fluctuations in human immunity, host susceptibility, and the selective pressures of antibiotic therapy may have caused the recent arrival of the streptococci that produce TSLS. Whatever the final explanation, students of streptococcal disease recognize that they are dealing with something new in their clinical experience, and they must be alert to the prompt treatment of any streptococcal infection. There is also the danger that ET-1 and ET-2 strains will spread more broadly in the community and that the toxin gene may continue to spread horizontally to unrelated clonal types of group A streptococci.

New Viruses, New Epidemics

The emergence of novel viral agents is restrained in part by the requirement to preserve the structural integrity of the virus and its relation to a specific ecological niche. New viruses may occur, in spite of evolutionary constraints, as a consequence of genetic mechanisms such as point mutations and genetic reassortment (*2*). This phenomenon is dramatically represented by influenza viruses, which frequently generate "new" viruses that cause epidemics and pandemics.

Influenza. Point mutations that alter critical sites on the major hemagglutinin glycoprotein antigen of influenza virus allow the virus to elude the immunity of the population that occurred after exposure to prior strains of influenza virus. Such changes in the virus account for the antigenic drift in the hemagglutinin of wild-type viruses that occurs from year to year. Because the new hemagglutinin bears some resemblance to the old, antibodies to the old hemagglutinin may, but do not always, neutralize the "new" virus. Therefore, the "new" virus may cause infection even in those who previously had influenza.

The second origin of "new" and novel influenza viruses is genetic reassortment (*26*). This results in the occurrence of an entirely new hemagglutinin antigen against which there is little or no immunity, and may give rise to a pandemic of influenza. This occurred in 1957 (Asian flu) and in 1968 to 1969 (Hong Kong flu) (*27*) (Fig. 3). Both viruses possessed the same neuraminidase. The viruses causing these epidemics are thought to have arisen as a result of the capture by human viruses of one or more external genes from avian influenza viruses at the time of co-infection of the two viruses in the same animal or human. Such events most likely occurred in China or elsewhere in Asia and resulted in new viruses.

The generation of these new viruses could occur during co-infection because the influenza viruses carry their genetic material in eight separate gene segments. During the course of co-infection with different strains, these genes can be reassorted or recombined, producing novel viruses that possess gene combinations unlike those of either parent. Thus, Kilbourne notes, "The process is analogous to sexual reproduction. Influenza viruses can make evolutionary leaps without the need to gradually accumulate numerous favorable mutations" (*2*). For these reasons influenza is a moving target, and worldwide surveillance is needed to determine the emergence of new strains and their use in formulating an up-to-date influenza vaccine.

AIDS—A New Disease?

The AIDS epidemic is clearly new. The first sporadic cases occurred in Africa, the United States, and elsewhere. The epidemic gained momentum throughout the 1980s. Currently, more than a million people are infected in the United States, and many millions are infected worldwide, particularly in Africa and Central and South America. If a cure is not found, most or all of these individuals will die of overwhelming secondary infections that occur as a result of the severe immune deficiency. The World Health Organization has predicted that the epidemic will spread widely in India and elsewhere in Asia unless a means is found to stem the advance.

Although the AIDS epidemic is certainly new (AIDS does not mimic any previously known pestilence), the data so far leave unanswered whether HIV-1 and HIV-2 are new (*28*). Some believe that these viruses were transmitted from African monkeys or other primates to humans, but the evidence for this is not conclusive. Africa is a known reservoir of the nonhuman primate lentiviruses termed simian immunodeficiency virus (SIV), but only one of a number of the SIV strains characterized so far is closely related to HIV-1 (*29, 30*), the virus currently causing the largest number of AIDS cases. AIDS caused by HIV-2 is rare in the United States but quite common in West Africa, and is now occurring in western India. HIV-2 is closely related to SIV isolated from captive rhesus macaques (*31*). Computer programs have been used to construct evolutionary trees to determine the relatedness of viruses by comparing genetic sequences for homologies (*32*). It has been suggested (*33*) that known SIV strains appear to be more closely related to HIV-2 than to HIV-1. Nevertheless, these evolutionary relations depend on the proper alignment of homologous sequences, and there are disputes concerning the interpretation of these alignments and the conclusions.

Whatever the origin of the AIDS viruses, it is likely that they have been around for at least a century (and perhaps longer in

Table 1. The budget of the National Institute of Allergy and Infectious Diseases as a percentage of the total budget of the National Institutes of Health (*39*).

Year	Percentage
1965	9.0
1970	9.2
1975	5.7
1980	6.3
1985	7.2
1990	11.0
1992	10.7

Central Africa), causing sporadic human infection. Mathematical models have been used (34, 35) to examine the time course of the AIDS epidemic and the spread of the disease from a hypothetical initial focus or single village in Africa. The models have sought to determine the length of time it would take for the virus, emerging in one village, to spread to surrounding villages and rise to a detectable level (a seroprevalence of 1%). These models assume sporadic, limited personal interactions between one local village and a set of surrounding villages in the isolated outback of Africa. Such restricted interactions between villages were the most likely pattern for the spread of AIDS in the earlier years of the epidemic. According to the model, the number of cases of HIV infection would increase faster with time (34). These considerations indicate that there may have been a passage of 100 years between the emergence of AIDS at its putative source and the outbreak of the epidemic during the 1980s.

It is also likely that the AIDS epidemic gained momentum and emerged from this local dormancy as a result of changing cultural patterns, urbanization, and the migration of peoples, as well as long-distance land travel along new highways and commercial routes. Because it was no longer restricted to isolated locales, the AIDS virus spread rapidly to urban areas. Similar historical circumstances have been noted (7) for the occurrence of bubonic plague. Old social habits allowed people to coexist with the plague bacillus in the Burma-Unnan region long before the Mongol invasion. These people adopted a life-style which, although it did not eliminate the microbe, curtailed its spread. However, social disruption subsequently favored the spread of microbes.

Just as social and economic changes of the Industrial Revolution promoted the outbreak of TB (9), social forces in the United States arising out of changing patterns of sexual behavior and the use of addictive drugs during the past 30 years have enhanced the spread of AIDS (36). There is ample evidence that the epidemic of sexually transmitted diseases (STDs) has also contributed to the spread of AIDS. Only research and a combination of social education and health programs will prevent the further spread of STDs and AIDS (37).

Strategies for the Future

In the 1960s and 1970s, there were frequent pronouncements that infectious diseases had been conquered and were no longer major threats to health (38). The medical and scientific community and the public generally accepted this verdict, and the major research effort in the 1970s was concentrated on great "killers and cripplers," heart disease and cancer.

The reasons for Burnet's optimistic view can be traced to the advent of the sulfonamide drugs in the 1930s and penicillin in the 1940s, when hundreds of new antibiotics were discovered to treat infectious diseases such as gonorrhea, syphilis, pneumonia, TB, and typhoid fever. New vaccines prevented epidemics of measles, meningitis, rubella, polio, and hepatitis.

In view of this declining interest in infectious diseases, it is not surprising that research support for microbiology and virology declined for many years at the National Institutes of Health (NIH). The budget of the National Institute of Allergy and Infectious Diseases (NIAID) as a percentage of the NIH budget from 1965 to 1992 is shown in Table 1 (39). In 1965, NIAID received 9% of the NIH budget, but this declined to 5.7% in 1975 (39). The decline was slowly reversed when the public and the scientific community were confronted with the series of unexpected plagues discussed here and elsewhere (40). Throughout the 1980s the NIAID budget continued to increase as the AIDS epidemic progressed and as other research initiatives were undertaken to develop new vaccines and new methods for the prevention and treatment of epidemic diseases.

It is likely that epidemics will continue to occur in the future. Changes in human social behavior and customs will continue to provide opportunities for microbes to produce unexpected epidemics. We must be aware of the possible consequences of altering our behavior individually and as a society. Furthermore, science cannot halt the future occurrence of "new" microbes. These emerge from the evolutionary stream as a consequence of genetic events and selective pressures that favor the "new" over the "old."

Therefore, public health requires the renewal and expansion of research on the epidemiology and biology of microbes and awareness to the possibility of new epidemics. Although clinicians in New York and California detected the first cases of AIDS, it was the nationwide surveillance system of the Centers for Disease Control that identified the epidemic nature of the disease and its mode of dissemination. Such cooperation was also true for TSS, Legionnaires' disease, and Lyme disease. It is necessary to expand surveillance efforts both in the United States as well as in other regions of the world.

Surveillance alone, however, cannot detect the unexpected emergence of future plagues or prepare the defense against them. The accomplishments thus far in the fight against AIDS are based on 40 years of biomedical research. Research into the survival of microbes and their adaptation to new habitats is required. In addition, it is necessary to understand their genetic make-up and ability to cause disease, as well as the immunological processes that are mobilized by the body against microbial invasion and infection.

In conclusion, the migration of people and changes in individual and social behavior foster the occurrence of epidemics caused either by old microbes of by new ones that that emerge as a consequence of genetic events that enhance virulence and pathogenicity. These various factors must be considered in the development of strategies to cope with future epidemics.

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Structure-Based Strategies for Drug Design and Discovery

Irwin D. Kuntz

Most drugs have been discovered in random screens or by exploiting information about macromolecular receptors. One source of this information is in the structures of critical proteins and nucleic acids. The structure-based approach to design couples this information with specialized computer programs to propose novel enzyme inhibitors and other therapeutic agents. Iterated design cycles have produced compounds now in clinical trials. The combination of molecular structure determination and computation is emerging as an important tool for drug development. These ideas will be applied to acquired immunodeficiency syndrome (AIDS) and bacterial drug resistance.

Will the next generation of pharmaceuticals arise from a combination of crystallography and computational methods (*1–5*)? While I share the enthusiasm for structure-based drug design (*6–8*), it is the newest of several approaches to the lengthy process of finding and developing therapeutic agents (Table 1). One important discovery procedure is high-volume "random" screening of natural products, corporate databases of compounds, or peptides and oligonucleotides. Another method is the interception of specific biochemical mechanisms. Vaccine development is yet another route to anti-infectives. Finally, there are well-developed "active analog" approaches to improve upon initial discoveries. Any of these techniques, singly or in combination, can play a pivotal role in finding new drugs.

Can we design drugs from first principles, creating a molecule with a specific mode of action and acceptable biological properties? Today's answer is "no." What we can reliably expect is to design inhibitors, especially enzyme inhibitors, and to begin the long process of drug development from a sensible starting point.

Fifteen years ago, Seymour Cohen proposed a general paradigm for developing drugs for infectious diseases (*9*). Infectious agents, such as viruses, bacteria, fungi, or protozoa, encode or carry their own crucial enzymes and nucleic acids, which serve as obvious targets for intervention. In the succeeding decade and a half, the ability to identify, clone, express, and purify proteins and nucleic acids has increased enormously, making highly specific in vitro assay systems commonplace. These assays, in turn, lead to effective strategies for the discovery of a wide variety of inhibitors (*10*). Structural techniques have also advanced, and high-resolution molecular anatomies can be determined by crystallographic and magnetic resonance experiments. Thus the pieces are in place to extend Cohen's concept to structure-based design (*1, 3, 7, 11, 12*).

I will draw examples from AIDS and bacterial drug resistance. These two major health problems have three features in common: recent starting points as public health issues, known etiologies, and a large number of macromolecules as potential targets (Table 2).

Screening

The vast majority of drugs in the marketplace were derived from discoveries in large-scale screens or from analog development programs. Robotic systems can perform thousands of tests per day by means of radioactive labeling or spectroscopic detection, and further improvements can be expected (*13*). It is feasible to scan an entire corporate database (for example, 100,000 to 500,000 compounds) in less than a year's time. The coupling of cell metabolism to microsensors opens the door to rapid surveys of toxicity and function at the cellular level (*14*). The only current approved drugs against human immunodeficiency virus (HIV) were detected with screening techniques (*15*) and so were the original generation of antibiotics.

Understanding the biological or biochemical mechanism of a disease often suggests the types of molecules needed for new drugs (*16, 17*). Examples are substrate or cofactor analogs for thymidylate synthase as antitumor agents (*18, 19*) or the development of the captopril family of antihypertensives (*17*). In a similar manner, clavulinic acid acts as a β-lactamase inhibitor (*20*). Such efforts represent a proven route from test tube to pharmacy.

Substrate-Based Design of Protease Inhibitors

There are circumstances in which the "rational" design of inhibitors can be performed without a target structure. A good example is a two-step protocol for developing protease inhibitors: (i) characterize the substrate specificities of the protease; and (ii) synthesize peptides with similar features but with the hydrolyzable amide bond replaced by a nonreactive "isostere." The peptides can subsequently be optimized by modifications in the side chains or backbone. This approach has been used for renin inhibitors (*21*) and for inhibitors of the HIV-1 protease (*22*). One can proceed further by adding specific moieties such as chloromethyl ketones or phosphonates that are capable of forming transition-state analog complexes with the enzyme. Among the examples are inhibitors of the *Schistosoma mansoni* cercarial elastase (*23*) and carboxypeptidase A (*24*). It is reasonable to expect to obtain peptidelike inhibitors with nanomolar inhibitory constants in in vitro assays after 1 year of effort.

Table 1. Drug development steps (*71*).

Step	Years
Discovery and lead generation	1–2
Lead optimization	1–2
In vitro and in vivo assays	1–2
Toxicology trials	1–3
Human safety trials	1
Human efficacy trials	1–2
Total development time	6–12

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DATE OF
CORRESPONDENCE: 10/01/92

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STAFF ASSIGNED:

ACTION REQUIRED: AS NECESSARY

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STAFF ASSIGNED:

ACTION REQUIRED: AS NECESSARY

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3094

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

OCT - 1 1992

To: Dr. D. Allan Bromley, Chairman
Federal Coordinating Council for Science,
Engineering, and Technology

Subject: HHS Proposed Tasks for the Critical Technologies Institute (CTI)

I am pleased to transmit to you suggestions for critical technologies that the CTI might undertake to study, as you requested in your memorandum of September 16, 1992.

The Report of the National Critical Technologies Panel, March 1991, identifies 22 technologies whose "timely development and deployment...is essential to satisfy such national needs as defense, economic competitiveness, public health, and energy independence." The Panel grouped these technologies into 6 broad areas, of which Biotechnology and Life Sciences was one; this area of emphasis was further specified to include applied molecular biology and medical technology. The Panel's report noted that the Department of Commerce's Emerging Technologies (Spring 1990), and the Department of Defense's Critical Technologies Plan (15 March 1990), consider similar technologies to be critical, specifically biotechnology and medical devices, diagnostics, and biotechnology materials and processes.

After consulting with FDA, NIH, and CDC, we feel that there are numerous opportunities for CTI to consider. Our suggestions fit within the general categories mentioned above, and are as follows:

Critical Technology: Biotechnologies

- Human gene and molecular therapies, including the introduction of specific genes; replacement of defective genes; regulation of specific gene expression; and the development of molecular targets for therapy. Specific technologic tools important in this area include computer resources and other methods for large-scale and rapid sequencing of DNA, with the goal of creating complete human genetic and physical maps.

- Cellular and tissue engineering; biological response modifiers and monoclonal antibodies; transgenic and other animals; and bioengineering. Specific technologic tools important to this area include development of "living tissue equivalents," such as artificial liver and pancreas, and

biohybrid organs generally, and large-scale production of biological materials, such as bioreactor and biosensor development.

- Structural biology; macromolecular assembly systems; and structure-based drug design. Development of the ability to determine the three-dimensional structure of a protein -- the prediction of the folded structure of a protein given its sequence -- remains one of the most significant problems in modern biology. Determination of the structures of large macromolecular assemblies at atomic resolution will require both adapting and improving existing technologies (such as over-expression and crystallization of macromolecules) and developing new ones.

Critical Technology: Biomaterials

- Biomaterials, such as new biocompatible materials; advanced materials, such as composites, ceramics, polymers for such applications as drug-delivery systems; and structural and functional prosthetic or other implants. Integrated materials science engineering tools important to this area include materials and fabrication processes such as surface treatment, nanofabrication, and biomimetics, material characterization and analysis, experimental and analytical stress analysis, and molecular modeling.

Critical Technology: Analytic and Measurement Technologies

- Advanced mass spectroscopy techniques, such as isotope dilution mass spectrometry, liquid chromatography- and gas chromatography-mass spectrometry-mass spectrometry, and atmospheric pressure ionization liquid chromatography-mass spectrometry-mass spectrometry; two-dimensional gas chromatography; and supercritical fluid extraction. These technologies are used to assess human exposure when human tissue samples are tested for toxic substances or their metabolites, and to assess health effects when tissue samples are tested for biomarkers of damage or dysfunction.

I hope that these suggestions prove useful in the continuing deliberations of the CTI as it begins its important mission to encourage innovative and integrative technologies.

James O. Mason

James O. Mason, M.D., Dr.P.H.

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9203082
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

****

FROM: CORDIA, Louis

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 09/30/92

SUBJECT: HE IS WRITING TO REQUEST INFORMATION ON HELATH CARE COSTS.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: D.A. Henderson

ACTION REQUIRED: DIRECT REPLY

STAFF ACTION: DIRECT REPLY

****

SENDER'S DUE DATE:

OSTP DUE DATE: 10/22/92 STAFF DUE DATE 10/22/92
DATE COMPLETED: DATE COMPLETED/DEPT: 10/15/92

****

COPIES TO: D. Allan Bromley

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:
PHONE: EXT:

REMARKS:

OSTP RECEIVED: 10/08/92 DEPT RECEIVED: 10/14/92
FILE: P-LIFE SCIENCES

CENTRAL FILES:

382

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

October 15, 1992

Dear Mr. Cordia:

Dr. Bromley has asked me to respond to your letter and the article from the ARKANSAS TIMES on the increasing cost of pharmaceuticals under government programs. This is certainly an important issue in health policy, as well as a timely one. I have forwarded your letter to Ms. Gail Wilensky, Deputy Assistant to the President for Policy Development, who has the expertise to answer your questions. Her direct mailing address is:

Ms. Gail Wilensky
Deputy Assistant to the President
for Policy Development
The White House
Old Executive Office Building
17th and Pennsylvania Avenue, N.W.,
Room 216
Washington, D.C. 20500

You will probably be hearing from her office shortly.

Sincerely yours,

D.A. Henderson, M.D., M.P.H.
Associate Director for Life Sciences

Mr. Louis J. Cordia
6908 Baylor Drive
Alexandria, Virginia 22307

3082

Louis J. Cordia
6908 Baylor Drive
Alexandria, VA 22307
(phone)703/768-3111
(fax)703/768-2156

September 30, 1992

The Hon. D. Allan Bromley
AP-Science & Tech. and Director
White House/OSTP
358 OEOB
Washington, DC 20506

Dear Dr. Bromley:

As I believe you are well aware, I have been working on health issues for quite some time, with particular concern over how government control over healthcare actually raises costs for Americans rather than lowering them.

Given the fact that healthcare has emerged as a major issue in the presidential election and that the key difference between the two major candidates is over how much of a role government will play --- President Bush wants less and Governor Clinton wants more, I thought you would appreciate a copy of an article that illustrates by example how government in its often laudable effort to help actually hurt the people. In an article in the September 10, 1992 ARKANSAS TIMES entitled "Drug Costs Doubled Under Controversial Program," it says,

> "a program to control the costs of Medicaid prescriptions in Arkansas ended up costing the state more than the drugs themselves."

As you know, I have long advocated the philosophical argument of limited government, believing that government intrusion in our lives and the marketplace often ends up hurting us when it tries to help. That is why I am most concerned about how much government control may be exercised in everyone's desire to bring high quality healthcare to all Americans.

In this regard I ask you to please forward by mail or fax any information you may have on this important subject --- particularly regarding the government's role in healthcare and its positive or adverse impact on the American people. Should you have any questions, please do not hesitate to call.

Sincerely,

Lou Cordia

Continued from page 10

ing to require additional staff and equipment, and the Human Services Department, which oversees the Medicaid program in Arkansas, was under a hiring freeze. The only way to avoid the restriction was to contract the program out.

The UAMS College of Pharmacy seemed a logical choice for the job, and its assistant dean, Dr. Walter J. Morrison, was interested.

Morrison devised a prior approval program. Whitlock approved it, and the contract with the College of Pharmacy was signed in January of this year. But alarms were sounded from the start.

An official of the Health Care Finance Administration (HCFA) in Dallas, which oversees the federal portion of Arkansas's Medicaid budget, wrote to DHS Deputy Director Kenny Whitlock warning of problems.

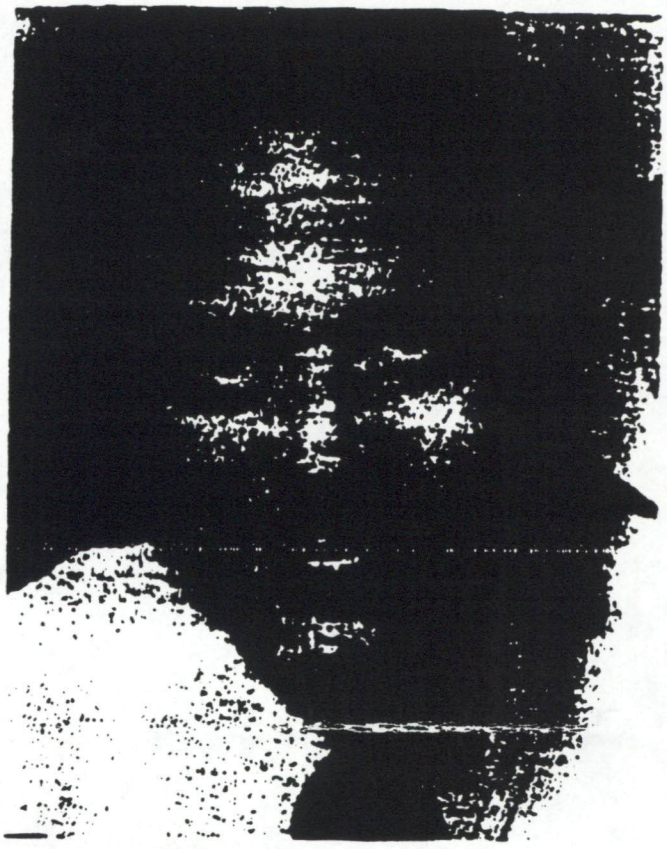
Don Hearn, chief of HCFA's Program Operations Branch, pointed out that it should have stipulated that DHS receive title to all equipment purchased for the program. He also advised Whitlock that time records would have to be kept for any College of Pharmacy employee working on the program.

"We also want to strongly urge you to consider the cost-effectiveness of this contract," Hearn wrote. "The average cost for a prescription in Arkansas is about $20.

balked when asked to sign over the equipment and provide the required time reports. Whitlock announced he was removing antibiotics—which accounted for 44 percent of the requests—from the requirement for prior approval. Then Morrison, who contended antibiotics had to be included if the program was to be effective—refused to renew the contract.

At the start of August, the staff at DHS took over the program. By then its scope had been greatly reduced.

Besides antibiotics, prior approval was also dropped for another class of drugs called benzodiazepines, which are used to treat stress.



CONTROLLING COSTS: U.S. Sen. David Pryor sponsored legislation to control drug prices.

"In the contract as written, the average cost per prior authorization request (based on an estimated 6,000 inquiries per month) is around $20... This could call into question the reasonableness of the contract for the necessary and efficient administration of the State Plan."

Nor were those the only objections. When the program went into effect in February, physicians from around the state shot letters to the DHS complaining that the process infringed on their professional judgment, increased their paperwork, and discouraged them from dealing with Medicaid patients.

Moreover, they questioned the sense of a program that required review of certain prescriptions but promised, as in the case of antibiotics, where time is critical, that all would be filled.

As time neared for the contract to be renewed, the relationship between DHS and the college had become badly strained. The staff at DHS was insisting that the agency be given title to nearly $80,000 in computers and other equipment the college had bought in starting the program. They also wanted the time records HCFA said it required.

And Whitlock was coming under increasing pressure from physicians to take antibiotics out of the review program.

By July, everything collapsed. Morrison Together, antibiotics and "benzos," as they're called, had accounted for 70 percent of all the drugs reviewed for prior authorization. Approval had been granted for all of the antibiotics and 96 percent of the benzos.

Gradually, after DHS took back control of the program, the extraordinary cost of its operation under the College of Pharmacy began to come to light.

A DHS review dated August 29 noted, for instance, that in July 1992, there were 919 approved requests for benzodiazepines. The average cost for one of these prescriptions was $13.34. But when the cost of reviewing each request was added, the total cost to Medicaid to filling the prescription was $35.70

DHS paid the College of Pharmacy just under $113,000 per month from February through July to administer the program. Half of that was to be paid with federal funds through HCFA. But HCFA notified DHS last week that it won't pay

Arkansas's Medicaid drug program, which is already over budget, now must pay for all of the UAMS contract. And since the College of Pharmacy says it isn't required to turn its computers over the DHS, the state agency faces the prospect of buying another set of computers to keep up with its burgeoning costs.

DRUG COSTS DOUBLED UNDER CONTROVERSIAL PROGRAM

Squabble over computers is just the tip of the iceberg.

BY MARA LEVERITT

A program to control the costs of Medicaid prescriptions in Arkansas ended up costing the state more than the drugs themselves.

Moreover, the contract for the program, which was designed and administered by the College of Pharmacy at the University of Arkansas for Medical Sciences, had so many problems that the federal Medicaid office has refused to pay its half of the more than $675,000 in operating costs.

The expense has put further stress on Arkansas's Medicaid pharmacy program, which was already so financially strapped that it has twice had to reduce benefits for the needy participants.

According to data obtained under the Freedom of Information Act from the state Human Services Department, which entered the contract with UAMS, the cost to review each request for a Medicaid prescription under the contract was $22.36. The average cost of the prescriptions requested was $21.45. That means that the total average cost of a prescription under the program was $43.81.

Ironically, the contract itself grew out of 1990 legislation sponsored by Arkansas Sen. David Pryor to control drug prices.

Before the 1990 law, Arkansas had operated on what's called an open formulary system; that is, doctors knew which drugs would be paid for by Medicaid, which wouldn't, and where exceptions were possible. Not many states had such a system, but most agree the Arkansas plan worked well.

The 1990 law changed the rules. It put into effect a nationwide system in which Medicaid could pay for any drug, so long as its manufacturer agreed to offer rebates.

Formulary systems such as Arkansas's were no longer allowed. The so-called prior authorization systems became the next best method for keeping a lid on costs.

As anyone who has ever bought a generic drug knows, some very expensive medications will do the same thing as other, less expensive ones. The trick with Medicaid is to be sure that doctors prescribe the cheaper drug.

Prior authorization requires doctors to submit their prescriptions for certain medications for review before they can be filled. They can avoid the hassle by prescribing some less expensive alternatives.

Still, it was expected that under the program, at least 6,000 requests for prior authorization would have to be reviewed per month. Establishing such a system was go-

Continued on page 12

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9203017
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

****

FROM: WOLFOWITZ, Paul: DEPARTMENT OF DEFENSE

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 09/26/92

SUBJECT: HE IS WRITING REGARDING THE JOINT DEFENSE SCIENCE BOARD/DEFENSE POLICY BOARD TASK FORCE ON CHEMICAL WEAPONS, BIOLOGICAL DEFENSE, AND PROLIFERATION.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: D.A. Henderson

ACTION REQUIRED: AS/IF NECESSARY

STAFF ACTION: AS/IF NECESSARY

****

SENDER'S DUE DATE:

OSTP DUE DATE: 10/14/92 STAFF DUE DATE 10/13/92
DATE COMPLETED: DATE COMPLETED/DEPT: 10/08/92

****

COPIES TO: D. Allan Bromley
NATIONAL SECURITY

****

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS: PER DR. HENDERSON, ACTION IS NOT NECESSARY.dic



OSTP RECEIVED: 10/02/92 DEPT RECEIVED: 10/06/92
FILE: P-LIFE SCIENCES

CENTRAL FILES:

Withdrawal/Redaction Sheet
(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01a. Letter	To: Allan Bromley From: Paul Wolfowitz Re: Task Force on Chemical Weapons, Biological Defenses, and Proliferation [2 copies] (2 pp.)	9/26/92	(b)(1)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [4 of 7] [1992]

Date Closed:	3/15/2010	**OA/ID Number:**	62038-008
FOIA/SYS Case #:	2005-0336-F	**Appeal Case #:**	
Re-review Case #:		**Appeal Disposition:**	
P-2/P-5 Review Case #:		**Disposition Date:**	
AR Case #:		**MR Case #:**	
AR Disposition:		**MR Disposition:**	
AR Disposition Date:		**MR Disposition Date:**	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P-3 Release would violate a Federal statute [(a)(3) of the PRA]
P-4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P-5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

Freedom of Information Act - [5 U.S.C. 552(b)]

(b)(1) National security classified information [(b)(1) of the FOIA]
(b)(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
(b)(3) Release would violate a Federal statute [(b)(3) of the FOIA]
(b)(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
(b)(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
(b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
(b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
(b)(9) Release would disclose geological or geophysical information

TRANSMIT CONFIRMATION REPORT

NO.	:	001
RECEIVER	:	212 988 8649
TRANSMITTER	:	PIA&DLS/OSTP
DATE	:	OCT 08'92 14:16
DURATION	:	02'16
MODE	:	FINE
PAGES	:	03
RESULT	:	OK

FAX Transmittal Sheet

DATE: 10/08/92

TO: Dr. Joshua Lederberg

ORGANIZATION: Rockefeller Univ.

TELEPHONE: 212/327-7809

FAX: 212/327-8651

FROM: Margaret Quinlan

TELEPHONE: 202/456-2892

FAX: 202/395-1571

NUMBER OF PAGES, INCLUDING COVER PAGE: 3

SPECIAL INSTRUCTIONS:

Withdrawal/Redaction Sheet
(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01b. Letter	To: Paul Wolfowitz From: Allan Bromley Re: Task Force on Chemical Weapons, Biological Defenses, and Proliferation (1 pp.)	7/14/92	(b)(1)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [4 of 7] [1992]

Date Closed:	3/15/2010	**OA/ID Number:**	62038-008
FOIA/SYS Case #:	2005-0336-F	**Appeal Case #:**	
Re-review Case #:		**Appeal Disposition:**	
P-2/P-5 Review Case #:		**Disposition Date:**	
AR Case #:		**MR Case #:**	
AR Disposition:		**MR Disposition:**	
AR Disposition Date:		**MR Disposition Date:**	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P-3 Release would violate a Federal statute [(a)(3) of the PRA]
P-4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P-5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

Freedom of Information Act - [5 U.S.C. 552(b)]

(b)(1) National security classified information [(b)(1) of the FOIA]
(b)(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
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(b)(9) Release would disclose geological or geophysical information

OSTP STAFFING SHEET

SUBJECT: Letter for Signature

ORIGINATOR: D.A. Henderson, M.D., M.P.H. PHONE: 2892

DATE ORIGINATED: 7/14/92 DATE DUE: _____ CORR TRACKING NO.: _____

EXTERNAL COORDINATION: _____

		COMMENTS	DATE
4	DIRECTOR	SIGNATURE	
3	CHIEF OF STAFF	CLEAR	
	GENERAL COUNSEL		
2	EXEC. ASST.	CLEAR	

ACTION REQUESTED: PLEASE RETURN TO ROOM 494 AFTER SIGNATURE FOR DUPLICATING AND DISTRIBUTION. Thanks,

Margaret

	COORDINATION		DATE	COMMENTS
1	Henderson, D. A.	Concur ✓ Nonconcur _____		
	Phillips, W.	Concur _____ Nonconcur _____		
	Ratchford, J. T.	Concur _____ Nonconcur _____		
	Wong, E.	Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		
		Concur _____ Nonconcur _____		

Withdrawal/Redaction Sheet
(George Bush Library)

Document No. and Type	Subject/Title of Document	Date	Restriction	Class.
01c. Memorandum	To: Allan Bromley From: D.A. Henderson Re: Biological Warfare Concerns (2 pp.)	7/14/92	(b)(1)	

Collection:

Record Group: Bush Presidential Records
Office: Science and Technology Policy, Office of (OSTP)
Series: Bromley, D. Allan, Files
Subseries: General Science Files
WHORM Cat.:
File Location: Life Sciences: General [4 of 7] [1992]

Date Closed:	3/15/2010	**OA/ID Number:**	62038-008
FOIA/SYS Case #:	2005-0336-F	**Appeal Case #:**	
Re-review Case #:		**Appeal Disposition:**	
P-2/P-5 Review Case #:		**Disposition Date:**	
AR Case #:		**MR Case #:**	
AR Disposition:		**MR Disposition:**	
AR Disposition Date:		**MR Disposition Date:**	

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P-1 National Security Classified Information [(a)(1) of the PRA]
P-2 Relating to the appointment to Federal office [(a)(2) of the PRA]
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P-6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.

PRM. Removed as a personal record misfile.

Freedom of Information Act - [5 U.S.C. 552(b)]

(b)(1) National security classified information [(b)(1) of the FOIA]
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(b)(3) Release would violate a Federal statute [(b)(3) of the FOIA]
(b)(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
(b)(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
(b)(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
(b)(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
(b)(9) Release would disclose geological or geophysical information

"Document Control"

TYPE: INFORMATION
ORIGINATOR: 02
DOCUMENT NUMBER: 9202960
STATUS I
DIRECTORATE STATUS

****

FROM: SIMON, Irwin B.: U.S. ARMY

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 09/25/92

SUBJECT: HE IS FORWARDING A VIDEO TAPE OF A PROCEEDURE THAT HE AND DR. BROMLEY DISCUSSED WHILE TRAVELLING.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

DA to view.

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:
DATE COMPLETED:

STAFF DUE DATE
DATE COMPLETED/DEPT:

****

COPIES TO: D. Allan Bromley
LIFE SCIENCES

Return afterwards to Dr. Bromley

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:
PHONE: EXT:

REMARKS: VIDEO TO DR. BROMLEY.

OSTP RECEIVED: 10/01/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF SCIENCE AND TECHNOLOGY POLICY
WASHINGTON, D.C. 20506

October 21, 1992

MEMORANDUM FOR ALLAN BROMLEY

FROM: **D.A. HENDERSON**

SUBJECT: **SIMON VIDEO TAPE ON TELEPRESENCE SURGERY**

I have viewed the tape which was sent. Conceptually, the concept is imaginative and should have applications for some types of surgery but, as Dr. Simon points out, the system is still in its infancy. For the system to apply, one would have to be able to visualize the organ (as in intra-abdominal surgery) and perform surgery which requires only limited, fairly simple manipulation. This is not to denigrate the approach, only to note that its application is necessarily limited. An approach embracing "virtual reality" is beyond my comprehension -- I don't quite fathom how it would be employed. (The tape isn't worth viewing, by the way.)

Over-out

"Document Control for Division of Life Science..."

TYPE: ACTION DOCUMENT NUMBER: 9202916
ORIGINATOR: 02 STATUS I DIRECTORATE STATUS C

****

FROM: HENDERSON, Albert

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 09/21/92

SUBJECT: HE IS FORWARDING A COPY OF IS REPORT "COST EFFECTIVENESS OF SCIENCE JOURNALS" AND OFFERS COMMENTS ON INDIRECT COST ABUSES.

****

DIRECTORATE ASSIGNED: LIFE SCIENCES

STAFF ASSIGNED: William Raub

ACTION REQUIRED: AS NECESSARY

STAFF ACTION: AS NECESSARY

****

SENDER'S DUE DATE:

OSTP DUE DATE: 10/12/92 STAFF DUE DATE 10/12/92
DATE COMPLETED: DATE COMPLETED/DEPT: 10/27/92

****

COPIES TO: D. Allan Bromley

****

WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS: ENCLOSURES TO LIFE SCIENCES; NO ACTION NECESSARY, PER BILL RAUB.

OSTP RECEIVED: 09/28/92 DEPT RECEIVED: 09/29/92
FILE: P-LIFE SCIENCES-INDIRECT COST

CENTRAL FILES:

2916

Albert Henderson

Box 2423 Noble Station
Bridgeport CT 06608-0423

203-380-0021 direct — 203-367-1555 messages — 203-380-1703 fax — Internet: 70244.1532@compuserve.com

Sept. 21, 1992

Allan Bromley, Director
Office of Science and
Technology Policy
Executive Office Building
Washington, DC 20506

re: **Indirect Cost Abuses**

Dear Dr. Bromley:

On hearing of your examination of cost abuses I hasten to enclose a pre-publication copy of **Cost Effectiveness of Science Journals, Report** and its **Supplement,** and to point out its relevance.

OMB Circular A-21 permits universities to negotiate part of their reimbursements based on the estimated use of its libraries by researchers. I believe no other national policy addresses funding of science information resources. The average reimbursement to the top 100 institutions is two points, something over $100 million total. The universities are not obligated to use this money for their libraries.

The **Report** provides details of cutting back library expenditures by many of these institutions (p. 79, 93: note 58) up to 56% during the 1980s. As a result, researchers must fill out tiresome forms -- and wait for days or weeks -- simply to browse through an article of possible interest in a journal that once was available in the library. In his report to American Association for the Advancement of Science in 1991, **Science: The End of the Frontier,** Nobelist Leon M. Lederman documented how the burden of red tape has been sapping the vitality of our best researchers. Also as a result of cutbacks, fewer and fewer libraries can supply photocopies of such articles. Even today, the British Library -- considered a source of last resort by many U.S. librarians -- supplies about 100,000 photocopied articles a year to U. S. researchers. Association for Research Libraries projects that in 25 years, no major North American library will be able to supply any article if the present trend is permitted to continue. The **Report** also points out that the major academic science libraries are used by the entire $120 billion R&D community (p. 77), 90% of which is off campus. These libraries are open to everyone. Therefore, the technical (science, engineering, medicine, agriculture) collections of these libraries should be considered national resources (p. 82), rather than exclusive property of their institutions.

As the person who prepared the enclosed material and as a citizen who is concerned about the lack of responsiveness to the complaints of librarians about their funding crisis, I would recommend specifically (A) that universities be required to purchase technical books and journals with the "indirect" amounts negotiated for library use and (B) that a permanent office for scientific and technical information be established, representing the interest of the entire R&D community, to assure continued quality of these information resources.

Sincerely,

Albert Henderson

UNCORRECTED

The Cost-Effectiveness of Science Journals

Advisory Panel for Scientific Publications

The R&D community, 90 percent of which is off campus, depends on academic library materials but is disregarded by the managers of science library collections. Recommendations are made for reforms in library management, evaluation of science journals by libraries, and management by publishers.

The Need for a Balanced View

In recent years, scientists and librarians have expressed concern about increases in the cost of library subscriptions to science journals. The numbers of users, printed pages, and journals have grown about 5 to 6 percent annually, doubling in fifteen years. Journal prices have increased also by the rate of inflation and in support of new technology. For reasons largely unrelated to science research and development, academic library budgets have not kept pace with this normal growth. Concern for adequate information resources has been overshadowed by discord among librarians, scientists, administrators, and publishers. Librarians and administrators have questioned the cost-effectiveness of science publishing. A number of major science publishers have resorted to debatable promotional strategies in order to compete for formerly secure library subscription renewals. The system of peer review has been challenged by substitutes that depend on numeric measures rather than evaluation of content or accomplishment. Further confusion results from different convention and varying usages of terminology within the technical community as well as a lack of reliable indicators on the use of libraries and science journals.

The Advisory Panel for Scientific Publications was organized to assist in the development of criteria to measure the cost-effectiveness of scientific journals. Between late 1990 and 1991, the panel examined a great deal of evidence, including published materials as well as facts and opinions gathered through

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1 École des Hautes Études en Sciences Sociales

interviews and correspondence. The views of librarians, scientists, commercial and noncommercial publishers, editors, economists, sociologists, and various official and quasi-official agencies have been considered and are reviewed in detail.

The Question of Cost-Effectiveness

The peer-reviewed scientific paper published in a primary science journal has been the means of reporting original research for over three centuries. During this period, primary research reports have been supplemented by many related formats: review papers, short communications and letters, methodology papers, news stories, patents, abstracts and extended abstracts, conference proceedings, interviews, etc. Services that publish only contents or indexes have been devised to provide new means of accession and control. Academic and national libraries have provided access to most of these publications for a wide audience of students and researchers. This combination of publication and depository provides the foundation for all science research.[1] Presumably, if one or the other were missing or substantially degraded, most technical progress would stop.

The economics of science journals was examined extensively in the 1970s and 1980s by King Research. Library and similar participation accounts for 10 percent of the total cost of scientific and technical journal communication. Publishers' participation accounts for 14 percent. The remaining 76 percent is derived from users and authors.[2] The King study points out the difficulty of establishing the benefit—or effectiveness—of scientific and technical journals, "even if scientific discovery is a pure public good."[3] In the closely related issue of establishing the benefit of scientific discovery, scientists point to studies by Edwin Mansfield and others who indicate returns on investment in research and development, in spite of the elusiveness of concrete connections within the grasp of the layperson.[4]

The literature of science research management rarely mentions the essential roles of science journals and libraries, which are apparently taken for granted. Perhaps the best way to illustrate the importance of libraries to scientists is to recount the experience of I.M. Singer. [5] As a young theoretical mathematician, Singer thought he could remove himself to the Isle of Capri to pursue basic research. After a month or so he realized that he could not reproduce known results easily without access to a good library. After three months, he left Capri for Oxford, England.

Thus, the predictable consequence of loss of economic vitality in science communications would be the debilitation of technical progress, because all science research and development begins with a review and understanding of the literature. The journals that report primary science research depend on academic and government research library subscriptions for their economic support. That support began to fade twenty years ago. In 1970 the annual costs

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associated with academic library purchases equaled about 1 percent of total R&D expenditure.[6] Alarmingly, as measured against either total higher education or research and development expenditures, academic libraries have lost substantial funding over the last two decades. In 1987/88, U.S. academic libraries spent $221 million less on journals and books than if they had been funded at 1970 levels—a loss of 20 percent.[7] A study by the British Publishers Association reports of loss of 28 percent—£6 million—between 1978/79 and 1987/88 in British university libraries.[8] In 1981 and 1982, thirteen German university libraries were forced to cancel 7,265 periodicals as a result of reductions totaling DM 18.7 million.[9]

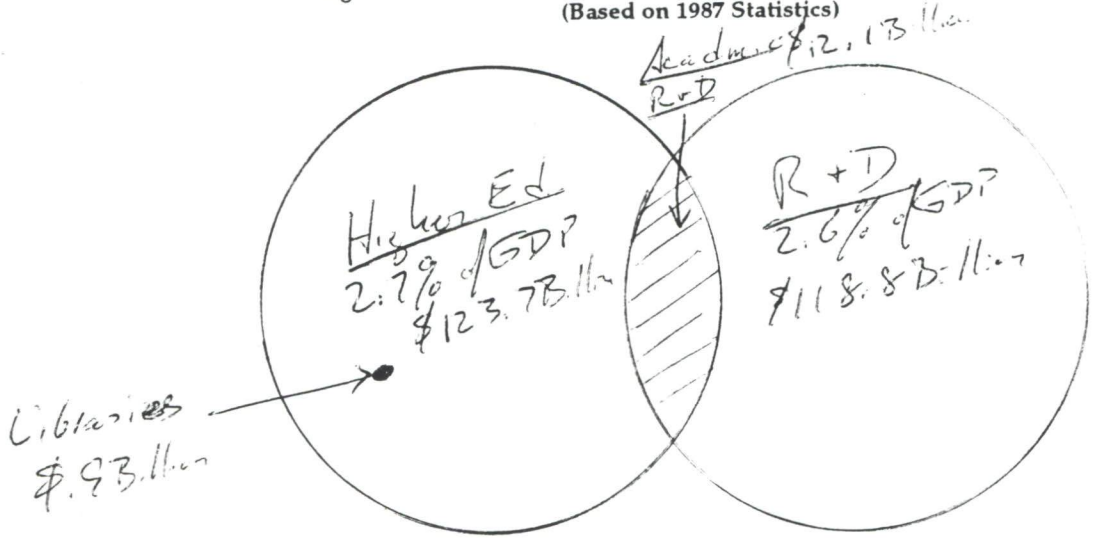
Inflation in the world of technical journals includes four distinct factors: (1) increased numbers of papers published as described by King and others (see note 1) as well as increased coverage of non-Western technology, including Soviet and Asian sources; (2) technical upgrades to the publishing process, including the use of translators and local "rewrite" editors, air courier services, replacement of typewriters by computers and desktop publishing equipment, fax machines and other telecommunications, electronic data interchange, and financial support of editors and conferences—all of which improve speed and quality of publication, but at a price;[10] (3) general increases in prices relating to salaries, paper, distribution, and printing; and (4) international monetary exchange fluctuations. The last two items often change unpredictably. Because publishers' subscription rates are set more than one year before costs are realized, they occasionally must be adjusted to consider changes in inflation or exchange one or two years after they have occurred.[11]

Management of Major Libraries

Except for a relative handful of association and government libraries, most major science library collections fall under the financial and administrative control of higher education institutions, where other priorities may subordinate the needs of science researchers. These libraries were organized long before electronic communications extended library services beyond the immediate campus and at times when campus communities were smaller and more insular.[12] Today users of a given library may be located anywhere in the world.[13] With the growth of science literature and increased numbers of science and other faculty, the specialized interests of a single researcher, particularly those off-campus are more diluted—or less important—in the view of the librarian than ever before (see figure 1).

The steep decline in library funding since 1970 has forced many science libraries to cancel subscriptions and to seek new cost-effective rationales in an atmosphere of crisis and triage.[14] Duplicate subscriptions were the first to go. In France, university libraries sacrificed French periodicals. Corporate and smaller special libraries canceled many subscriptions on the assumption their users had access to nearby major academic, government, and association li-

FIGURE 1
U.S. Higher Education vs. R&D Finance and Control of Major Science Libraries
(Based on 1987 Statistics)



Note: The R&D community, 90 percent of which is off campus, depends on academic library materials but has little influence on management of science library collections. (Not drawn to scale)

braries.[15] Unfortunately even such major national depositories as the British Library have cut subscriptions in order to pay other expenses.[16]

The major college and research libraries of the world are more than national resources. As repositories of the accumulated knowledge of human progress, a few thousand libraries throughout the world provide information services internationally to all researchers and all other libraries. To be effective, such libraries must provide a stable resource unaffected by cyclic or temporary conditions.[17] In order to maintain a reasonable level of excellence, a research library's collections must double every fifteen years.[18] Important correlations are found between the size of a university library and its rating for excellence in graduate teaching and research.[19]

The importance of collection size and comprehensiveness for the researcher becomes clear with the understanding of its use. Scientists and engineers read from an average of about 13 scholarly journals, but they subscribe only to 5.4 journals. Scientists rely on library copies of journals for about one-fourth of their reading. Most reading of library copies is of older articles, in journals that were initially subscribed to by the scientists but discarded. Perhaps more important, 24 to 60 percent of scientists' reading results from browsing through a journal, as opposed to specific searching based on bibliographies, databases, citations, etc.[20]

With increased availability of technological means for resource sharing, many librarians and administrators have adopted a formula that balances the cost of

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a subscription per use against the cost of acquiring photocopies of articles. Where the use of a journal is relatively low, the equation suggests it would be more cost-effective to cancel the subscription and rely on distant resources accessed routinely via interlibrary loan (ILL).

Responding to decreasing library subscription renewals resulting from application of this formula requires science publishers to increase their prices to meet overhead and prepress costs, which may exceed 80 percent of the total cost of production, in addition to reconciling prices with rising costs of increased pages and inflation. Other economic considerations include technological inflation, where publishers adopt new technologies that speed processing and add to the quality of the finished product; this also adds to increased costs and therefore increased prices. Organizational and marketing costs associated with a new journal also directly effect its price.[21]

Photocopying

Interlibrary loan was one of the earliest elements of resource sharing. Today, a substantial number of "loans" take the form of photocopies that need not be returned. As subscriptions are cut, interlibrary loans rise. Libraries canceling substantial numbers of journal subscriptions may become little more than mailboxes for transmission and receipt of ILL requests. The statistics for Online Computer Library Center (OCLC) 1979—1988 ILL activity show that requests for journal articles rose by a factor of ten. Academic and research libraries generated 2 million online requests for loans or photocopies in 1988/89, up 500 percent in ten years.[22]

Meanwhile, the issue of payment of copyright use in academic libraries has not yet been fully confronted. In 1987, the U.S. Register of Copyrights was told, "It is evident that use of the Copyright Clearance Center by academic research libraries has been and continues to be negligible."[23] In the United States the Copyright Clearance Center (CCC) has made much progress in collecting copying fees. It can report substantial payments now, derived mainly from the private sector. However, the university pilot program it began several years ago has not been concluded. As of 1987, CCC reported 60 academic libraries as registered users; 46 had never reported any copying.[24] Donald W. King testified in 1987 that libraries use photocopies as a substitute for subscribing to infrequently read journals to avoid costs of paying the journal price, processing the issues, and maintaining them. "I can see no reason . . . that publishers should not receive payment in the form of royalties for this use of article information. The law seems clear," he concluded.[25]

Systematic photocopying of journal articles occurs outside the United States. Notable among major sources are the British Library at Boston Spa and, in France, CADIST (Centres d'acquisition et de diffusion de l'information scientifique et technique) which was created in 1980 as an ultimate resource for French universities that were sacrificing local subscriptions as a result of curtailed library budgets.[26]

Financing Major Science Libraries

The causes of the decline in academic library funding follow the pattern of fiscal management that led New York City and other institutions into crisis more than once. The usefulness of library materials spans a considerable number of years; therefore, library materials expenditures should be capitalized. Taking cash away from areas of the capital budget to pay current expenses (such as expanded security, new sports activities, new study or research programs, inflation-impacted salaries and utilities) or to accommodate another area of capital purchase (such as the acquisition of a computer) has always been an easy option for the fiscally irresponsible. Stanford University, for instance, has canceled over $600 thousand worth of library subscriptions to science journals since FY 1987/88 while the university received over $70 million a year for research overhead—supposedly justified in part by the need to maintain a high-quality library collection. It reportedly misapplied $1.35 million to housing, a yacht, and a shopping center while the library went begging.[27] In another example, Louisiana State University recently established two new institutes: the Pennington Biomedical Research Center and the Center for Advanced Microcomputer Devices. Yet the LSU library materials budget remained stuck at the 1985 level of $2.1 million.[28] LSU's libraries as a percentage of LSU's general and educational expenditures received about 23 percent less in 1989/90 than they did in 1981/82.[29] Texas A&M, which canceled 998 serials in 1987, offers a third example of gutting the library budget with obvious disregard for long-term consequences. Cancellations included 122 periodicals in science, 78 in medicine, and 106 in technology. At the time, Texas A&M was ranked eighth among U.S. universities in R&D expenditures. Its $220 million spent on research was more that the University of California at Berkeley, Columbia, Cornell, Harvard, Penn, University of Southern California, Stanford, or Yale. Yet it spent less on library materials than any of them.[30]

It takes years before the consequences of poor management are noticed. Politics keeps the accomplices quiet. Scientists at major research universities are asked to tolerate incrementally greater frustration than the total deprivation described by I.M. Singer. No one will be the wiser until years later when a roof collapses or a school fails tests of accreditation. In many instances the new programs are inferior, the products of poor management. For example, of 852 U.S. colleges and universities that have computer and information science departments created since the 1960s, fewer than 100 have programs accredited by IEEE/ACM today.[31]

Sources of Confusion

Most library managers are isolated from the publishers and scientists that their institutions deal with daily. Campus administrators are even further removed. The education of such business managers has become so specialized that an advanced degree is no guarantee of any appreciation of the process

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and requirements of science research. It is clear from the literature of library management—mostly by its omissions—that the relationships among researchers, publishers, and libraries are not clearly understood. There are many areas of perplexity.

Some writers, for instance, suggest that there is an "explosion" of 40,000 or more science periodicals when only a small fraction—under 10 percent—qualify for serious consideration in terms of offering original reports and analyses of scientific research; the rest are popular and ephemeral ventures. The "explosion" has little relevance in an area where a steady five percent annual growth can be traced for over three centuries, as noted earlier. Statistics offered by Ulrich's and ISI's databases suffer from commercial as well as regional biases;[32] they must be analyzed and evaluated to be useful. Conventions differ among countries: in the United States, publication of a discovery does not affect the author's right to file for a patent; in many other countries, that right is abandoned by prior publication.[33] It also differs by discipline: physicists may publish discussions about their research and preliminary results in many informal ways, without being "published";[34] while much of biomedical research is constrained by the "Ingelfinger" rule that precludes publication in the *New England Journal of Medicine* after interviews reported by a "throwaway" medical newspaper or television.[35] A conference proceedings of extended abstracts in solid state chemistry may be considered ephmeral, to be replaced by peer-reviewed reports of research results in a primary journal. In areas of applied technology such as passive solar energy, the proceedings would be considered the only reporting—and therefore of archival significance—of many research projects.[36] If "authorship," "co-authorship," and the requirements of author responsibility were more clearly defined, such management problems as editors' quality control would be of much less interest today.[37] It is clear that most librarians and others have only a modest idea of the processes of research and publication that deliver each year $1 billion worth of journals and books to U.S. campus library mailrooms. Science publishing is a tiny industry serving a vast and intricate stream of R&D activity, often through academic libraries that scientists neither finance nor manage.

Political Considerations

Campus politics undoubtedly plays a role in determining funding and consequent imperatives for redefining cost-effective relationships among scientists, publishers, and libraries.[38] One can easily infer that a number of university budget officers, upon hearing suggestions that journal price increases sprung from "publishers' greed," would feel righteous in placing embargoes on increased funding to pay for higher-priced subscriptions. In a further inference, some librarians would be reluctant to criticize their superiors' budget policies. The libraries of some of the most passionate critics of publishers and scientists have lost considerable funds in proportion to their university's total expenditure. For example, the library budget at LSU of outspoken critic Charles

Hamaker was down over 23 percent between 1981/82 and 1989/90; John Lubans' library at Duke was down 30 percent for the same period. The library budget of Gary D. Byrd at the University of North Carolina was down nearly 10 percent.[39]

Quantitative vs. Qualitative Evaluation

Science research, and consequently science publishing, is intricate and esoteric. Nonspecialists cannot read and understand reports that have not been written for a general audience. Librarians and administrators, being responsible for justifying large expenditures of money, are confounded. In the best of circumstances they have sufficient money to do their jobs on the basis of faculty requests and profiles of interest. More recently, the apparent scarcity of funds has fragmented the scientific community, competing for the few dollars left, in such a way as to provide little or no reasonable advice at all. Only a few relatively primitive indicators of science publishing and use are available for guidance. Reliable indicators of research library uses are fewer still.

Many criticisms leveled at publishers' quality control may have merit.[40] Peer review does not have a perfect record; many anecdotes of its weaknesses have been published.[41] Nonetheless its accomplishments are enormous, and no substitute is in sight. The weak links in the chain of quality are the ethics of authors, the abilities (and library resources) of editors and referees, and the limitations of laypeople who have responsibilities related to policy, management, and administration.

To most scientists, the idea of evaluating a science journal on the basis of arbitrary measures such as cost "per-citation" or "per-kiloword"[42] should be as offensive as judgments of the value of research or researchers on the basis of citation counts.[43] Value can be assigned only by a user, no matter what the citation count, word count, or cost might be.[44] Where a journal's scope is as broad as an undergraduate degree, more readers may be interested, resulting in a large number of citations, especially if publication frequency is high and the number of pages per year is large. In spite of a high number of citations, the interest of a particular reader may be less concentrated—if averaged on a "per page" basis—than if the scope of the journal were as narrow as a doctoral dissertation. The essence of cost-effectiveness must focus on content, quality of content, presentation, production, and especially its usefulness to a particular reader or group of readers.[45]

The tactic of inferring inappropriate profit motives of commercial publishers[46] and unworthy career motives of academic researchers[47]—implying that the two elements have somehow conspired at the expense of academic libraries—may test the ethical and legal boundaries of certain not-for-profit associations (see note 42). Chartered and tax-exempted to support education and dissemination of information in science, such associations each have a mission that requires them to encourage and assist, rather than smear, authors, editors, and publishers whose activities advance their goals. Minimum standards of good

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faith and responsibility require their reports to be fair and balanced. Who would benefit by the failure of commercially published journals or commercial publishers? Who would benefit by the failure of junior researchers to advance their careers?

Although university-employed scientists are eager to further their careers by being published, few examples of fragmentary, banal, or fraudulent papers are produced. More than half of all science papers are supplied by 20 percent of the authors[48]—who probably have little artificial need to add numbers of papers to their CVs. Most of the complaints seem to rise from non-scientists—or from editors who may seek to promote their own journals by suggesting that others may publish less valuable material. A recent article in *Science* claiming that half of all articles published went uncited was soundly debunked by letters from furious readers.[49] A closer look at citation statistics reveals that many authored items counted by ISI are not original reports of research but letters, notes, review articles, news stories, editorials, etc.[50] More important, perhaps, King notes that not all users of journal articles produce citations.[51]

This is not to claim that there are no problems connected with author mediocrity and fraud. Such problems are shared by all editors, who seek every means possible to produce a publication of high quality. Evaluations by users connected with the content of a journal—some uses of which may produce citations—appear to be the only measurements acceptable to reasonable judgement.

Library use studies, such as recently reported by Milne and Tiffany,[52] or Bustion and Treadwell,[53] are methodologically unsound, particularly when subscriptions are cancelled in spite of faculty advice of the "essential" nature of the journals or when the study is brief and conceived after the subscriptions are canceled. The absence of reliable indicators to show use of research information in science libraries is an anachronism. Grocery, drug, and record stores report weekly via modern technology the activity of each item. Yet academic librarians, science publishers, and policymakers are forced to rely on crude measures, estimates, and makeshift studies.[54]

Recommendations

The new cost-effective solutions being pursued by libraries suffer from two major weaknesses: (1) the lack of involvement by the science community in library funding and management, and (2) the lack of understanding of science communication either in microcosm or within its overall social and economic context. The considerations of the panel focus first on why the burden of determining cost-effectiveness and making funding decisions should be directed by the R&D user community together with librarians and other administrators; second, why library materials budgets should be justified in relation to specific programs and institution expenditures and, nationally, in relation to Gross Domestic Product and total research and development spending; and third, on the need for balanced, instructive discussions of the mechanics and

requirements of science publishing, science libraries, and the needs of the communities they serve.

The Advisory Panel offers three sets of recommendations for cost-effective management of subscriptions to science journals within the scope of R&D and higher education activity.

1. Library Management and Finance

Identify major academic, public, and national science libraries as central depositories for comprehensive collections in science and technology.

- As national resources of economic significance, such libraries should be publicly financed and maintained and be controlled by a directorate that represents the entire research and development community as well as librarians and educators.
- Such library directorates must be responsible for justifying and maintaining adequate funding.
- The impact of new information technologies on the ability of researchers to keep up with or change their field of interest should be studied closely and continuously in order to provide responsible information for the library and R&D communities.
- The cost-effectiveness of a given science publication can be reasonably evaluated only with review by its users.
- Quantitative measures should not be considered reliable tools for library management until they are complete and understood; citation impact and cost-per-kiloword measures are empty values unless they are modified by refinements that take into account differences in use and content.
- Sophisticated, comprehensive library use statistics are necessary to understand the relationship of a library to research and education communities that use it. "Blind" data respecting the privacy of each user should be gathered for every transaction, indicating the type of user (undergraduate, graduate, faculty, corporate, commercial, etc.) and the user's indication of type of use (assigned reading, browsing, copying for personal use, copying for distribution, citation-directed, etc.).
- Price indices used by libraries to budget future costs should be segmented by discipline and specialty, taking into account changes in research activity resulting in publication as well as inflation and international monetary exchange.
- New fees would compensate academic libraries for use by off-campus organizations, whether they be commercial or not-for-profit.

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- Academic libraries should voluntarily pay fees or royalties for interlibrary loan photocopies procured as substitutes for journal subscriptions; such fees may be paid through a license bundled with the subscription price or be paid per copy produced.
- Preservation of library collections should be of greater concern in the choice of paper and bindings by publishers and in the choice of copying machines by librarians.

2. *Surveys and Comparisons of Science Journals*

A publisher who wishes to provide balanced educational surveys (in contrast to reviews of books or periodicals) of science publishing should invite cooperation and review prior to publication; offer to publish in complete form rebuttals and comments from all publishers involved; or, offer to exclude with no prejudice or comment the publications of publishers who decline to cooperate with the presentation. Responsibility for designing the survey or review should be placed in the hands of individuals with no perceptible bias or conflict of interest by virtue of association with the publishers involved.

- Considerations of prices of science publications should include all prices and other sources of income, such as advertising, page charges, royalties and permissions, reprint sales, contracts and grants, dues, investments, contributions, etc. that would relate to meeting direct and overhead costs and provide a fair and balanced view of economic activity.
- Cost comparisons should include all types of cost, such as marketing expenses, printing and paper, postage, editorial labor, typesetting and other prepress, organization, overhead, and other administrative expense; and costs should be reduced to account for cash donations, gifts, subsidies, subventions, tax exemptions, in-kind donations of goods and services, and other direct and indirect cost reductions.
- Publications selected for comparison should be closely matched in terms of coverage, content, frequency, circulation, language, and other services or benefits included in the subscription price.
- Surveys and reviews of science publications must consider the quality of content as well as price, number of pages or words, citation impact, etc.
- Publishers who have a tax-exempt educational purpose to encourage dissemination of science information should not abuse the trust accorded to that position by disparaging and otherwise unfairly competing with other publishers who also further that purpose.
- Periodical price indexes published for science libraries must take into account changes in number of printed pages and frequency of issue.

3. Science Publishing

Science publishers and editors must make a stronger effort to establish a clearer understanding of the publication process among authors, prospective authors, and librarians.

- As the technical community has grown, the meanings of terms like *publish, peer review, proceedings, co-author,* and *research* have deteriorated until consensus has been lost except within various specialty groups, where conventional meanings may vary considerably. Therefore, each journal should clearly identify in its statement of editorial aims and scope whether it publishes original research papers, review papers, editorials, news items, abstracts, association business reports, and other such specific categories; and each item published should be specifically identified.
- The instructions to authors published in each journal must define "co-authorship," specify where a journal uses peer review, and clarify its requirement for originality and exclusive publication, particularly with respect to controlled-circulation periodicals, conference proceedings, newspapers, and other media generally considered to be ephemeral.

Major Sources of Reference

Many published references and private conversations have contributed to the present study. In our review of the need for a study of cost-effectiveness of science journals, we have focused on four particularly influential sources.

1. *Scientific Journals in the United States, Their Production, Use and Economics,* by Donald W. King, Dennis D. McDonald, and Nancy K. Roderer (see note 1) provides a major source of reference. King's summary of the economics of the scientific journal system is excellent and remains very useful. If weaknesses must be pointed out, its confinement to U.S. journals and subscribers in today's context is very important; many adjustments and enhancements would be required to embrace the truly international nature of science publishing; the United States accounts for only 22 to 45 percent of science papers [55] and about one-third of institutional subscriptions in the world market.[56] Time has also taken its toll as technology, regulation, and economics post advances not fully foreseen in 1980, although King's 1987 testimony to the Register of Copyrights is useful.
2. The second major object of focus is the Association for Research Libraries (ARL) report (see note 14) of its serials prices project. Published in May 1989, it was distributed to the staff of over 100 of the largest research libraries (over 80 percent of the top research universities in

the United States are ARL members) in North America on the eve of the 1989/90 fiscal year.[57] Its conclusions were reported widely in the library press. Referring often to the publishers' surveys (see note 42) as factual reports rather than promotional articles, it summarizes much of what many librarians feel about the situation. Again often by omission, it demonstrates many of the gaps and misunderstandings that contributed to the need for our panel to provide a balanced view. Although the panel disagrees with the conclusions of the ARL report, the factual information it supplies provides considerable coverage of the problem faced by research libraries. A major omission in the ARL report is the presentation of data reported by member libraries relating library to university budgets: many academic libraries have failed to maintain their position within their universities' budgets. According to unpublished ARL statistics, 65 of 90 reporting libraries show decreased percentages of their universities' budgets; 19 show positions diminished more than 20 percent (ranging as high as 56 percent) since 1981/82;[58] 18 report increases ranging as high as 64 percent; 7 show no change at all. Twenty-six other important science institutions that reported incomplete or no figures showing changes in the proportion of their library to total expenditures include Auburn, Baylor College of Medicine, California Institute of Technology, University of California at San Francisco and Santa Barbara, Carnegie Mellon, CUNY, Clemson, Columbia, Georgia Tech, Illinois-Urbana, Kansas State, MIT, Mississippi State, New Mexico State, North Carolina State, Northwestern, Oklahoma State, Princeton, Rockefeller University, Stanford, SUNY at Stony Brook, Tufts, Utah State, Virginia Commonwealth, Yeshiva University—all among the top 100 institutions receiving U.S. federal science grants. We would like to acknowledge the cooperation of ARL staff in providing and discussing these data.

3. A third is the group of seven publishers (see note 42) who published articles on the prices of journals, claiming to be based on fair surveys. These articles are widely cited and have probably misled many librarians who have relied on the prestige of their sources. By their inadequacy they have contributed considerably to concerns about how a fair analysis of cost-effectiveness should be conducted. The panel suggests that these publishers would not publish surveys of this type if they covered scientific instruments and were authored by representatives of the maker of one of the instruments, rather than promotions of their own publications. Further, the panel suggests that the workmanship offered in most of the surveys is so obviously slipshod that it would not have been published if the topics were crystals, chemicals, mechanics, energy, optics, or some other area of science rather than subscription renewals. All seven publishers' studies reviewed by the panel suffer

from the same apparent conflicts of interest and bias by offering or implying conclusions that their journals are a "better buy."

4. Finally, a report of library weeding by Memorian University (St. Johns, NF, Canada) librarians Dorothy Milne and Bill Tiffany (see note 52) demonstrates the isolationist approach of some librarians. They query their faculty but discount their replies and further fail to involve them in making decisions that will surely affect the career of the researcher more than that of the librarian. Their method of studying actual use of journals in their library is so incomplete and open to bias and manipulation as to be useless. Every serial had to be identified by at least one faculty member as being important for a teaching or research program. Nonetheless they canceled over 20 percent of the subscriptions, saving $291,000 but quite possibly crippling present and future programs. Ironically, their conclusions indicate that the journals of eight major commercial publishers are more cost-effective than the average of their total collection, and the most prestigious journals are not cost-effective, thus claiming to refute the "cost-effective" surveys of the seven publishers mentioned earlier.

Notes

1. Donald W. King, Dennis D. McDonald, and Nancy K. Roderer, *Scientific Journals in the U.S.: Their Production, Use, and Economics* (Stroudsburg: Dowden, Hutchinson & Ross, 1981), 7–18. Citing *Little Science, Big Science*, by Derek de Solla Price (New York: Columbia, 1979) as an authoritative summary of bibliometric history and analysis, King notes that scientific and technical information has doubled every fifteen years for over three centuries, an annual growth rate of about five percent. Information furnished by a number of major science and technology databases supports this notion:

Abstract Database	Approximate Number of Records (millions)	Recent Annual Growth (%)
Engineering Information	3.0	3.2
Biosis Previews	9.0	6.8
Physics Abstracts (INSPEC)	2.5	8.2
Chemical Abstracts	9.7	11.3

2. King, McDonald, and Roderer; *Scientific Journals*, 221. Interestingly, *Federally Funded Research: Decisions for a Decade: Summary*, recently published by the U.S. Office of Technology Assessment (Washington, D.C., Sup. Docs. 1991, p. 21) refers to White and McCain's notion that the relative cost of publishing a paper has *decreased*, with increases in the number of pages published outpacing the investment in research and development since 1965 ("Bibliometrics," in *Annual Review of Information Science and Technology* 24 [1989]: 119–96).
3. King, McDonald, and Roderer, *Scientific Journals*, 238–42.
4. Nobelist Leon M. Lederman ("Science: The End of the Frontier?" suppl. to *Science*, Jan. 1991, p. 13 cites "Academic Research and Industrial Innovation," by Edwin Mansfield (*Research Policy*, in press). Eugene Garfield's editorial, "Assessing the Benefits of Science in Terms of Dollars and Sense" (*The Scientist*, 12 Nov. 1990, p. 14) adds references to the others, especially *Technology and the Pursuit of Economic Growth*, by Nathan Rosenberg and David C. Mowery (New York: Cambridge Univ. Press, 1989).
5. "Mathematics," by I. M. Singer, in *The Joys of Research*, ed. Walter Shropshire Jr. (Washington, D.C.: Smithsonian Institution Press, 1981), 44.
6. U.S. Dept. of Education, National Center for Education Statistics, *Digest of Education Statistics 1982* (Washington, D.C.: GPO, 1983), Table 182, indicates $247,668,000 expended for books and other library materials by 2,535 U.S. college and university libraries: 0.8993 percent of total expenditures for all U.S.

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colleges and universities. National Science Board, *Science and Engineering Indicators—1989* (Washington, D.C.: GPO 1989 NSB 89–1), Appendix table 4-2, reports R&D expenditures for 1970 totaling $26,134,000,000.

7. *Digest of Education Statistics 1989*, Table 25, provides total expenditure figures for all U.S. colleges and universities of $27,541 million for 1970/71 and $123,700 million for 1987/88. If expenditures for library materials had been maintained at 0.8993 percent they would have been $1,112.4 million.

   U.S. Dept. of Education, National Center for Education Statistics, *Academic Libraries: 1988* (NCES 90-374), Table 2a, shows $891.3 million spent by 3,438 institutions on library materials for 1987/88 (0.7205 percent of total college and university expenditures shown above), $221.1 million less than suggested by the projection based on the percentage indicated above (note 6).

   King, McDonald, and Roderer, *Scientific Journals*, pp. 218 *ff.*, focusing strictly on scientific and technical journals, offer a different perspective. They indicate that the total costs (acquisition, processing, maintenance, storage, and client service) of U.S. libraries for 1977 were $434 million. This equals about 1 percent of the total R&D cost of $42,783 million for 1977 (shown in Table 4-2 of *Science and Engineering Indicators—1989*).
8. *University and Polytechnic Libraries Book and Journal Expenditure from 1978/79 to 1987/88* (London: Publishers Association, 1990).
9. Noted by Mary Holmes, librarian at the European Molecular Biology Laboratory in Heidelberg, Germany, in *Nature* 323 (25 Sept. 1986): 359.
10. Based on conversations with Martin B. Gordon of Gordon & Breach, John Tagler of Elsevier, and Robert Miranda of Pergamon Press.
11. Albert Henderson, "Forecasting Changes in Periodicals Prices," *Serials Librarian* 21,4 (1992; in press).
12. According to *Digest of Education Statistics 1989*, Table 190, senior instructional faculty increased 56 percent (from 474,000 to 741,000) in the United States between 1970 and 1988. *Science and Engineering Indicators—1989* reports, "The number of doctoral scientists and engineers whose primary or secondary work activity was academic R&D reached 155,000 in 1987—a 65 percent increase over the number in 1977" (p. 106).

    According to OECD's *Main Science and Technology Indicators* (1990/1), Tables 10 and 12, higher education systems continue to train research scientists and engineers at rates higher than the growth of various national labor forces. OECD reports a nearly 19 percent increase in the overall ratio of research scientists and engineers per thousand labor force for eight major industrialized nations over a six-year period.
13. Online Computer Library Center (OCLC) reports that libraries participating in its interlibrary loan system provide access to 20 million items located in 26 countries (*OCLC Newsletter*, (July/August 1989, p. 12).
14. The *Report of the ARL Project on Serials Prices* (Washington, D.C.: Association of Research Libraries, May 1989) provides a summary and many details of the effects of inadequate funding. In a commentary in *New Scientist* ("The Price of Knowledge," 19 Nov. 1987, p. 64), science editor Marc Nicholls predicted that budget cuts would result in the reduction of the number of libraries in Europe and the United States where comprehensive coverage could be found.
15. Observations were provided by John Tagler of Elsevier Science Publishing and Robert Miranda of Pergamon Press, Inc., in telephone interviews, Spring 1991. Also see Marie-France Rochard, "Spectroscopie Documentaire," *Bull. Bibl. Française* 32,3 (1987).
16. *The Bookseller* (30 Nov. 1990, p. 1611) cited a report appearing in *Library Association Record* that the British Library's subscriptions to over 200 important science journals were being dropped in order to pay to relocate staff from London to Boston Spa.
17. The "background" statement by Ann Okerson ("Of Making Books There Is No End"), in the *ARL Report*, points out that libraries have had problems meeting serials prices more than once, notably in the 1920s and 1930s when inflation affected the Deutschmark, as well as in the 1970s and the late 1980s.
18. Fremont Rider, in *The Scholar and the Future of the Research Library* (New York: Hadham, 1944), developed the notion of excellent libraries tending to double in size every fifteen years, which is often accepted but not always found to be precisely true, as in follow-up studies by H., William Axford ("Rider Revisited," *College and Research Libraries*, 23 July 1962, pp. 345–47) and George Piternick ("Library Growth and Academic Quality," *College and Research Libraries*, 24 May 1963, pp. 223–29). The same historical growth factor for technical literature and the population of technically trained authors and users was observed by Price in *Little Science, Big Science*.
19. Piternick ("Library Growth") found, in addition, that mean collection size of the top ten universities, rated according to the Keniston-Berelson rank order of excellence in graduate teaching and research, included twice as many volumes and the mean of the second group and three times as many as the mean of the third group in 1946 and 1960.

    Patricia Battin, of the Commission on Preservation and Access, noted ("Endangered Species and Libraries: Collision, Collusion, or Collaboration," *Scholarly Publishing—An Endangered Species. Proceedings of the 10th Annual Meeting of the Society for Scholarly Publishing*, Washington, D.C., 1988, pp. 1–8) that, historically, the nineteenth- and early twentieth-century American scholar or scientist was forced to go

to Europe to be taken seriously because only in Europe could comprehensive library collections be found. She reports that modern scholars are beginning to resume the complaint of one hundred years ago. Browsing is a central method for research in spite of advances in technology for bibliographic control. Scholars and scientists need to have physical access to journals in complete, unbroken runs.

20. King, McDonald, and Roiderer, *Scientific Journals*, pp. 163–80. More recently, Eric Almquist reported findings of a survey of 680 chemists, geneticists, and computer scientists employed in government, academic, and research positions: 45 percent of scientists' "information encounters" occurred in their personal libraries and files, gathered over a number of years. Almquist noted that junior scientists were less dependent on their personal collections than older colleagues, probably because their personal files were not as extensive (Chris Goodrich, "SSP Rountable Charts an Electronic Future," *Publishers Weekly*, Nov. 8, 1991, pp. 41–42).

21. King, McDonald, and Roderer, *Scientific Journals*, pp. 269–80. Inflation causes prices of all goods and services to rise. Many library management writers refer to the annual review, "Price Index for 19—: U.S. Periodicals," published by *Library Journal* on or around April 15. It is sponsored by the Library Materials Price Index Committee of the Resources Section of the American Library Association Resources and Technical Services Division. Prepared largely by the Faxon Company, these analyses refer to the Consumer Price Index (CPI) issued by the U.S. Bureau of Labor Statistics (see *Handbook of the Bureau of Labor Statistics*). The CPI refers to a standard "market basket" of goods and services with quantities that are unchanged from year to year. Nowhere does the periodicals price index make any allowance for the substantial increases in the numbers of pages supplied by most science research journals. Nevertheless, the authors wonder about the reasons for the upward trend in prices greater than CPI. Science and technology price increases outpace many other broad categories.

The periodicals price index published in *Library Journal* is not entirely representative of its universe, because it samples an unchanging number of U.S. journals while the universe increases. Many new journals are developed because the progress of science no longer fits old definitions.

Frederick Lynden ("Library Materials Budget Justifications," *Book Research Quarterly* 5,4 [Winter 1990]: 68–74) describes a comparison of local price increases with the Higher Education Price Index and figures published in *Library Journal*. The *Library Journal* ten-year average showed an 11 percent annual increase. Yet the total serial budget was projected at 22.1 percent. Cost studies, on the other hand, provide data on actual local expenditures. He recommends that price indexes and local cost studies may complement each other, being useful in preparing budget proposals. Local figures, however, are stronger indicators than indexes.

Albert Henderson points out ("Forecasting Periodicals Prices") that there is a relatively simple way to understand the relationship between the U.S. Periodicals Price Index (and similar indexes) and the Consumer Price Index (CPI). For instance, between 1977 and 1990 the CPI rose an average of 6.1 percent annually. All U.S. periodicals averaged 10.8 percent, while the average annual rise in U.S. chemistry and physics periodicals was 12.1 percent. Looking closely at the difference, one realizes that the average annual variable between CPI and price increases of science periodicals is about 6 percent, most of which can be explained by growth in the number of pages published. A number of studies by librarians such as James M. Matarazzo ("Scientific Journals: Page or Price Explosion?" *Special Libraries* [Feb. 1972]: 53–58), Herbert S. White and Bernard M. Fry ("Economic Interaction between Special Libraries and Publishers of Scholarly and Research Journals," *Special Libraries* [March 1977]: 109–14), and Kenneth E. Marks et al. ("Longitudinal Study of Scientific Journal Prices in a Research Library," *College and Research Libraries* 52,2 [March 1991]: 125–38) also take the position that increased journal prices are largely a result of the combination of increased pages and inflationary cost increases.

Elsevier Science Publisher's John Tagler (in telephone interviews, spring 1991) would add another factor: "technological inflation." Where typewriters were once acceptable, computers are now essential; electronic data transfer to index and abstract services is desirable; air courier service and fax have replaced first-class mail. Tagler also noted that cost increases specific to publishing (printing, paper, distribution, etc) may not be reflected in a consumer-oriented inflation index. The cost of British printing, for instance, has risen faster than consumer prices since 1970.

The organizational expense of development and marketing would be higher in a commercial operation traditionally concerned with competitive growth, share in a market that is burgeoning, and service to the entire science community. In contrast, an association controlled by its editors, who traditionally tend to define their scope "once and for all," has no interest in absorbing new developments beyond that scope or in underwriting related activities. Hence the need for new associations and commercial publishers to underwrite new publishing ventures.

Periodicals produced in different countries are also subject to fluctuations of local inflation and monetary exchange. Science periodicals are particularly subject to international subscribership and production, since a publisher may easily undertake production in other countries subject to a variety of costs and international exchange rates.

Among the policies singled out for criticism by many librarians is the price differential between European and North American subscriptions to journals produced in Europe. Air distribution worldwide is seldom mentioned but a costly requirement of any publisher promising rapid dissemination of

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research information. So is the maintenance of local offices and staff. Each distribution option has its own combination of not only direct but administrative costs. The cost of physical distribution is an important element in any price, increasing substantially with increased frequency of publication and varying from country to country.

22. *OCLC Newsletter* (July/Aug.1989) reported that requests for serials rose from 19.4 to 42.1 percent between 1979 and 1988 (p. 16), while total online interlibrary loan requests rose over 400 percent from 923,836 in 1980/81 to 4,284,438 in 1988/89 (p. 20). Taking 19.4 percent of 924,000 yields 180,000 in 1979; 42.1 percent of 4,284,000 is 1,804,000.
23. "Testimony submitted on behalf of The Copyright Clearance Center, Inc., by Alexander C. Hoffman," in *Report on Library Reproduction of Copyrighted Works (17 U.S.C. 108)* (PB88-212014 Washington, D.C., NTIS, 1988), 280.
24. Ibid., p.32
25. "Testimony of Donald W. King," in *Report on Library Reproduction*, 222.
26. Rochard, in "Spectroscopie Documentaire."
27. In 1987/88 a major serials cancellation program was initiated at Stanford University Library. Four to five hundred subscriptions were cancelled to save $100,000, with a further $200,000 reduction in science acquisitions funds projected, according to Ann Okerson ("Of Making Many Books There Is No End," p. 19). Anthony de Palma reported in the *New York Times* (23 July 1991, p.A14) that Stanford University has misposted to indirect research costs $1.35 million of its billings for federal research grant indirect costs. [On March 14, Karen de Witt noted that Stanford had received a total of $1.8 billion in federal research contracts and grants, including $605 million to cover indirect costs, since 1980.]
28. "Serials Pricing and Library Budgets: A Librarian's Point of View," by LSU librarian October Ivins, *SSP Letter* 12,8 (Sept./Oct. 1990): 3–7.
29. Derived from unpublished statistics supplied by Association of Research Libraries, 1991.
30. Marifran Bustion and Jane Treadwell, in "Reported Relative Value of Journals versus Use: A Comparison," (*College and Research Libraries* 51,2 [March 1990]: 142–51) note that faculty are asked to identify "essential" serials prior to the cancellation. Some faculty members refused to participate. After the cancellations, the library undertook a brief but admittedly flawed study of usage limited to the current periodicals room. The rankings of R&D expenditure may be found in *Science and Engineering Indicators—1989* , Appendix table 5-6.
31. Market Data Retrieval (Shelton, Conn.) reports 852 computer science department heads at four-year institutions and 314 at junior colleges as of summer 1990. Only 95 accredited programs were listed in "Computer Science Programs Accredited by the Computer Science Accreditation Commission (CSAC) of the Computing Sciences Accreditation Board (CSAB)" (*Communications of the ACM* 33 [11 Nov. 1990]: 134–36). The CSAB was created in 1984.
32. The *ARL Report on Serials Prices* quotes the 40,000 figure as mentioned in the *New York Times* by science writer William Broad and also (p. 33) by Gerald W. Bracy in the *Chronicle of Higher Education*. A year later, David P. Hamilton, writing in *Science* ("Publishing by—and for?—the Numbers," 250 [7 Dec. 1990]: 1331–32) claims Bowker/Ulrich's database lists 74,000 science titles.

    Science Citation Index reports covering 3,192 source publications in 1990, down considerably from the 3,367 covered in 1985. The number of source items covered (625,432 in 1986; 590,841 in 1990) has also dropped, while all other indicators suggest the numbers should have increased.
33. "The Patent Game: Raising the Ante," by Eliot Marshall, in *Science* (5 July 1991): 24.
34. Representing the American Institute of Physics at the meeting of the journal pricing discussion group of the Association of College and Research Librarians on Jan. 7, 1990, Prof. Henry Barschall was reported to have stated that he believed in multiple publishing on a research project, including a letter, an article, and then perhaps articles in journals that reach different audiences and require a different language ("Birds Eye View," column compiled by Debra Polansky and Corrie Marsh, in *Against the Grain* 2,1 [Feb. 1990]: 13).
35. The "Ingelfinger Rule" is an unusual convention, recognized only in certain areas of clinical and biomedical research. It was first proclaimed by Franz J. Ingelfinger in "Shattuck Lecture—The General Medical Journals: For Readers or Repositories?" in *New England Journal of Medicine (NEJM)* (which was then edited by Ingelfinger) (vol. 296 [1977]: 1258–64). The rule excludes from consideration for "peer-reviewed" and prestigious publication by *NEJM* any article the substance of which has been mentioned in any other publication, including "throwaways."

    Not every biomedical researcher agrees with the Ingelfinger rule. *Science* (211 [6 Feb. 1981]: 561) reported a dispute between *Journal of the American Medical Association (JAMA)* and *NEJM* over the Ingelfinger rule. Editorials in *JAMA* complained that the rule caused scientists to refuse to discuss their unpublished research. *NEJM* editor Arnold S. Relman admitted that he actively discouraged scientists from discussing their work with the press, including holding of press conferences. Further debate was reported in an article in the *New York Times*, "With Lives at Stake, Issue Is Secrecy of Data" (15 Jan. 1991), where Lawrence K. Altman noted the purpose of the rule was to overcome competition from trade publications and that a later *NEJM* editor, Relman, extended the rule to include publicity in newspapers and television. Altman cites an instance where *NEJM* rejected an article on the first instance

of AIDS transmitted by blood transfusion because a government agency released an alert to doctors.

36. Many "proceedings" are considered ephemeral; some are not. The *Proceedings of the Society for Experimental Mechanics*, for example, is peer-reviewed, and publication in it is considered a contribution to the archival record. Where conference proceedings are the only published record of research, they are of archival significance to scientists and engineers who otherwise might wastefully repeat work already done.
37. Multiple publication, very long delays in publication, plagiarism, high multiplicity of authors, and listing co-authors who have not contributed to intellectual content were the most important issues needing attention, according to editors polled by the editorial policy committee of the Council of Biology Editors (*Ethics and Policy in Scientific Publication* [Bethesda, Md.: Council of Biology Editors, 1990], 108–11).
38. Indiana University Dean Herbert S. White has reviewed these issues in articles such as "Scholarly Publishers and Libraries: A Strained Marriage" (*Scholarly Publishing* 19,3 (1988): 125–29) and "Librarian Burnout" (*Library Journal*, 15 March 1990, 64–65).
39. Budget position change statistics were derived from unpublished reports supplied by the Association of Research Libraries. LSU acquisitions librarian Charles Hamaker is a frequent speaker at meetings of professional librarians and the author of a number of articles such as "Serials Costs and the Carrying Ability of Serials Budgets 1987" (*Serials Librarian*, 1988, 129–134, which complains that the combined billings of Elsevier, Springer, and Pergamon represent 2.5 percent of LSU's serial titles but 19 percent of its current subscription costs. John Lubans Jr. is the author of "Scholars and Serials: Will Electronic Journals Save Us from the Heartbreak of Scholarly Drivel, the Embarrassment of Book Budget Bankruptcy, the Halitosis of Salami Publication, and the Morbid Obesity of Our Collections?" (*American Libraries*, March 1987, 180–82), the title of which speaks for itself. Gary D. Byrd authored "An Economic 'Commons' Tragedy for Research Libraries: Scholarly Journal Publishing and Pricing Trends" (*College and Research Libraries* 51,3 [May 1990]: 184–85, in which he bemoans the situation of research libraries where "individuals are allowed unrestrained freedom to exploit them for personal gain."
40. See Altman, "With Lives at Stake"; also his article, "Errors Prompt Proposals to Improve 'Peer Review' at Science Journals" in the *New York Times*, 6 June 1989. Another work of interest is CBE's *Ethics and Policy in Scientific Publication*, which offers substantial detailed discussions and recommendations. Robert A. Day, *How to Write and Publish a Scientific Paper*, 3d ed. (Phoenix: Oryx Press, 1988) provides many strong recommendations for authors and editors, often referring to the *CBE Style Manual*, published by the Council of Biology Editors, 5th ed. (Bethesda, Md., 1983).
41. Stephen Lock, as editor of the *British Medical Journal*, was well qualified to review the strengths and weaknesses of the peer-review process as applied to many different disciplines and situations (*A Difficult Balance* [London: Nuffield Provincial Hospitals Trust, 1986]). While recounting many failures of peer review, Lock also supplied details of alternatives that failed, including the 1961 experiment of the U.S. National Institute of Health to disseminate "unevaluated preprints" to "information exchange groups" and a similar plan by the American Psychological Association. Lock's book is summarized in a review by Bernard Dixon ("Peer Review—In the Best Interests of Science?" in *New Scientist* 109, 1498 [6 March 1986]: 58), who agrees with Lock that peer review is the only viable option.
42. A number of publishers have issued surveys that compare their journals with journals of other publishers on the basis of "cost-per-1000 words," "cost-per-citation-impact," or similar qualitative measures. Their presentation so closely mimics presentation of science research that librarians and other readers are misled. Their conclusions generally find that their journals are more cost-effective than journals of other publishers, particularly those of commercial publishers. They are:

    American Chemical Society: (unpublished but reported via the *ARL Report on Serials Prices*, p.30).

    American Institute of Physics: Henry H. Barschall, "The Cost of Physics Journals," *Physics Today* (Dec. 1986): 34–36, and "Cost Effectiveness of Physics Journals," *Physics Today* (July 1988): 56–59).

    American Mathematical Society: "Survey of American Mathematical Research Journals," in its *Notices* 30 (1983): 715–19; and 33 (1986): 287–91.

    American Mineralogical Society: Paul H. Ribbe, "Assessment of Prestige and Price of Professional Publications," *American Mineralogist* 73 (July 1988): 449–69.

    American Physical Society: H. H. Barschall and J. R. Arrington, "The Cost of Physics Journals: A Survey," *Bulletin* 33,7 (July 1988): 1437–47).

    International Union of Crystallography: S. C. Abrahams and R. A. Matula, "Crystallographic Publishing in Retrospect and Prospect," *Acta Crystallographica* A44 (July 1988): 401–10.

    Optical Society of America: Myers Consulting Services, "Price Comparison Study of Optical Periodical Literature 1984–1986," *Optics News* (May 1988): 21–25, revised Oct. 1988, pp. 24–28.

    Many of the surveys point out specifically that commercial publishers' "per-kiloword" prices are higher than association publishers'. Other surveys present the data in an obviously biased way and leave such conclusions to the reader. The American Chemical Society reports its conclusions but shares the data with no one. The surveys suffer from inappropriately small samples, biased samples, inconsistent comparisons, inadequate presentation of data, discussions of examples not found in the data, lapses in logic, confusing statements of purpose, and other evidence of bias, such as "testimonial-type" statements

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and deliberately persuasive language. Publication dates, May through July, are clearly timed to coincide with the annual review of subscription renewals made in every science research library. Finally, the surveys uncritically cite each other in support of the desired findings. In a letter to *Chronicle of Higher Education* (3 Jan. 1991, p.B4), Christopher Schneider points out a number of errors in the representation of data by the American Institute of Physics which were repeated in its second survey in spite of complaints made of similar errors in its first survey.

43. *Science* ("No Citation Analyses Please, We're British," 252 [3 May 1991]: 639) recently reported that British academics "loathe" the use of citation counting as a measure of content and achievement, in a summary of a report published in response to a request for ways to produce quantitative assessments of the research performed by university departments.

44. In "Journal Deselection in a Biomedical Research Library: A Mediated Mathematical Approach" (*Bulletin of the Medical Library Association* 78,1 [Jan. 1990]: 45–48), librarian Richard K. Hunt notes that there was little correlation between citation impact factor and patron interest as the result of a journal deselection survey at the biomedical library of Lawrence Livermore National Laboratory. Forty percent of the canceled subscriptions had an impact factor greater than one, while 177 subscriptions that were retained also had an impact factor greater than one. Ranked by impact factor, Hunt felt that all 289 titles would appear roughly equivalent.

45. Abrahams and Matula ("Crystallographic Publishing") suggest that important crystallographic papers published in *Acta Crystallographica* are more likely to be read and used than if published in relatively unspecialized journals such as *Angewante Chemic, Inorganic Chemistry, Journal of the American Chemical Society, Physical Review,* etc. It is also easy to infer from their presentation that the "cost per 1000 characters" of crystallographic materials will be lower where there is a concentration of articles of interest.

46. The accumulation of claims by association publishers (see note 42) and others that prices of commercial publishers are unfairly high resulted in ARL commissioning a study by Economic Consulting Services, Inc., to analyze the profits of four major commercial publishers—Elsevier, Pergamon, Plenum, and Springer-Verlag—for the period 1973–1987. Although the writers admit they have no access to circulation data and specific costs essential to fair analysis, their report, "A Study of Trends in Average Prices and Costs of Certain Serials over Time" (published in *ARL: Report on Serial Prices*) concluded that commercial journal publishers' prices have risen faster than their costs, implying excessive growth of profits.

    The authors of *ARL Report on Serials Prices* complain of the obligation of for-profit publishers to put monetary gain before service objectives (p. 35) and cite the profit of Pergamon Press, which was stated in the annual report of British Printing Corporation. In its summary (p. 40), the report writers refer to the importance of the role of "profit-seeking" publishers in creating the serials crisis. Among their recommendations (p. 42), they encourage removal of publication of research results from commercial publishers in favor of noncommercial channels.

    Other demonstrations of attacks on commercial publishers include: Duke University librarian John Lubans Jr. uses the word "greedy" among others to characterize publishers' prices in his commentary, "Scholars and Serials." B. H. Blackwells Ltd. subscription agency manager John B. Merriman notes in an article, "Publishing and Perishing?" (*Nature* [28 Sept. 1989]: 349–50), that commercial publishers are generally accused of overproducing, overpricing, and making excessive profits. Dennis P. Carrigan, assistant dean of library science at the University of Kentucky (in "Publish or Perish: The Troubled State of Scholarly Communication," *Scholarly Publishing* 22, 3 [April 1991]: 131–42, quotes A. F. Spilhaus, executive director of the American Geophysical Union, calling on scientists at a meeting of the American Association for the Advancement of Science to refuse to purchase, publish in, or work for any journal that is overpriced or marginal. He also called on scientists to advise their libraries to cancel subscriptions to such publications.

47. Lubans ("Scholars and Serials") quotes Edward Huth, editor of *Annals of Internal Medicine* (speaking to a meeting of the American Association for the Advancement of Science reported in *Chronicle of Higher Education*, 5 June 1986, pp. 5, 9) testifying about false authorship, "salami" publication, and unnecessary reissue of papers.

    The *ARL Report on Serials Prices* (p. 33) cites an article by William Broad ("The Publishing Game: Getting More for Less," *Science* 211 [13 Mar. 1981]: 1137–39), who quotes editors of *American Journal of Psychiatry,* and *New England Journal of Medicine*. Some examples of outright fraud and irresponsibility are provided. However, the message conveyed by the editors interviewed was essentially that their journals reject any submission not meeting their standards—wherever they can. They claim papers they reject appear in other journals. It is not clear, however, whether the papers rejected demonstrated poor research and/or writing. Papers are often rejected by journals for other reasons, including being outside the scope, too narrow, insufficiently novel, or, in the case of *NEJM*, violating the "Ingelfinger Rule" (see note 35).

    The writers of *ARL Report on Serials Prices* reason that pressure to publish has contributed to an oversupply of papers, not all of agreed value, that provides much of the content for increases in pages published. Carrigan ("Publish or Perish") also catalogs the comments of many association publishers and university administrators suggesting that academic career requirements, rather than service to scholarship, motivate many writers to produce articles of questioned value.

48. Estimated by Price in *Little Science, Big Science*, p. 226.
49. Hamilton; "Publishing by—and for?—the Numbers." Only a few of the letters received by *Science* could be published: see vol. 251, 22 March 1991, pp. 1408–10, and vol. 251, 29 March 1991, p. 1546.

    In an editorial in the *Scientist* (18 March 1991, p. 12), *Science Citation Index* publisher Eugene Garfield noted that there is little understanding, and no study, of why some papers go uncited. Many additional studies and observations have been made of the citation statistics produced by Institute for Scientific Information (ISI). In "Some Results on the Function and Quality of Citations," Michael J. Moravcsik, and P. Muragesan (*Social Studies of Science* 5 [1975]: 86–92) concluded that many citations in *Physical Review* were perfunctory. Michael H. MacRoberts and B. R. MacRoberts observed in "Quantitative Measures of Communications in Science: A Study of the Formal Level" (*Social Studies of Science* 16 [1986]: 151–72) that attribution is often assumed, and authors will take a shortcut and cite a review article, which contains no original material, rather than cite the original primary research report. They also note evidence of many errors.
50. *Journal Citation Index* (1989, p. 61) reports 559,399 source items covered by *Science Citation Index* for 1989, including 4,728 anonymous source items. Its analysis continues, enumerating 411,176 "articles," 37,306 meeting abstracts, 39,118 notes, 32,152 letters, 19,045 editorials, 12,050 reviews, 4,505 corrections, 1,438 discussions, 583 book reviews, 1,544 biographical items, 4 chronologies, 356 software reviews, 113 hardware reviews, and 9 database reviews. No statistics are provided for the number of articles that are review articles, methodology reports, original research reports, or essays; no statistics indicate how many articles are written in English, how many in other languages.
51. King, McDonald, and Roderer, *Scientific Journals in the United States*, p. 170.
52. In "A Survey of the Cost-Effectiveness of Serials: A Cost-per-Use Method and Its Results," Dorothy Milne and Bill Tiffany (*Serials Librarian* 19, 3/4 [1991]: 137–41) explain that they asked library patrons to mark a tag affixed to each copy (issue or bound volume) used. Because of notable underrecording by patrons, they simply multiplied the marks by 1.5. Dividing the cost of the subscription by the number of uses provided a "cost-per-use" figure which then was compared with the cost of an interlibrary loan. If the cost-per-use for the subscription was higher, the title was considered for cancellation. They also noted that a significant number of "cost-ineffective" serials receive substantial use, and they recommend replacing subscriptions with a good document delivery system. No mention is made of payment of fees for photocopies received in place of subscriptions.
53. In "Reported Relative Value of Journals versus Use: A Comparison" (*College and Research Libraries* 51, 2 [March 1990]: 142–51), Marifran Bustion and Jane Treadwell repeatedly note flaws in their methodology, which depended on reshelving data only in the current periodicals room of Texas A&M library during the Spring 1988 semester.
54. Carlos Kruytbosch, director of Science Indicators Group of the National Science Foundation, noted (in a telephone interview, 16 May 1991) that science library collections were generally mixed with other materials and there were no statistics available for technology library collections' growth, size, or use.
55. *Science and Engineering Indicators—1989*, Appendix Table 5–23.
56. John Tagler, Elsevier Science Publishing, in correspondence and telephone interviews, spring 1991.
57. *Science and Engineering Indicators—1989*, Appendix Table 5–6.
58. The following nineteen libraries lost over 20 percent of their funding as a percentage of their universities' educational and general expenditures 1981/82 to 1989/90:

ARL Institution	Percentage Change
Arizona	– 30.8
Boston	– 25.9
California–Berkeley	– 20.8
California–Irvine	– 26.2
California–Riverside	– 22.4
Duke	– 30.6
Houston	– 42.6
Louisiana State	– 23.4
McGill	– 22.2
Manitoba	– 20.4
Michigan State	– 40.0
Oregon	– 40.7
Pennsylvania State	– 24.1
Rice	– 32.8
Suny–Buffalo	– 41.8
Texas	– 48.6
Texas A&M	– 56.4
Toronto	– 28.2
York	– 31.7

Cost Effectiveness of Science Journals

SUPPLEMENT

to the Report published in

PUBLISHING RESEARCH QUARTERLY Fall 1992

Prepared for

Lewis Klein, *Chairperson*
Howard University

ADVISORY PANEL FOR SCIENTIFIC PUBLICATIONS
Foundation for International Scientific Cooperation

by

Albert Henderson

HENDERSON ASSOCIATES
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TO: D. ALLAN BROMLEY

DATE OF CORRESPONDENCE: 08/11/92

SUBJECT: ESTABLISHING A SPECIAL PROGRAM TO PROVIDE THOUSANDS OF RESEARCH POSITIONS, BOTH IN INDUSTRY AND ACADEMIA FOR YOUNG AMERICAN PH.D SCIENTISTS

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DIRECTORATE ASSIGNED:

STAFF ASSIGNED: William Raub

ACTION REQUIRED:

STAFF ACTION: DIRECT REPLY

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CONTACT PERSON:

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REMARKS: Damar forwarded the letter to Dr. Raub for action.

P—

OSTP RECEIVED:

DEPT RECEIVED: 08/12/92

FILE: Life Sciences

CENTRAL FILES:

MQ

Should Bill Lair do a direct reply on this one. The guy keeps calling. It's an OK letter. He does a great job on this stuff. Thanks

Dan

2405

THE WHITE HOUSE

WASHINGTON

October 13, 1992

Dear Dr. Nelson:

This is in response to your letter urging that the federal government provide more research funds for young scientists.

I empathize with the sentiments you express on behalf of yourself and others who seek a research career but are frustrated by the keen competition for funds. I wish I could tell you that the strains of recent years will prove to be transitory and that success rates for research proposals will rebound upward soon. But, in all candor, that is not what I envision. All indicators suggest that competition such as we are experiencing now will be the norm for many years to come. The more favorable episodes during the 1960s and 1980s thus are best regarded as anomalies unlikely to recur within the foreseeable future.

I say this notwithstanding President Bush's consistently strong emphasis on science and technology. By according research and development a higher priority that many other activities of government, he has led the effort to elevate research support to record levels, especially for basic science and certain critical technologies. But the competition has not abated because these dollar increments have been offset to a considerable extent by growth in the number of applicant scientists and engineers.

The projected scenario for the fiscal year now commencing leaves little room for optimism. Although heretofore the Congress has reacted favorably to many of the President's budget requests for science and technology, this time around it seems disinclined to fund any of the Presidential initiatives up to the level requested. Thus, needs and opportunities for research will continue to outstrip resources, making intense competition inevitable and demanding judicious priority-setting.

Such prospects create understandable temptation to call for redirection of funds from other areas of government spending -- such as assistance to institutions and individuals within nations that were part of the former Soviet Union. Others share your point of view. Bear in mind, however, that, as the President and Congress struggle daily to achieve multiple objectives -- both domestic and foreign --, resource limitations force tradeoffs of extraordinary difficulty. For example, as an ardent advocate for research and development, I nevertheless would be hard-pressed to deny that facilitating the transition of the former Soviet Union to a collection of stable, nonadversarial democracies enhances our national security. Peace is a far better climate for most types of research than is war.

Although I remain optimistic that the federal government will continue to support science and technology generously, I see no alternative but to scale down our ambitions to match our resources. That will require careful planning and difficult choices at all levels. Young scientists and engineers will be well-advised to be open-minded about career options in industry, government laboratories, and not-for-profit research institutes as well as universities. Much of the strength of the US system lies in its institutional diversity. Those embarking on a research career in these uncertain times should plan to take full advantage of that.

Sincerely yours,

D. Allan Bromley
Assistant to the President
for
Science and Technology

Gene A. Nelson, Ph.D.
7374 Brookside Parkway
Cleveland, OH 44130-5468

"Document Control for Division of Life Sciences"

TYPE: ACTION DOCUMENT NUMBER: 9202405
ORIGINATOR: 04 STATUS DIRECTORATE STATUS C

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FROM: NELSON, GENE A.

TO: D. ALLAN BROMLEY

DATE OF CORRESPONDENCE: 08/11/92

SUBJECT: ESTABLISHING A SPECIAL PROGRAM TO PROVIDE THOUSANDS OF RESEARCH POSITIONS, BOTH IN INDUSTRY AND ACADEMIA

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED: William Raub

ACTION REQUIRED:

STAFF ACTION: DIRECT REPLY

****

SENDER'S DUE DATE:

OSTP DUE DATE: STAFF DUE DATE 08/28/92
DATE COMPLETED: DATE COMPLETED/DEPT: 10/13/92

****

COPIES TO:



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WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS: Damar forwarded the letter to Dr. Raub for action.



OSTP RECEIVED: DEPT RECEIVED: 08/12/92
FILE:

CENTRAL FILES:

MQ

Donald Bill Lamb— do a direct reply on this one. The guy keeps calling. It's an OK letter. He does a great job on this stuff. Thanks

Dan

Gene A. Nelson, Ph.D
7374 Brookside Parkway
Cleveland, OH 44130-5468
(216) 891 - 8809 [Voice/FAX]
Internet e-mail: au195@Cleveland.Freenet.edu

August 11, 1992

D. Allan Bromley Ph.D. - Director OSTP
The Assistant to the President for Science & Technology
Executive Office Building
Washington DC 20506
(202) 456 - 7116 Voice
(202) 395 - 3261 FAX

DAB
Do you want to respond to the letter? He has also called!
D
8/12

Dear Dr. Bromley:

Today I received a copy of a letter dated July 29, 1992 that you sent to Ms. Cynthia Walsh of Albuquerque, NM. You outlined the rationale for providing $35 million to fund Soviet science centers in Moscow and Kiev, and the federal role in providing additional funds to support ...a great many young Soviet scientists who are in desperate plights lacking not only jobs also even the basic necessities of life....

I have briefly spoken to the President in person, when he visited Cleveland on May 21, 1992, and have also corresponded with him and staffers about the fact that this is also a problem in the United States that demands immediate attention.

There is a U.S. R&D funding crisis that is affecting thousands of young scientists placing a significant number of them in the same challenging situations as their Soviet counterparts.

With the Wolpe hearings on April 8, 1992 written up in SCIENCE Vol 256, (10 April 1992 p. 172) the truth of the poor employment situation for young American Ph.D. scientists began to be acknowledged. Recognizing the dearth of up-to-date published statistics regarding unemployment and underemployment of young scientists, I have initiated a survey. This survey has been publicized via the Young Scientist's Network (YSN), ELECTRONIC ENGINEERING TIMES, and The American Association of Concerned Engineers. Preliminary data is available and points to significant problems, both in unemployment and underemployment.

Prompt action such as establishing a special program to provide thousands of research positions, both in industry and academia is necessary in order to make positive use of today's Ph.D.s and to also signal students "in the pipeline" that the United States values the direct and indirect investments that science students make in earning a Ph.D. in science. Possible funding mechanisms include special federal appropriations and tax incentives for the private sector.

I am an unemployed young Ph.D. scientist who is active in an electronic network called "The Young Scientist's Network" (YSN). [The YSN was described in a SCIENCE article, Vol. 256 (1 May 1992 p. 606)].

My research demonstrates that R&D underfunding has been a long-term problem in the United States that has recently become much worse.

I have made significant investments in preparing to become a scientist, and am well qualified. In summary, I was a finalist at the International Science Fair (Fort Worth, TX - 1969) and earned my B.S. in 1973 from Harvey Mudd College (HMC) in Claremont, CA. HMC has been ranked as the "best specialty engineering college in America" by U.S. News & World Report for the past three years. I have worked at NASA-JPL in Pasadena, CA.

I earned my doctorate in Biophysics from SUNY at Buffalo in 1984. With student loans, I could not afford the "postdoc" route and have worked in the clinical diagnostics industry. Since 1985, I have endured

worked in the clinical diagnostics industry. Since 1985, I have endured three terminations and over three years of no salary stemming from technical programs being ended and from the loss of R&D funds caused by leveraged buyout. With a dearth of opportunities for Ph.D.s in Cleveland, Ohio, I attempted to start a technology intensive business without success.

My wife will also be facing the same bleak situation shortly. She is completing her Ph.D. in Biochemistry from the University of Akron.

I look forward to hearing your action plan about this situation.

Sincerely,
Gene A. Nelson, Ph.D.

File: Bromley.txt

"Document Control"

TYPE: INFORMATION
ORIGINATOR: 02
DOCUMENT NUMBER: 9202960
STATUS I
DIRECTORATE STATUS

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FROM: SIMON, Irwin B.: U.S. ARMY

TO: DR. D.A. BROMLEY

DATE OF CORRESPONDENCE: 09/25/92

SUBJECT: HE IS FORWARDING A VIDEO TAPE OF A PROCEEDURE THAT HE AND DR. BROMLEY DISCUSSED WHILE TRAVELLING.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:
DATE COMPLETED:

STAFF DUE DATE
DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:
PHONE:
EXT:

REMARKS: VIDEO TO DR. BROMLEY.

OSTP RECEIVED: 10/01/92
DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

2960

Irwin B. Simon, M.D.
3279 Cove Way
Marina, California 93933-2231

25 September, 1992

D. Allan Bromley
Science Advisor to the President
The White House
1600 Pennsylvania Avenue
Washington, D.C.

Dear Dr. Bromley,

You may recall our conversation on board USAir flight #419 from Indianapolis to San Francisco on 23 September, 1992. As promised I have forwarded a copy of our videotape regarding the Telepresence Surgical System being developed by our group at SRI, International.

It is my firm belief that Telepresence represents a significant advance in surgical minimally invasive techniques. While Telepresence Surgery is only in its infancy, I believe that we may be in human clinical trials in as little as 3 to 5 years. Five years does not appear to be overly optimistic.

Our other work involves the Virtual Reality Surgical Simulator. I do not have a video that I can forward to you at this time. Several generations of computing power from now may make this a practical device for instruction of surgical residents and the acquisition of surgical skills and development of new surgical technique. I will be presenting some of our work at the Virtual Reality Conference and Exhibition in Washington, D.C. on the first and second of December.

I hope that you enjoy this video and I look forward to your comments.

Sincerely,

Irwin B. Simon, M.D.
MAJOR, MC, USA
Director, Surgical Endoscopy Unit
Fort Ord, California 93941-5800

"Document Control"

TYPE: INFORMATION DOCUMENT NUMBER: 9202494
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS
****

FROM: DIAL, DWIGHT: AMERICAN SHEEP INDUSTRY ASSOCIATION

TO: DR. D.A. BROMLEY

DATE OF
CORRESPONDENCE: 08/18/92

SUBJECT: LETTER TO THE PRESIDENT REQUESTING SIGNATURE OF S.544.

****
DIRECTORATE ASSIGNED: STAFF ASSIGNED:

ACTION REQUIRED: STAFF ACTION:

****
SENDER'S DUE DATE:
OSTP DUE DATE: STAFF DUE DATE
DATE COMPLETED: DATE COMPLETED/DEPT:

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COPIES TO: LIFE SCIENCES
D. Allan Bromley

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WHITE HOUSE TRACKING #: CONTACT PERSON:
PHONE: EXT:
REMARKS:

OSTP RECEIVED: 08/27/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

2494

ASI

American
Sheep Industry
Association

6911 South Yosemite Street
Englewood, Colorado 80112-1414
303/771-3500 FAX 303/771-8200

August 18, 1992

The Honorable George Bush
President of the United States
Executive Office of the President
The White House
1600 Pennsylvania Avenue NW
Washington, D.C. 20500

RECEIVED
92 AUG 27 A8:40
OSTP
MAIL ROOM

Dear President Bush:

The American Sheep Industry Association (ASI) as the national voice of the 110,000 sheep producers in the United States respectfully urges you to sign S. 544, "The Animal Enterprise Protection Act of 1992."

S. 544 provides sorely needed enhanced federal protection to farms, ranches, research facilities and legitimate animal exhibitions from growing radical activist violence. The bill, passed on suspension by the House (with 264 cosponsors) and by unanimous consent in the Senate, is a focused, balanced approach to these protections achieved by animal users, members of Congress, federal law enforcement experts, animal welfare and legal groups.

S. 544--and House companion H.R. 2407--has been one of the highest legislative priorities for nearly three years of intense effort by a national coalition of farmers, ranchers, agribusiness and agriculture groups, biomedical and ag research, colleges, universities, zoos, aquaria, rodeos, circuses, exhibition groups and citizen organizations.

This vital legislation enables state and local authorities to draw upon and coordinate with federal expertise and facilities when confronted by criminal activity of radical activists. In the last decade, there have been well over 100 recorded incidents in over 25 states causing tens of millions of dollars in damage to vital food production and medical research. S. 544 will be a powerful deterrent to these act actions.

ASI respectfully urges your signature on S. 544. Thank you for your consideration of our views, and your Administration's continued, strong support of American agriculture.

Sincerely,

Dwight Dial

Dwight Dial
Chair, ASI Legislative Council

"Document Control"

TYPE: INFORMATION DOCUMENT NUMBER: 9202705
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

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FROM: WILSON. JIMMIE: NATIONAL CATTLEMEN'S ASSOCIATION

TO: PRESIDENT BUSH

DATE OF
CORRESPONDENCE: 08/17/92

SUBJECT: A REQUEST URGING THE PRESIDENT TO SIGN S.544 THE ANIMAL ENTERPRISE PROTECTION ACT OF 1992.

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:
DATE COMPLETED:

STAFF DUE DATE
DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:
PHONE: EXT:

REMARKS:

OSTP RECEIVED: 09/08/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

NATIONAL CATTLEMEN'S ASSOCIATION
1301 Pennsylvania Ave. N.W. • Suite 300 • Washington, D.C. 20004-1701 • (202) 347-0228

Headquarters:
5420 South Quebec Street • P.O. Box 3469 • Englewood, Colorado 80155 • (303) 694-0305

2705

August 17, 1992

The Honorable George Bush
President of the United States
The White House
1600 Pennsylvania Avenue, NW
Washington, D.C. 20500

Dear Mr. President:

On behalf of the 240,000 cattle producers in the United States represented by the National Cattlemen's Association. I write to urge you to sign S.544 *The Animal Enterprise Protection Act of 1992*.

This legislation is needed to provide federal protection to farms, ranches, feedlots, research facilities and legitimate animal exhibitions from growing radical activist violence.

S.544 passed Congress with a very broad based bipartisan support. It also had a very broad based industry support.

As cattle ranchers and feeders, our members are potentially exposed to violent acts of destruction from certain activist groups. S.544 will serve as a deterrent to these actions.

We respectfully urge your signature on S.544 .

Sincerely,

Jimme L. Wilson

Jimme L. Wilson
President

"Document Control"

TYPE: INFORMATION DOCUMENT NUMBER: 9202706
ORIGINATOR: 02 STATUS C DIRECTORATE STATUS

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FROM: EWING, PATRICK: AMERICAN VEAL ASSOCIATION

TO: PRESIDENT BUSH

DATE OF
CORRESPONDENCE: 08/17/92

SUBJECT: A REQUEST ENCOURAGING THE PRESIDENT TO SIGN S.544, "THE ANIMAL ENTERPRISE PROTECTION ACT OF 1992".

****

DIRECTORATE ASSIGNED:

STAFF ASSIGNED:

ACTION REQUIRED:

STAFF ACTION:

****

SENDER'S DUE DATE:

OSTP DUE DATE:
DATE COMPLETED:

STAFF DUE DATE
DATE COMPLETED/DEPT:

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COPIES TO: D. Allan Bromley
LIFE SCIENCES

****

WHITE HOUSE TRACKING #:

CONTACT PERSON:
PHONE: EXT:

REMARKS:

OSTP RECEIVED: 09/08/92 DEPT RECEIVED:
FILE: P-LIFE SCIENCES

CENTRAL FILES:

AMERICAN *Veal* ASSOCIATION

August 17, 1992

President George Bush
Executive Office of the President
The White House
1600 Pennsylvania Avenue Northwest
Washington, DC 20500

Dear President Bush:

On behalf of the 2,000 veal growers, and our allied industry groups consisting of feed manufacturers, meat packers, veterinarians, educators and animal health care providers, I encourage you to sign S.544, "The Animal Enterprise Protection Act of 1992."

This legislation, one of the highest legislative priorities in Congress for three years, is a result of great effort by a broad based coalition of farmers, ranchers, agribusiness groups, farm and commodity organizations, biomedical and ag research institutions, and other animal-related organizations, associations and businesses.

Co-sponsored by 264 members of the House of Representatives and passed in suspension along with unanimous consent of the Senate, the bill extends needed protection under Federal law to farmers and research facilities when they are faced with acts of vandalism and violence on their property and person.

Your approval and signature will again indicate your strong support of the free enterprise system, a tough stance on crime and, especially, your concern and support for American agriculture.

Sincerely,

Patrick Ewing

Patrick Ewing
President, American Veal Association

PE/jw

Ken Cheatham, Executive Director
1804 Naper Blvd. Suite 418 Naperville, IL 60563
Telephone: 708-505-8521 FAX: 708-505-4974